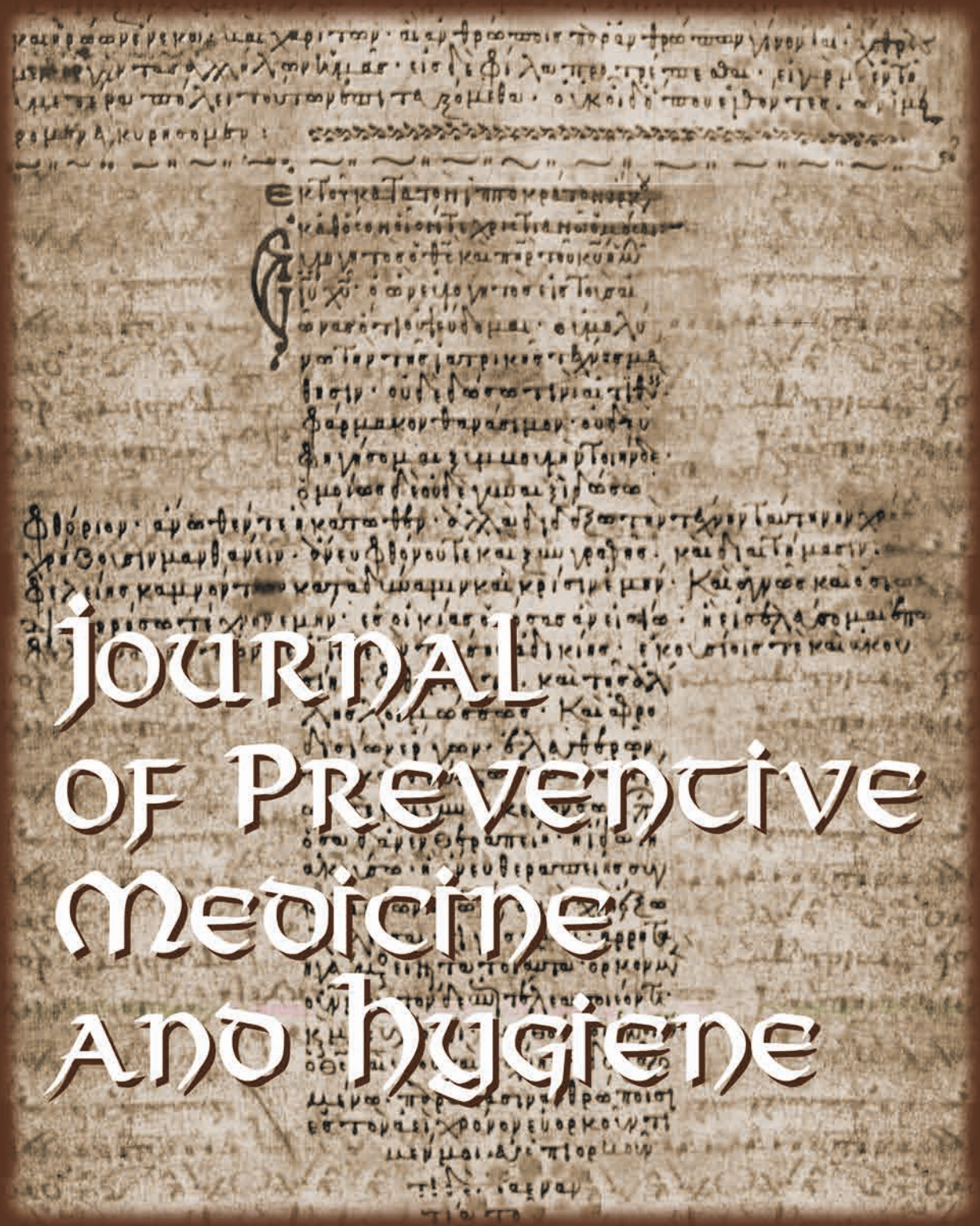
ISSN 2421-4248

vol. 65 n. 2

June 2024

Cited in Index Medicus / Medline
NLM ID 921440 (Pub-Med)



The original document of Hippocrates' oath

Journal of Preventive Medicine and Hygiene

The Journal has been accreditated, on occasion of the 17th December 2004 Meeting of the Executive and Scientific SItI Councils, by the Italian Society of Hygiene, Preventive Medicine and Public Health

PACINI EDITORE MEDICINA

Journal of Preventive Medicine and Hygiene

Managing Editor: Patrizia Alma Pacini

Publisher: Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa, Italy
Tel. +39 050 313011 - Fax +39 050 3130300
info@pacinieditore.it - www.pacinimedicina.it

Published online July 2024

Authorization Tribunal of Genoa, Italy n. 507 - 10/6/1960
Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore srl registration n. 6269 - 29/8/2001).

Contents

HEALTH PROMOTION

University students in Central Italy: do they follow proper dietary habits?

VIGIANI NICOLA[1], QUERCIOLI CECILIA[2,3], FANTI ELISA[3], FRILLI ELEONORA[3], MESSINA GABRIELE[3,4], NICOLA NANTE[3,4]

[1] Food and Nutrition Hygiene Unit - East Area, Local Health Authority, Southern East Tuscany, Arezzo, Italy;
[2] Health Care Management, Local Health Authority, Southern East Tuscany, Siena, Italy;
[3] Post Graduate School of Public Health, University of Siena, Siena, Italy;
[4] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy

Keywords

University students • Food habits • Diet • Food frequency questionnaire • Lifestyle

Summary

Background. *Eating a healthy diet is acknowledged as one of the main factors in preventing malnutrition and non-communicable diseases. As young students represent a group more prone to poor dietary habits, the aim of this study was to analyse the dietary habits of a group of undergraduate students attending university in a city of central Italy, Siena.*

Methods. *4,700 students were invited to participate in a cross-sectional study completing an online self-administered questionnaire about their food habits. The obtained data were analysed by Microsoft Excel 2021 and Stata 17 software, through the Mann-Whitney and the Kruskal-Wallis test; a p-value < 0.05 was considered statistically significant.*

Results. *The students living at home consumed more fruit, vegetables, pasta, meat, fish, packaged foods, fruit juices, beer and wine; the only statistically significant differences were found for pizza and snacks. Even the gender influenced the consumption of many foods; women consumed more vegetables and coffee/tea, while males ate more pasta, meat, packaged foods, pizza, fries and beer.*

Conclusions. *With the transition from secondary school to university, students are continuously challenged to make healthful food choices and they must be self-disciplined to take care of themselves. It would be important for health campaigns to be promoted in young adults to help them make the right choices.*

Introduction

Eating a healthy diet is universally acknowledged as one of the main factors in preventing malnutrition and non-communicable diseases (NCDs) such as type 2 diabetes and cardiovascular diseases [1], therefore a healthy and balanced lifestyle should be promoted across all age groups [2]. According to the World Health Organization (WHO) Healthy Diet Fact Sheet a healthy diet should include at least 400 g (*i.e.* five portions) of fruit and vegetables per day, pulses, nuts and whole grains, less than 10% of the total energy intake should come from free sugars, less than 30% of total energy intake should come from fats and lastly, we should consume less than 5 g of salt per day.

As many health habits are formed at a very young age, the promotion of a proper lifestyle should be focused among adolescents and young adults [3]. In fact, numerous studies show that poor dietary habits appear to be very popular between both high school and university students, in particular the consumption of fast food is high and it could be associated with a weight gain from adolescence to adulthood [4-6].

During the critical passage from high school to university, as the students independence increases and the living situation changes [7], young adults are repeatedly put to the test with making wholesome food choices [8]. Choices inherent eating habits during the university years are influenced by several factors, such as peers ascendency, class schedule, alcohol consumption, nightlife and even economic situation [9, 10]. In fact, once they start university, not only they start having poor dietary habits, but they also start consuming excessive quantity of alcohol and decreasing their physical activity [11]. Consequently, the years spent at university represent a very critical era that is able to influence both the lifestyle and the eating habits of the following adulthood and, as this age group might soon play a parental role, their health is closely related to the one of new generations [12, 13].

University students can be divided into two groups, those who continue living at home with their parents and those that are attending universities far from their usual residence and are forced to live away from home, known as displaced students. Special attention should be paid to university students, as they represent a group that is particularly prone to poor dietary habits [14]. In Italy, a study showed that non-displaced students consumed higher quantities of cooked vegetables, fish, meat products, chips, bread/cereals, pulses, cooked meals and sandwiches, while displaced students consumed more raw vegetables, beer and other alcoholic drinks, raw/cold meals, frozen meals and ready meals [15]. The same results were observed in Spain where it was noted that

displaced students consumed fast food more frequently compared to before they started university [9].
University students should be considered as a vulnerable group, especially the displaced ones, as they seem to move towards unfavourable food choices. Thus, it is important to assess the issue and to implement strategies to promote long-term health in this particular population [9].
The aim of this study was to analyse the dietary habits and the changes in eating patterns of a group of undergraduate students attending university in a city of central Italy, Siena.

Materials and methods

From May to June 2023, four thousand seven hundred students attending different degree courses at the University of Siena received an email and were invited to participate in a cross-sectional study about their food habits. The students had to complete an online questionnaire that had been revised by two committees, the first one was Careus (Committee for Ethical Research in the Humanities and Social Sciences), which reviewed the questions from an ethical point of view, and the second one was SPC (The University Survey Policy Committee), which selected the sample and then sent the questionnaire. SPC selected the sample randomly by matriculation number, selecting all students with one or more final matriculation numbers that had not already been used for the last carried out surveys until a sample size of 20/25% of the population, considered to be representative of all the students, was reached. The undergraduate students, who were selected, received an email with the self-administered questionnaire and the instructions and were asked to complete it online; the enrolment was voluntary and anonymous. Preliminary information was provided about the purpose, the protocol and the method of the study including the guarantee of anonymity (according to the Legislative Decree no. 196/2003 "Code concerning the protection of personal data"). The survey remained open for 21 days and two reminder emails were sent after 7/10 days (for the first reminder) and after 10/15 (for the second) to those who did not respond.
The research was carried out in accordance with the World Medical Association Declaration of Helsinki; it does not report any experiment on human or biological human samples, nor research on identifiable human material and data because it is an observational survey conducted by an anonymous questionnaire among university students. Indeed, in order to protect the privacy of subjects and confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity (stated in the article n. 23 of the above-mentioned Helsinki declaration) the research was wholly conducted anonymously; thus, no identifiable personal data are reported.

Characteristics of the questionnaire

The survey consisted of 15 questions, and it allowed us to obtain information about age, weight, sociodemographic characteristics, as well as dietary habits.
The first part was dedicated to the demographic aspects, with questions regarding age, weight, height, parents' educational qualifications and students' socioeconomic status. The second section investigated the socio-cultural backgrounds to learn whether the students were living at home with their families or not. The third one was the part about the eating habits, in particular it was asked where the meals were eaten and it also included the validated Food Frequency Questionnaire (FFQ), developed on the model used by Papadaki and Scott [16]. The FFQ list contained fresh fruit, cooked and raw vegetables, potatoes, rice and pasta, chips, pulses, meat products, fish, snacks, sauces, meat and poultry, bread and cereals, dairy, cakes (including sweets, sugar, chocolates, biscuits, ice cream, cakes, scones and pastries), eggs and pizza. While for the beverages it included fresh fruit juice, milk, non-alcoholic beverages, wine, beer, spirits and coffee/tea. Consumption frequency for each food item was measured as "never", "1-3 times per month", "1-2 times per week", "3-4 times per week", "5-6 times per week", "once per day", "more than once per day". The participants were also asked whether they perceived that their eating habits had changed since starting university or not.

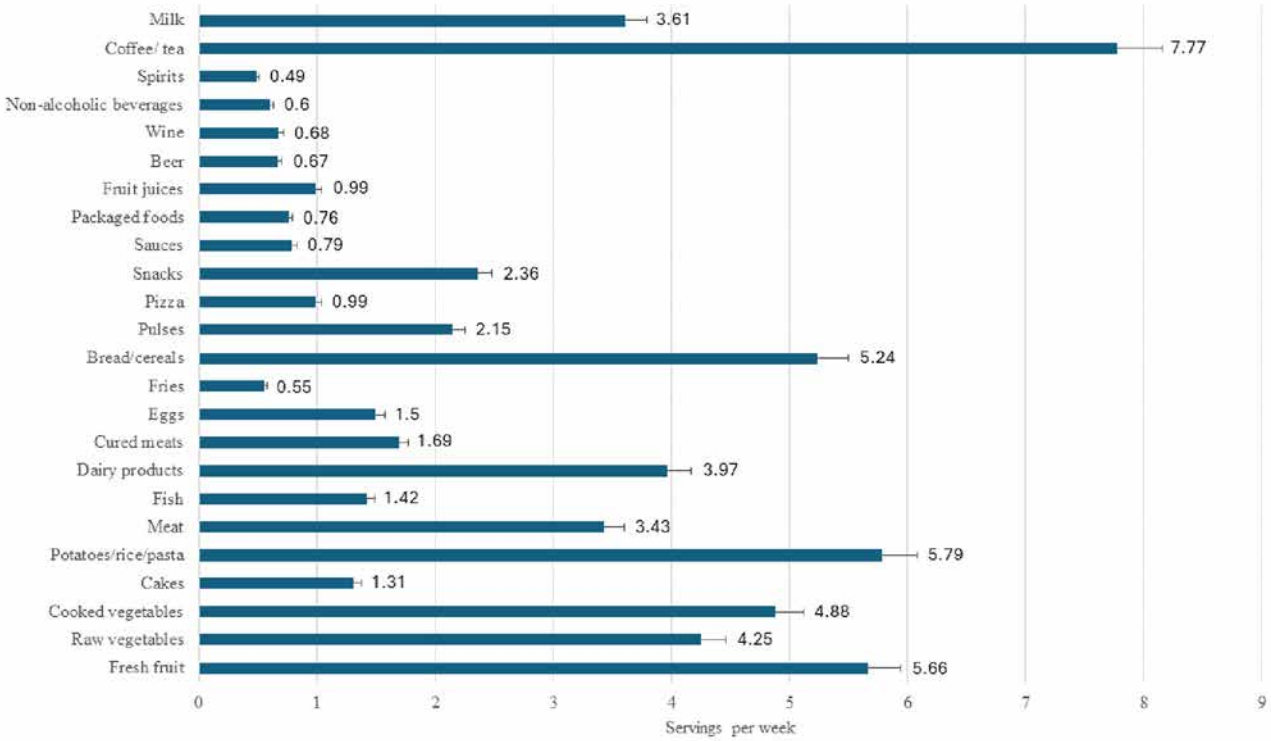
Statistical analysis

The answers provided in the questionnaire had been collected in a database using Microsoft Excel 2007. Data for individual food items in the food frequency questionnaire were transformed to servings per week (servings/week). As in the study by Papadaki and Scott, it was assumed that "times" could be equated to "portions", therefore "never" was transformed to "0 times per week", "1-3 times per month" was transformed to "0.5 times per week", "1-2 times per week" was transformed to "1.5 times per week", "3-4 times per week" became "3.5 times per week", "5-6 times per week" became "5.5 times per week", "once per day" became "7 times per week" and "2 times per day" became "14 times per week".
The per capita weekly consumption of each food or beverage was then calculated by taking the sum of the values for all students in the population of reference and dividing the result by the total number of individuals. The obtained data were analysed by Stata17 software. The Mann-Whitney test was used to detect changes in food intake for students living at and away from home, while the Kruskal-Wallis test was used to track dietary intake changes according to gender and mean and SD were calculated; a p-value < 0.05 was considered statistically significant.

Results

The survey closed with only 508 completed questionnaires out of 4,700 invitations sent out (10.8%), of whom 321

Fig. 1. Mean weekly consumption of foods and beverages.



students (63.2%) still lived at home with parents during their studies and 187 students (36.8%) lived away from their families. The students were classified by age, specifically 71 (14%) were 19 or 20 years old (yo), 144 (28.3%) were 21 or 22 yo, 190 (37.4%) were between 23 and 25 yo and finally 103 (20.3%) were older than 26 yo, and by gender, 126 (24.8%) were male, 379 (74.6%) were female, 2 (0.4%) would rather not answer and 1 (0.2%) did not identify with either gender.

BMI (kg/m^2) was calculated with data regarding weight and height and the mean resulted 22.65, with a statistically significant difference between the two genders (female students BMI = 22.16 *vs* male students BMI = 23.93, p = 0.0001), but no differences between displaced and non-displaced students were observed.

As concerns the main meals, the majority of the students (86.4%) stated they have breakfast at home; only a small group (8.8%) said they don't have it, while the rest have breakfast at the bar (4.7%). The 25.3% of the students declared to have lunch at home, the 31.1% eats at university food prepared at home, the 38.9% has lunch in the canteen and lastly a proportion of students (2.5%) claimed to choose other solutions (bars, takeaways, *etc.*), with no differences between the two groups. Finally, almost all the students consumed dinner at home.

The most consumed foods, as shown in Figure 1, were potatoes/rice (5.79 servings/week), fresh fruit (5.66 servings/week), bread/cereals (5.24 servings/week), cooked vegetables (4.88 servings/week), while the most consumed drinks were coffee/tea (7.77 servings/week) and milk (3.61 servings/week). The students reported a lower consumption of fish (1.42 servings/week), pizza (0.99 servings/week), packaged foods (0.76 servings/week), fries (0.55 servings/week).

The students that lived at home reported a larger (even if not statistically significant) consumption of fresh fruit, cooked and raw vegetables, pasta/rice, meat, fish, cured meats, bread/cereals, pulses, packaged foods, fruit juices, beer, wine than student living away from family as shown in Table I. The only statistically significant difference was found for pizza (1.03 servings/week *vs* 0.92, p = 0.0422). In contrast, the students living away from home consumed significantly more sauces and spirits but only the difference between the snacks consumption was statistically significant (2.66 servings/week *vs* 2.19, p = 0.0424). The frequency of consumption of milk, coffee/tea, non-alcoholic beverages, fries, eggs, dairy products, cake were similar in the two groups of students.

Referring to changes in dietary habits, 89.5% of the students noted some modification since starting university with no significant differences between students living at home (86.6%) or far away from it (94.6%), as shown in Figure 2, or between males and females.

The gender appeared to influence the frequency of consumption of many foods as it can be seen in Table II. Women demonstrated to consume, with statistically significant differences, a greater amount of raw vegetables (4.6 servings/week *vs* 3.2, p = 0.002), cooked vegetables (5.3 servings/week *vs* 3.7, p = 0.0001) and coffee/tea (8.1 servings/week *vs* 6.8, p = 0.025).

Tab. I. Mean weekly consumption of food and beverages of students living at and away from home.

	Students living away from home		Students living at home		
	Mean	SD	Mean	SD	p-value
Fresh fruit	5.55	4.6	5.73	4.7	0.63
Raw vegetables	4.1	3.54	4.34	3.66	0.43
Cooked vegetables	4.75	3.56	4.96	3.65	0.46
Cakes	1.31	1.56	1.3	1.5	0.89
Potatoes/rice/pasta	5.63	3.02	5.88	3.1	0.35
Meat	3.3	2.41	3.5	2.66	0.5
Fish	1.37	1.21	1.44	1.15	0.34
Dairy products	3.93	3.09	3.99	3.11	0.88
Cured meats	1.56	1.43	1.77	1.94	0.76
Eggs	1.51	1.02	1.5	1.13	0.51
Fries	0.53	0.66	0.56	0.65	0.63
Bread/cereals	4.9	3.38	5.44	3.55	0.11
Pulses	1.93	1.56	2.28	2.05	0.13
Pizza	0.92	0.63	1.03	0.64	*0.04
Snacks	2.66	2.89	2.19	2.58	*0.04
Sauces	0.85	1.21	0.76	1.08	0.23
Packaged foods	0.69	0.95	0.8	1.41	0.3
Fruit juices	0.87	1.56	1.07	1.94	0.4
Beer	0.62	1.04	0.69	1.26	0.39
Wine	0.59	0.86	0.73	1.12	0.16
Non-alcoholic beverages	0.62	1.1	0.59	1.09	0.49
Spirits	0.54	0.79	0.46	0.6	0.54
Coffee/ tea	7.93	4.61	7.67	4.54	0.5
Milk	3.51	3.4	3.66	3.26	0.67

SD: standard deviation. Levels of significance were assessed by the Mann-Whitney test, a p-value < 0.05 was considered significant and marked with an asterisk in the table.

In contrast, males consumed significantly more potato/rice/pasta (6.9 servings/week *vs* 5.4, p = 0.0002), meat (4.3 servings/week *vs* 3.1 p = 0.0001), packaged foods (1.1 servings/week *vs* 0.6, p = 0.016), pizza (1.2 servings/week *vs* 0.9, p = 0.024), fries (0.7 servings/week *vs* 0.5, p = 0.013), beer (1.2 servings/week *vs* 0.5, p = 0.0001) and non-alcoholic beverages (0.9 servings/week *vs* 0.5, p = 0.010).

Lastly, statistically significant differences were found among the students living away from home depending on their gender, as female students consumed more raw vegetables (p = 0.001) and cooked vegetables (p = 0.0003), while male students consumed more meat (p = 0.008), fish (p = 0.012) and beer (p = 0.009). Instead, the male students who lived at home with their families showed a significantly higher frequency of consumption of potato/rice/pasta (p = 0.0007), meat (p = 0.0018), fries (p = 0.016), packaged foods (p = 0.045), beer (p = 0.0002) and non-alcoholic beverages (p = 0.048), while female students consumed more cooked vegetables (p = 0.0356) and coffee/tea (p = 0.019).

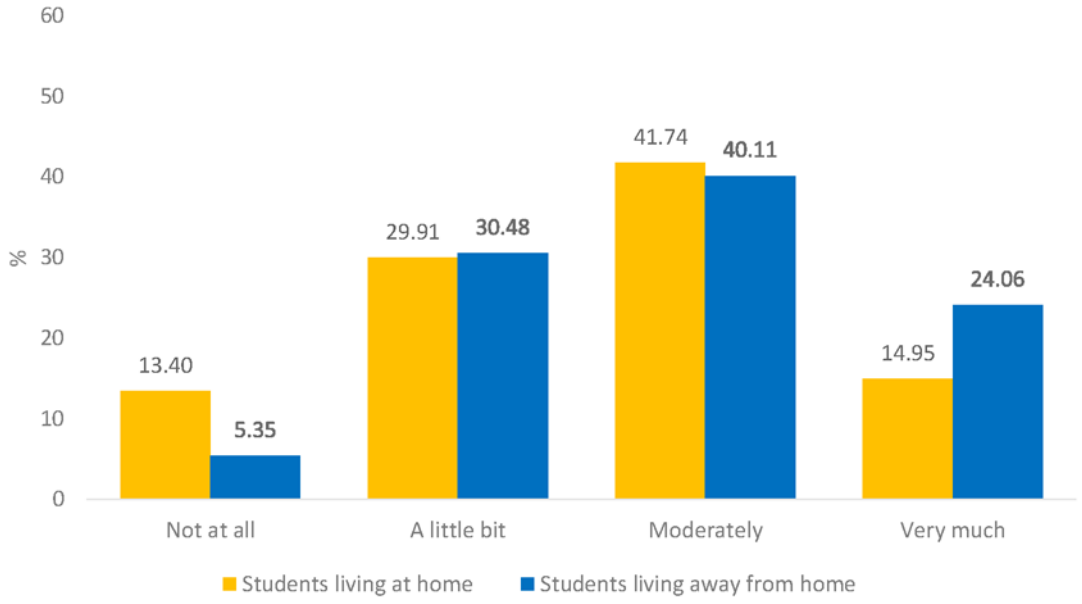
Regarding the students' socioeconomic status and their parents' educational qualifications, the students that have preferred not to respond to the first question showed a higher consumption of fries (p=0.006) and pizza (p=0.015), while those who make ends meet easily consume a higher quantity of spirits (p = 0.0037). Regarding the parents' educational qualifications, the students whose father has a post graduate degree consumed more meat (p = 0.01), more wine (p = 0.0003) and more pizza (p = 0.039), pizza was more eaten also between students whose father stopped after elementary school; while the students whose mother has a post graduate degree consumed more wine (p = 0.0014).

Discussion

This study found out that university students did not show much interest in the questionnaire topics as only 10.8% responded to the survey and the ones that did it, despite improvements in recent years maybe due to health promotion campaigns such as OKkio alla salute for children and Health Behaviour in School-aged Children-HBSC for adolescents [17], showed some difficulties in following a proper lifestyle. Healthy and unhealthy eating habits influence the Quality of Life (QOL), a concept that indicates the general wellness of person and societies [18].

The majority of the students reported to consume their meals at home or at university with homecooked food; this could represent a money saving method or it could be related to the quality of canteen food as reported in other studies [19]. In contrast with what can be read in the literature, in this study it emerged that only 8.8% of

Fig. 2. Differences in how much dietary habits have changed since starting university between students living at and away from home.



students did not eat breakfast, unlike a group of Italian adolescents, in which more than 40% skipped this meal, highlighting an improvement in eating habits growing up [20].

The results of this study are in agreement with others reporting the adoption of unhealthy food habits among college students, especially with regard to the low consumption of fruit and vegetables, fish, eggs, and the excessive consumption of cured meats and dairy products [21, 22]. The difficulties to adopt a diet complying with the guidelines are a problem that affects many college students from several origins and with different dietary habits.

However, it is crucial to understand that some of these wrong dietary habits can already be established in children and adolescents; this could make bad habits persist in young adults and make it even more difficult to change them. As a matter of fact, an Italian study about adolescents reported that 7 out of 10 adolescents did not consume vegetables daily and 1 in 2 did not consume both fruit and vegetables daily, moreover boys had a higher prevalence of incorrect dietary habits than girls [20].

Most of the statistically significant differences in this survey were linked to the gender. In particular, the women in our study, in agreement with previous studies [15, 21, 23-25], consumed significantly more fruits and vegetables and less ready meals and alcoholic beverages than men; this could be because they are better informed about the nutritional value of foods, or maybe because they are more attentive and sensitive to weight control [26, 27]. As shown in a previous study, also during adolescence, girls tend to have a healthier diet, in fact it was reported that 67,5% of girls did not consume vegetables daily versus 77,9% of boys [20]. Moreover, females consume more coffee/tea than male students, as it was found also in other studies and this could be linked to women faster metabolism of caffeine [28]. However, in general, both females and males consumed high quantity of caffeine both for social reasons and to increase mood and alertness [29].

Although the changes in dietary habits involved a significant number of students, the phenomenon mainly affected those who lived away from family [30]. The university students who lived with their parents declared to eat a lot more fruits, vegetables, pasta/rice, meat, fish, cured meats, bread/cereals, pulses, packaged foods, fruit juices, beer, wine. Students living with families seemed to have a better diet, and this could be due to family support both financially and in terms of food choices; a cross national study about adolescents showed that, already in that age group, the family' socioeconomic status can influence dietary habits and could be related to a higher prevalence of obesity [31]. Otherwise, displaced students, maybe because of a lack of time or inexperience in the kitchen, tend to eat healthy foods less frequently [15, 21].

The reasons that could influence university students in making food choices are numerous: comfort and convenience of fast food, taste, self-discipline, physical and social environment surrounding them (availability and accessibility, appeal and prices of food products), gender, attention to weight and beliefs, time and convenience. Another important reason could be the budgetary constraints that the whole worlds is facing right now [32-36].

Compared with other surveys conducted a few years back in northern and southern Italy [15, 21], we have noticed fewer statistically significant differences between students who lived with or without theirs parents and it could be interesting to carry out further studies to understand the reason for this divergence. In particular,

Tab.II. Mean weekly consumption of food and beverages of students based on the gender.

	Female students		Male students		I'd rather not answer		I dont't identify with either gender		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
Fresh fruit	5.73	4.74	5.52	4.47	3.5	2.82	1.5	-	0.76
Raw vegetables	4.61	3.8	3.2	2.77	3.5	2.82	0.5	-	*0.002
Cooked vegetables	5.29	3.74	3.71	2.96	3.5	0	1.5	-	*0.0001
Cakes	1.26	1.35	1.46	1.96	0.25	0.35	0.5	-	0.32
Potatoes/rice/ pasta	5.42	2.99	6.89	3.09	6.25	1.06	5.5	-	*0.0002
Meat	3.13	2.38	4.34	2.9	4.5	1.41	0.5	-	*0.0001
Fish	1.35	1.11	1.61	1.27	2.75	3.88	0.5	-	0.17
Dairy products	3.83	3.12	4.33	3.02	5.25	2.47	7	-	0.1
Cured meats	1.63	1.76	1.83	1.76	2.5	1.41	7	-	0.15
Eggs	1.44	1.01	1.68	1.24	3.5	2.82	0.5	-	0.07
Fries	0.47	0.49	0.74	0.88	2.75	3.88	1.5	-	*0.012
Bread/cereals	5.26	3.49	5.22	3.53	6.25	1.06	0	-	0.31
Pulses	2.15	1.94	2.16	1.74	2	2.12	1.5	-	0.99
Pizza	0.93	0.54	1.18	0.85	1	0.7	1.5	-	*0.02
Snacks	2.39	2.8	2.28	2.44	2.5	1.41	1.5	-	0.92
Sauces	0.73	1.04	0.99	1.32	1.75	2.47	1.5	-	0.34
Packaged foods	0.63	0.95	1.09	1.84	2.5	1.41	3.5	-	*0.016
Fruit juices	0.93	1.08	1.14	1.8	3.5	4.94	0.5	-	0.31
Beer	0.49	0.74	1.16	1.83	3.5	4.94	0.5	-	*0.0001
Wine	0.66	0.97	0.75	1.18	1.75	2.47	0.5	-	0.97
Non-alcoholic beverages	0.51	0.98	0.88	1.38	0.25	0.35	0.5	-	*0.01
Spirits	0.46	0.65	0.52	0.61	2.75	3.88	0.5	-	0.33
Coffee/ tea	8.11	4.5	6.76	4.61	7.75	8.83	7	-	*0.025
Milk	3.52	3.36	3.86	3.2	5.5	0	0.5	-	0.66

SD: standard deviation. Levels of significance were assessed by the Kruskal Wallis test, a p-value < 0.05 was considered significant and marked with an asterisk in the table.

it would be useful to understand why the diets of the two groups of students have become more similar over the years.

It is important to consider that this study has some limitations. One of them could be that, even if the initial sample could have been representative of all the university students, the answers were not as many as we expected as only 10.8% of the students responded. Another thing to take in consideration is that the majority of the respondents were female, usually more attentive and sensitive about healthy eating habits, so the male population could not have been represented properly. Lastly, it would have been useful to know which faculty the students were attending as some of them may include nutrition courses and this may have influenced some answers.

Conclusions

With the transition from secondary school to university, when independency increases, students are continuously challenged to make healthful food choices and they must be self-disciplined to take care of themselves. According to data from the World Health Organization, 86% of deaths and 77% of the loss of healthy life years in Europe are caused by chronic diseases [37]. Modifiable risk factors, combined with other non-modifiable causes such as age or genetic predisposition, are responsible for the majority of deaths from chronic diseases worldwide; therefore, it is important for health promotion campaigns to be promoted in young adults to help them make the right choices regarding eating healthy. To design appropriate health promotion campaigns in universities, to improve the students' lifestyle and to prevent many chronic degenerative diseases, it is fundamental to plan harmonized surveillance systems designed to detect risk factors. Since the lack of harmonized measurements and methodologies among countries, it is useful to develop more effective and internationally applicable policies [38].

Acknowledgements

The authors would like to thank the University of Siena for contributing to the development of the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The data that support the findings of this study are available from the corresponding author, E.F., upon reasonable request.

Conflicts of interest statement

None declared.

Authors' contribution

NV, EF and EF: conceptualisation of the study; EF and EF: data curation; EF and EF: formal analysis; EF and EF: investigation; EF and EF: methodology; NN: project administration; EF and EF: resources; EF and EF: software; NV, CQ, GM and NN: NV, CQ, GM and NN: supervision; EF and EF: validation; writing-original draft preparation; EF, EF, NV, GM and NN: writing-review and editing. All authors have read and agreed to the published version of the manuscript.

References

[1] United States Census Bureau. An Aging World: 2008. Census.gov. Available at: https://www.census.gov/library/publications/2009/demo/p95-09-1.html (Accessed on: 20/01/2023).

[2] Rapporto annuale 2023 - La situazione del Paese. Available at: https://www.istat.it/it/archivio/286191 (2023) (Accessed on: 30/06/2023).

[3] Il Censimento permanente della popolazione in Piemonte Anno 2021. Available at: https://www.istat.it/it/files//2023/09/Piemonte_Focus-2021_Censimento-permanente.pdf (Accessed on: 30/06/2023).

[4] Eurostat. Statistics Explained: population structure and ageing. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing#The_share_of_elderly_people_continues_to_increase (Accessed on:25/10/2023.

[5] Statistics | Eurostat. Population structure indicators at national level. Available at: https://ec.europa.eu/eurostat/databrowser/view/DEMO_PJANIND__custom_964289/bookmark/map?lang=en&bookmarkId=1276db8f-938f-4f55-a801-e0151d01702f (Accessed on: 25/10/2023).

[6] Demography 2023 edition - Interactive publications - Eurostat. Available at: https://ec.europa.eu/eurostat/web/interactive-publications/demography-2023 (Accessed on: 25/10/2023).

[7] Istat Annuario Statistico Italiano 2022. Capitolo 4. Sanità e Salute. Available at: https://www.istat.it/storage/ASI/2022/capitoli/C04.pdf (Accessed on: 25/10/2023).

[8] Haggerty JL, Reid RJ, Freeman GK, Starfield BH, Adair CE, McKendry R. Continuity of care: a multidisciplinary review. BMJ 2003;327:1219-21. https://doi.org/10.1136/bmj.327.7425.1219.

[9] Coleman EA, Boult C, & American Geriatrics Society Health Care Systems Committee. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc 2003;51:556-7. https://doi.org/10.1046/j.1532-5415.2003.51186.x.

[10] Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc 2004;52:675-84. https://doi.org/10.1111/j.1532-5415.2004.52202.x. Erratum in: J Am Geriatr Soc 2004;52:1228.

[11] Coleman EA, Smith JD, Frank JC, Min SJ, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the Care Transitions Intervention. J Am Geriatr Soc 2004;52:1817-25. https://doi.org/10.1111/j.1532-5415.2004.52504.x.

[12] Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22. https://doi.org/10.1016/S0140-6736(20)30925-9. Erratum in: Lancet 2020;396:1562.

[13] Gazzetta Ufficiale. Piano Nazionale di Ripresa e Resilienza. Decreto-Legge 24 febbraio 2023. Available at: https://www.gazzettaufficiale.it/eli/id/2023/02/24/23G00022/sg (Accessed on: 30/06/2023).

[14] Gazzetta Ufficiale. Decreto 23 maggio 2022, n. 77. Available at: https://www.gazzettaufficiale.it/eli/id/2022/06/22/22G00085/sg (Accessed on: 28/06/2023).

[15] Savioli G, Ceresa IF, Gri N, Bavestrello Piccini G, Longhitano Y, Zanza C, Piccioni A, Esposito C, Ricevuti G, Bressan MA. Emergency Department Overcrowding: understanding the factors to find corresponding solutions. J Pers Med 2022;12:279. https://doi.org/10.3390/jpm12020279.

[16] Ackroyd-Stolarz S, Guernsey JR, MacKinnon NJ, Kovacs G. The association between a prolonged stay in the emergency department and adverse events in older patients admitted to hospital: a retrospective cohort study. BMJ Qual Saf 2011;20:564-9. https://doi.org/10.1136/bmjqs.2009.034926.

[17] Pines JM, Pollack CV Jr, Diercks DB, Chang AM, Shofer FS, Hollander JE. The association between emergency department crowding and adverse cardiovascular outcomes in patients with chest pain. Acad Emerg Med 2009;16:617-25. https://doi.org/10.1111/j.1553-2712.2009.00456.x.

[18] Pines JM, Shofer FS, Isserman JA, Abbuhl SB, Mills AM. The effect of Emergency Department crowding on analgesia in patients with back pain in two hospitals. Acad Emerg Med 2010;17:276-83. https://doi.org/10.1111/j.1553-2712.2009.00676.x.

[19] Rapporto Osservasalute 2022. Stato di salute e qualità dell'assistenza nelle regioni italiane. https://osservatoriosullasalute.it/wp-content/uploads/2023/06/ro-2022-volume_completo.pdf (Accessed on: 25/10/2023).

[20] Boockvar K, Vladeck BC. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc 2004;52:855-6. https://doi.org/10.1111/j.1532-5415.2004.52230_15.x.

[21] Ministero della Salute-Commissione Consultiva. Piano per il miglioramento del sistema emergenza/urgenza 2005. Availabe at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_856_allegato.pdf (Accessed on: 28/06/2023).

[22] Shepperd S, Iliffe S, Doll HA, Clarke MJ, Kalra L, Wilson AD, Gonçalves-Bradley DC. Admission avoidance hospital at home. Cochrane Database Syst Rev 2016;9:CD007491. https://doi.org/10.1002/14651858.CD007491.pub2.

[23] Sorlini M, Perego L, Silva S, Marinoni G, Zucchi A, Barbaglio G, Azzi M. Il modello CReG (Chronic Related Group) di presa in carico territoriale della cronicità: esperienza pilota dell'ASL di Bergamo - fase progettuale. Ig Sanita Pubbl 2012;68:841-61.

[24] De Koning ER, Boogers MJ, Beeres SL, Kramer ID, Dannenberg WJ, Schalij MJ. Managing hospital capacity: achievements and

lessons from the COVID-19 pandemic. Prehosp Disaster Med 2022;37:600-8. https://doi.org/10.1017/S1049023X22001169.

[25] Kenny JF, Chang BC, Hemmert KC. Factors affecting emergency department crowding. Emerg Med Clin North Am 2020;38:573-87. https://doi.org/10.1016/j.emc.2020.04.001.

[26] Di Martino G, Cedrone F, Di Giovanni P, Romano F, Staniscia T. Impact of COVID-19 pandemic on oncological surgery activities: a retrospective study from a Southern Italian Region. Healthcare 2022;10:2329. https://doi.org/10.3390/healthcare10112329.

[27] Van Dusen RA, Abernethy K, Chaudhary N, Paudyal V, Kurmi O. Association of the COVID-19 pandemic on stroke admissions and treatment globally: a systematic review. BMJ Open 2023;13:e062734. https://doi.org/10.1136/bmjopen-2022-062734.

[28] Roth GA, Vaduganathan M, Mensah GA. Impact of the COVID-19 pandemic on cardiovascular health in 2020: JACC state-of-the-art review. J Am Coll Cardiol 2022;80:631-40. https://doi.org/10.1016/j.jacc.2022.06.008.

[29] de Lange M, Carvalho AS, Brito Fernandes Ó, Lingsma H, Klazinga N, Kringos D. The Impact of the COVID-19 Pandemic on Hospital Services for Patients with Cardiac Diseases: A Scoping Review. Int J Environ Res Public Health 2022;19:3172. https://doi.org/10.3390/ijerph19063172.

[30] Angelini M, Teglia F, Casolari G, Astolfi L, Boffetta P. Decrease of visits and hospital admissions for cancer patients during the COVID-19 pandemic. A systematic review and meta-analysis. Z Gesundh Wiss 2023:1-7. https://doi.org/10.1007/s10389-023-01857-w.

Received on February 8, 2024. Accepted on May 31, 2024.

Correspondence: Eleonora Frilli, University of Siena, Via Aldo Moro 2, 53100 Siena, Italy. E-mail: frilli2@student.unisi.it

How to cite this article: Vigiani N, Quercioli C, Fanti E, Frilli E, Messina G, Nicola N. University students in Central Italy: do they follow proper dietary habits? J Prev Med Hyg 2024;65:E117-E124. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3194

HEALTH PROMOTION

Trust levels toward health care and government: insights from TrustMe, an Italian cross-sectional study

ALESSANDRO SCACCHI[1], GIUSEPPINA LO MORO[1], GIANMARCO GIACOMINI[1], FEDERICO TORCHIO[2], CARLA MARIA ZOTTI[1], FABRIZIO BERT[1,3], ROBERTA SILIQUINI[1,4]
[1] Department of Public Health Sciences, University of Turin, Turin, Italy; [2] ASL TO5, Chieri, Italy; [3] ASL TO3, Turin, Italy; [4] AOU City of Health and Science of Turin, Turin, Italy

Keywords

Trust • COVID-19 • Italy • Survey

Summary

Introduction. *Negative trends of trust in governments have been described around the world. This study aimed to describe the distrust level in the National Health Service (NHS) and in governmental management of the pandemic, one year after the start of the COVID-19 vaccination campaign.*
Methods. *A survey was distributed in February 2022 among a convenience sample. Outcomes were measured through validated tools: Revised Health Care System Distrust Scale, and the COVID-SCORE-10 questionnaire. Associations were assessed using multiple linear regression models.*
Results. *A total of 2111 questionnaires were collected (54.8% female, median age 43 years [IQR = 34-50]). Distrust in the NHS had a median level of 12 [IQR = 10-14], while trust in the government had a level of 47 [IQR = 35-60]. COVID-19 vaccine hesitancy, high educational attainment, worse economic status, low conventional and digital health literacy, as well as the presence of conspiracy thoughts and distrust in the NHS were significantly associated with lower trust in government during the COVID-19 pandemic. Lack of trust in governmental actions, along with low education and health literacy, as well as the presence of conspiracy thoughts and worse perceptions of one's own health, were associated with greater distrust in the NHS.*
Conclusions. *Overall, low levels of trust in both the government and the NHS have emerged. Since the determinants of reduced trust in institutions can be very diverse and that such levels of distrust after a pandemic can last for an entire generation, tailored interventions are needed to rebuild adequate levels of trust in institutions among the population.*

Introduction

Trust is a multidimensional construct that is generally ascribed as an assumption about others [1] as well as a fundamental element in human interaction [2]. Individual trust levels may vary in a positive or negative way. Lack of trust can produce distrust, which is a different and productive feeling [3]. Distrust relays on the competencies of the trustee, doubting that a task or a goal will be fulfilled [4] and it is based on rational thinking. Finally, the violation of individual trust can lead to feelings of betrayal and scepticism, configuring a loss of trust [5]. Although there are several categories of trust [6] this study is focused on two forms of institutional trust, toward healthcare service and government, on a public health perspective. Institutional trust can be defined as a belief of trust in values and competencies of an institution [7].
Trust in healthcare services refers to healthcare systems including hospitals, clinics, nursing homes, labs, insurance companies and pharmaceutical companies [8]. It does not involve trust in doctors, which is part of interindividual trust [9]. Trust in healthcare services is a pivotal factor to work efficiently in healthcare policy. High levels of trust in institutions responsible for citizens' wellbeing and for controlling hazards lead people to perceive certain decisions (like lockdowns and wearing masks) more positively [6]. Especially in large scale crises, such as economic crises, natural disasters or pandemics, the threatened groups tend to bind together against the external threat, in order to overcome it [10]. Yet, people could respond to the same events sceptically and could develop conspiracy theories, as has already happened in previous pandemics [11]. In such events, public health institutions are interlaced with governmental ones in managing people's wellbeing and safety, so that trust in government is fundamental as well as trust in public health. Indeed, it produces sociability, which in turn leads to altruistic behaviours and acceptance of recommendations such as preventive measures to avoid a disease from spreading [12, 13].
Moreover, trust in healthcare service was found as a predictor of vaccine acceptance and related to previous vaccine compliance, as well as trust in government relates to vaccine intention [14]. Conversely, it is known that distrust in healthcare can lead to avoidance of care services and potential damages for public health [15], acting as one of the main vaccine hesitancy drivers [16]. Even out of vaccine topic, trust in healthcare service was related to positive public health behaviours, like participation to screening for breast cancer. Lack of trust in healthcare, nevertheless, can negatively impact on the continuity of care for breast cancer [17].
However, trust is unstable over time and demotivation could significantly decrease its levels. For instance,

during COVID-19 pandemic, the feeling of "pandemic fatigue" came out [15]. Some people found themselves exhausted from social and economic repercussions of restrictions and started doubting on their efficacy by a lack of trust, so that they were no longer able to fully understand the need of COVID-19 tackling and followed these measures less strictly [15].

Already before the recent pandemic, decreasing levels of trust in social, economic and governmental institutions were reported, especially from those on lower incomes and lower levels of education [2]. While there are already studies assessing trust in healthcare institutions or in government in Italy during the pandemic [15, 18] still little is known since the advent of vaccines. In Italy, COVID-19 vaccinations were introduced at the end of 2020 and in July 2021 the government introduced the "Green Pass" certificate, required for access to various public venues and events. The pass, based on the EU certificate, could be obtained through vaccination, recovery from COVID-19, or a recent negative test. The government later expanded its use, making it mandatory for workplace entry and requiring vaccination for those over 50 and school and university staff [19]. Specifically, from February 2022 COVID-19 vaccination was mandatory for individuals with more than 50 years [20]. Therefore, the primary aim of the present study was to evaluate the level of trust in Italian health and government institutions from a sample of the general population, one year after the beginning of the COVID-19 vaccination campaign. The secondary aim was to explore potential determinants of reduced trust in institutions, focusing also on participants' health literacy and vaccination status.

Methods

Study design and questionnaire

TRUSTMe was an observational and cross-sectional study. Opportunistic sampling was performed by administrating a questionnaire on people who came to receive COVID-19 vaccination in the healthcare agency hubs of the local health unit ASL TO5, in province of Turin (309,862 inhabitants). The research protocol was approved by the Ethics Committee of the University of Turin (prot. N. 2784 18/02/2022). Data were collected during last two weeks of February 2022, when people could receive either booster doses or primary vaccination cycle against COVID-19. It should be noted that, from 1st February 2022, for people older than 50 years, COVID-19 vaccination (concerning booster dose, too) was declared mandatory [20]. We administered a paper questionnaire during the waiting time before the interview with a doctor or after the vaccination, during the observation phase. We included only people older than 18, able to understand the survey and who gave an informed consent for the study enrolment.

In the survey we collected sociodemographic data, such as gender, age, level of education, work status, and nationality. Then, we explored vaccine-related data: COVID-19 dose to be received, COVID-19 infection during last 6 months, and compliance to tetanus vaccine in past 10 years as proxy for vaccination behaviour before the pandemic. Considering that COVID-19 vaccination campaign began in Italy in early 2021, participants were considered as "COVID-19 vaccine hesitant" if they were getting the first or the second dose of the primary cycle at the time of the survey and they did not get COVID-19 in the six months preceding the survey. In addition, we investigated data about impact of the pandemic (consequences on health or economy of self or relatives), perceived economic status, daily social media usage, frequency of fact-checking information on social media.

Finally, the following validated tests were administered to each participant. We used the eHealth Literacy Scale (eHEALS) [21, 22], an 8-item questionnaire that evaluates digital health literacy: the perceived competence of search, evaluate and put in action information about health found online. Digital health literacy was considered not adequate if the score was below 26 [23]. The European Health Literacy Survey (HLS-EU-Q6) [24] was used to evaluate health literacy, with 6 items whose answers ranged from very difficult (1 point) to very easy (4 points). The total score is a mean of the items' score. The higher the score, the higher is health literacy. The Self-Rated Health single item (SRH) [25] was selected for evaluating self-perceived general health: a single-item tool, which can predict mortality and healthcare services [26]. The Single item Conspiracy Belief Scale [27] was used to assess conspiracy beliefs: the answer ranges from 1 to 9 points, where a higher score represents greater conspiracy level.

The last two instruments were the two outcomes of the present study. We explored distrust in healthcare system through a 4-item adapted version of the Revised Health Care System Distrust Scale (RHCSDS) [8]. Each item has an answer with 5 options, with a total score ranging from 4 to 20 points. A higher score represents higher distrust. Then, we assessed perception about decisions and responsibilities of the government in tackling the pandemic using the COVID Score 10 questionnaire items (COVID-SCORE-10) [28] a 10-item tool whose score correlates with trust in government. The scoring is based on 5 options per each item, ranging from 5 to 100 total points. A higher score represents a greater trust.

Statistical analysis

We performed descriptive analysis for each variable, indicating frequencies and percentages for categorical variables and median and interquartile range (IQR) for scalar variables, since Shapiro-Wilk test showed non-normal distributions. We analysed the differences in distribution of the two outcomes across each categorical variable using the non-parametric test of Mann-Whitney for dichotomic variables and non-parametric test of Kruskal-Wallis for non-dichotomic variables.

The associations between the variables explored in the questionnaire and the two outcomes were analysed by multivariable linear regression models. Data were analysed with STATA Statistical software (v17), and statistical significance was set to $p < 0.05$. Missing values were excluded.

Results

Descriptive analysis

A total of 2111 citizens completed the survey. The median age was 43 years (IQR= 34-50) and 54.8% were women. Only 19.0% of the sample had a university degree. A good economic status was perceived by 72.1% of participants. COVID-19 vaccine hesitant individuals were 18.1%. Self-perceived health was considered excellent or very good by 38.6% of participants. Digital health literacy was sufficient for 40.5%, with a median score of 25.00 (IQR = 20.00-30.00). The health literacy median score was 2.66 (IQR = 2.33-3.00). The median score of conspiracy beliefs was 5.00 (IQR = 4.00-7.00). Regarding the outcomes, a median score of 12 (IQR = 10-14) was measured for distrust in healthcare, whereas the median score of trust in government was 47.5 (IQR=35.00-60.00). Detailed descriptive analysis of all categorical items is shown in Table I.

Significant differences in healthcare distrust score's distribution were found across gender, education levels, perceived economic and health status, compliance with anti-tetanus vaccine, COVID-19 vaccine hesitancy, and consequences of the pandemic on economic status. Significant differences in government trust score's distribution were found across gender, perceived economic and health status, nationality, consequences of pandemic on self or relatives' health or economy, digital health literacy, compliance in anti-tetanus vaccine, and COVID-19 vaccine hesitancy (Tab. I).

Multivariable regression models

The multivariable analysis showed a significant negative correlation between healthcare distrust and having a university degree ($b = -0.33$, $p =< 0.001$), health literacy ($b = -0.37$, $p = 0.02$), and trust in government ($b = -0.06$, $p =< 0.001$). Instead, a positive association with healthcare distrust was reported for participants with low self-perceived health status ($b = 0.23$, $p = 0.03$) and conspiracy beliefs ($b = 0.29$, $p =< 0.001$). Trust in government was negatively associated with COVID-19 vaccine hesitancy ($b = -4.1$, $p < 0.001$), having a university degree ($b =-2.07$, $p < 0.001$), a low self-perceived economic status ($b = -2.7$, $p = 0.02$), digital health literacy ($b = -3.01$, $p =< 0.001$), conspiracy beliefs ($b = -0.71$, $p =< 0.001$), and distrust in healthcare system ($b = -2.8$, $p =< 0.001$). Last, trust in government had a positive association with health literacy ($b = 3.45$, $p =< 0.001$). Multivariable analyses' results are shown in Table II.

Discussion

The main aim of the TRUSTMe study was to assess, in a general population sample, healthcare distrust levels and trust levels toward government performance in handling the COVID-19 crisis one year after the beginning of the vaccination campaign in Italy. Potential determinants associated with these main outcomes, such as health literacy and vaccine hesitancy, were also assessed.

TRUSTMe found high levels of distrust in the healthcare system, even higher than those found in earlier research from USA [29, 30]. Moreover, our findings showed a reduction of trust levels in Government performance during the pandemic, considering 2020 Italian data [28]. Overall, if compared to earlier studies, our results may depict a less encouraging scenario. However, it is known that during crises there is a rise in trust levels, thanks to the calls to action of both Government and public health institutions [31]. Indeed, during the COVID-19 pandemic, citizens were exhorted and incited to follow socially restrictive measures in order to tackle the disease from spreading. Making people feel responsible may have accentuated the so-called "rally around the flag" effect [32], which in turn may have led to higher levels of cooperation and national cohesion. It is possible that trust in institutions could have benefited from this effect as well [33].

However, the Italian strategy for the COVID-19 pandemic focused mainly on prevention, firstly with lockdown, then with non-pharmacologic measures like social distancing and personal protective equipment usage. Also, during the vaccination campaign various social restrictions were actualized, such as green passes and mandatory vaccination in some cases [34]. This could have eventually led to a reduction of trust in institutions, with more than a few cases of discontent being exploited [35]. This discontent went along with vaccine hesitancy, consistently with earlier literature [36]. Even in this case, from our analyses vaccine hesitancy came out as a significant negative factor against trust in government policies. In this respect, tackling measures enacted by the government may have been felt as coercive or excessive.

TRUSTMe was carried out in February 2022 after the outbreak of the Omicron variant in December 2021, during which the highest peak of contagions in a short period of time since the beginning of the pandemic was detected [37]. Many could have interpreted this as due to the scarce effectiveness of the efforts made in following the recommendations, so that trust levels could have decreased with the "pandemic fatigue" phenomenon [38].

Multivariable analysis showed that distrust in the NHS and positive judgment of the government's handling of the pandemic were inversely associated. After all, trusting the work of the NHS, one could be very likely to mirror the values of prevention and public health protection. At the same time, with high levels of trust in the NHS, one could believe that the government has managed the pandemic crisis to the best of its ability. Vice versa, higher trust in

Tab. I. Sociodemographic and attitudinal variables: descriptive analysis and non-parametric tests.

Characteristic (n)	N. (%)	Healthcare distrust	Trust in government
		Median [IQR]	Median [IQR]
Gender (n = 2053)			
Male	927 (45.2)	**12 [10-13]**	**50 [35-62.5]**
Female	1126 (54.8)	**12 [10-14]**	**47.5 [32.5-57.5]**
Educational level (n = 2065)			
None or elementary-middle school	652 (31.6)	**12 [11-14]**	47.5 [32.5-60]
Secondary school	1020 (49.4)	**12 [10-14]**	47.5 [35-60]
Postsecondary education	393 (19.0)	**11 [10-13]**	47.5 [35-60]
Occupational status (n = 2053)			
Employed	1517 (73.9)	12 [10-14]	47.5 [32.5-60]
Student	133 (6.5)	11 [9-13]	50 [35-55]
Unemployed	403 (19.6)	12 [10-14]	47.5 [35-60]
Perceived economic status (n = 2042)			
Good-excellent	1472 (72.09)	**12 [10-13]**	**50 [35-60]**
Low-scarce	570 (27.91)	**12 [11-14]**	**42.5 [27.5-52.5]**
Nationality (n = 1959)			
Italian	1790 (91.4)	12 [10-14]	**47.5 [32.5-57.5]**
Other	169 (8.6)	11 [10-13]	**52.5 [45-62.5]**
Consequences of the pandemic on one's own health or that of loved ones (n = 2066)			
No	1697 (82.1)	12 [10-13]	**50 [35-60]**
Yes	369 (17.9)	12 [10-14]	**45 [32.5-55]**
Consequences of the pandemic on the economic status of the family (n = 2057)			
No	1508 (73.3)	**12 [10-13]**	**50 [35-60]**
Yes	549 (26.7)	**12 [11-14]**	**42.5 [30-52.5]**
Daily use of social media (n = 2060)			
No	570 (27.7)	12 [10-13]	50 [36.25-60]
Yes	1490 (72.3)	12 [10-14]	47.5 [32.5-60]
Fact-checking social media information (n = 2052)			
Rarely	407 (19.8)	12 [11-14]	47.5 [32.5-57.5]
Sometimes	434 (21.2)	12 [11-13]	50 [35-60]
Often	570 (27. 8)	12 [10-14]	47.5 [35-57.5]
Always	641 (31.2)	12 [10-14]	47.5 [32.5-60]
Perceived health status (n = 2095)			
Excellent-very good	808 (38.5)	**12 [10-13]**	**50 [35-62.5]**
Good	936 (44.7)	**12 [10-13]**	**47.5 [35-57.5]**
Fair-bad	351 (16.8)	**12 [11-14]**	**42.5 [25-55]**
Received tetanus vaccine booster in the last 10 years (n = 2015)			
No	1103 (54.7)	**12 [10-14]**	**47.5 [32.5-57.5]**
Yes	912 (45.3)	**12 [10-13]**	**50 [35-60]**
COVID-19 vaccine hesitancy (n = 2017)			
Not hesitant	1652 (81.9)	**12 [10-13]**	**50 [35-60]**
Hesitant	365 (18.1)	**12 [11-14]**	**45 [27.5-55]**
Digital Health Literacy (n = 1983)			
Adequate	803 (40.5)	12 [10-14]	**50 [37.5-62.5]**
Not adequate	1180 (59.5)	12 [10-14]	**47.5 [32.5-57.5]**

* Scale from 1 to 4; **: Scale from 8 to 40; *** Scale from 4 to 20; **** Scale from 0 to 100; ***** Scale from 1 to 9. In bold the statistically significant differences ($p < 0.05$) calculated using Kruskal-Wallis or Mann-Whitney tests. N: number; IQR: InterQuartile Range.

governments is correlated with vaccine acceptance [39] together with acceptance toward other preventive measures enacted during previous epidemics, like Ebola [40] or SARS [41]. So, both trust in government and in the NHS are fundamental for a proper functioning of policy [42] and healthcare [43]. Low levels of trust are associated with poorer mental and physical health status [44]. While societies with greater trust in institutions were marked by better perceived health among citizens [45] and a lower mortality for COVID-19 [46].

As for trust level determinants, from our results, distrust in the NHS was associated with perceiving one's health as poor. Maybe, those who feel their health status as poor could think that they are not sufficiently cared for by the NHS. It is true indeed that, during the pandemic, many activities were suspended, especially regarding chronic

Tab. II. Multivariable regression models.

Variable	Healthcare distrust		Trust in government	
	b (CI 95%)	p-value	b (CI 95%)	p-value
Age	0 (-0.01; 0.01)	0.97	0.04 (-0.04; 0.12)	0.34
Female gender	0.19 (-0.08; 0.46)	0.17	-1.47 (-3.33; 0.39)	0.12
COVID-19 vaccine hesitant	0.15 (-0.2; 0.51)	0.39	**-4.1 (-6.5; -1.7)**	**< 0.001**
Educational level:				
Ref: primary education/none				
Secondary school Postsecondary	-0.25 (-0.57; 0.07)	0.13	-1.64 (-3.84; 0.55)	0.14
Postsecondary	**-0.69 (-1.10; -0.28)**	**< 0.001**	**-4.38 (-7.17; -1.58)**	**< 0.001**
Occupational status				
Ref: student				
Employed	-0.27 (-0.85; 0.32)	0.37	0.14 (-3.84; 4.13)	0.94
Unemployed	-0.31 (-0.68; 0.06)	0.1	2.44 (-0.08; 4.96)	0.06
Fact-checking social media information				
Ref: seldom/never				
Sometimes	-0.09 (-0.53; 0.36)	0.7	0.09 (-2.93; 3.11)	0.95
Most of the times	0.1 (-0.32; 0.52)	0.63	1.1 (-1.77; 3.96)	0.45
Always	0.05 (-0.36; 0.47)	0.8	-0.33 (-3.16; 2.5)	0.82
Perceived health status				
Ref: excellent				
Good	0.16 (-0.13; 0.45)	0.29	0.98 (-1; 2.97)	0.33
Fair or bad	**0.51 (0.07; 0.94)**	**0.02**	-2.55 (-5.52; 0.42)	0.09
Perceived economic status as bad	0.11 (-0.23; 0.44)	0.54	**-2.7 (-5.01; -0.39)**	**0.02**
Nationality: foreigners	-0.05 (-0.57; 0.48)	0.87	3.5 (-0.13; 7.12)	0.06
Consequences of the pandemic on one's own health or that of loved ones	-0.19 (-0.53; 0.15)	0.28	-1.13 (-3.47; 1.21)	0.34
Consequences of the pandemic on the economic status of the family	0.24 (-0.09; 0.56)	0.15	-2.18 (-4.41; 0.05)	0.06
Received tetanus vaccine booster in the last 10 years	-0.23 (-0.49; 0.04)	0.09	0.79 (-1.02; 2.6)	0.39
Daily use of social media	-0.11 (-0.43; 0.21)	0.50	-1.7 (-3.88; 0.48)	0.13
Health Literacy Score*	**-0.37 (-0.68; -0.06)**	**0.02**	**3.45 (1.34; 5.57)**	**< 0.001**
Inadequate Digital Health Literacy	-0.24 (-0.52; 0.03)	0.09	**-3.01 (-4.91; -1.11)**	**< 0.001**
Conspiracy level**	**0.29 (0.24; 0.35)**	< 0.001	**-0.71 (-1.1; -0.31)**	**< 0.001**
Distrust in the NHS***	-	-	**-2.8 (-3.15; -2.45)**	**< 0.001**
Trust in government****	**-0.06 (-0.07; -0.05)**	**< 0.001**	-	-

* Scale from 1 to 4; ** Scale from 1 to 9; *** Scale from 4 to 20; **** Scale from 0 to 100.

conditions and outpatient care. Conversely, many resources were diverted to manage the pandemic [47], also lengthening waiting times [48].

Conspiracy thoughts resulted to be associated with little trust both in the NHS and in government actions. Conspiracy theorists tend not to believe the official version of events [49]. This scepticism could have manifested itself also regarding COVID-19 [50], disbelieving in the existence of the COVID-19 disease and seeing protective measures in a bad light [51,52], as it already happened before [53].

Based on our findings, high levels of health literacy were significantly associated with lower distrust in the NHS and less confidence in the government's management of the pandemic. Health literacy is a major determinant of virtuous health behaviours and good health status [54]. Indeed, good health literacy enables individuals to better understand and express their own health needs, as well as a better understanding of the work of institutions. On the other hand, previous research [55] reported how citizens with inadequate health literacy levels may have had difficulty understanding certain measures, especially during a pandemic. Our sample's median health literacy level, according to the validation study of the test we used [54], is definable as problematic. This finding highlights a social and public health problem of health literacy deficiency in our population. Citizens with inadequate levels of health literacy tend to eat less healthily, drink more alcohol, exercise less and smoke [54, 56], as well as they tend to ignore preventive policies [57].

Adequate digital health literacy was positively associated with trust in government's performance. Given that many online services were implemented during the pandemic, like green passes or the possibility of booking swabs and vaccinations, those with poorer digital health literacy may have had difficulty orienting themselves. Then, the infodemic resulted in the spread of misinformation, and those with poor digital health

literacy could have been more easily deceived, believing in fake news [52]. Eventually, this could have led them to trust the government less.

According to our results, low education levels were negatively correlated with trusting the NHS, consistently with earlier research [58]. On the contrary, in some cases [59], it is associated with greater trust in institutions.

In addition, we found that higher education correlated with less trust in government. It is possible that citizens with better education levels had a broader perspective, such that they expected more comprehensive and more far-sighted policies, instead of measures that could have been perceived as far too paternalistic, like green passes or mandatory vaccinations. Better educated citizens are more likely to demand better performances from institutions [60].

Moreover, perceiving one's economic status as poor was correlated with little confidence in government. Restrictive measures for tackling the COVID-19 from spreading surely had serious negative effects on many people and on their work activities. Indeed, many workers were not only at risk to pause their activities, but also to lose their job.

In such a situation, one must wonder how it would be possible for institutions to gain people's trust. Given that citizens already have access to an adequate amount of information, if not even excessive [61] it should not be a matter of information and knowledge, but rather of the foundations of the relationship between institutions and citizens.

Lastly, the collapse of trust in institutions after a pandemic could also last over a generation as it happened before with the Spanish flu [62], so that it will be crucial to identify tailored interventions for each less trusting population. To better address future public health challenges, like new vaccination campaigns (not only for COVID-19), trustful citizens will be strong allies. Adequate levels of trust in government are also essential for facing upcoming challenges like climate and energy crises, which require citizens' complete cooperation to achieve a truly sustainable development [63].

Strengths and limitations

TRUSTMe was the first study in Italy to investigate trust in health and government institutions after the beginning of vaccination campaign against COVID-19. Our results can offer a new public health perspective on this topic, considering that the sample was large and was obtained at a time when all segments of the population were presenting within the vaccine hubs, drawing a comprehensive picture of societal perceptions, including both the vaccine hesitant and the non-hesitant. Then, we adopted validated tests to assess the variables of interest. However, this study has some limitations. The cross-sectional nature of the study allowed us to only explore relationships and to investigate only a fraction of the population. It should be noted that the opportunistic sampling, while practical and efficient, can introduce several biases, *e.g.* the selection bias and the response bias. Although we cannot exclude the presence of such biases, to mitigate these distortions we employed several strategies: using broad inclusion criteria, ensuring a diverse sample within the vaccinated population; providing neutral questionnaire administration as the questionnaire was administered in a non-coercive manner, either before the interview with a doctor or during the observation period after vaccination, to minimize the influence of the vaccination experience on responses; assuring participants anonymity and confidentiality. Finally, the sample, although large and diverse, consisted of citizens from a single local health unit that may not be representative of the entire Italian population and the picture of vaccine hesitant individuals is limited only to those of them who showed up at the vaccine hub, while the more tenacious citizens did not.

Conclusions

TRUSTMe study found higher levels of distrust in the NHS and governmental management of the pandemic in the Italian population, if compared with the past or other countries. COVID-19 vaccine hesitancy, a high level of education, a worse economic situation, low conventional and digital health literacy, as well as the presence of conspiratorial thoughts and distrust in the National Health Service were significantly associated with low trust in governmental management of the pandemic. This last element, along with low levels of education and health literacy, as well as the presence of conspiratorial thoughts and perceiving one's health as poor were associated with distrust in the NHS. Improving levels of trust in institutions is a mission that needs to be accomplished as soon as possible in order to best address new policy and public health challenges, such as future vaccination campaigns and energy-climate crises, possibly minimizing the enacting of paternalistic measures.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research received no external funding.

Authors' contributions

RS, FB, CZ, AS, GG, GLM: conceptualisation; AS, GG, GLM: methodology; AS, GG, GLM: formal analysis; AS, FT: investigation; AS, GG, GLM: data curation; AS, GG: writing-original draft preparation; RS, FB, CZ, FT, GLM: writing-review and editing; AS, GG: visualisation; FB: supervision; AS, GG: project administration. All authors have read and agreed to the published version of the manuscript.

References

[1] Hendriks F, Kienhues D, Bromme R. Trust in science and the science of trust BT – Trust and communication in a digitized world: models and concepts of trust research. In: Blöbaum B, ed, Cham: Springer International Publishing 2016, pp. 143-59. https://doi.org/10.1007/978-3-319-28059-2_8.

[2] Flew T. The global trust deficit disorder: a communications perspective on trust in the time of global pandemics. Journal of Communication 2021;71:163-86. https://doi.org/10.1093/joc/jqab006.

[3] Lewicki RJ, McAllister DJ, Bies RJ. Trust and distrust: new relationships and realities. Academy of Management Review 1998;23:438-58. https://doi.org/10.5465/amr.1998.926620.

[4] Mcknight D, Chervany N. While trust is cool and collected, distrust is fiery and frenzied: a model of distrust concepts. Proceedings of the Americas Conference on Information Systems 2001.

[5] Hall MA, Dugan E, Zheng B, Mishra AK. Trust in physicians and medical institutions: what is it, can it be measured, and does it matter? Milbank Q 2001;79:613-39. https://doi.org/10.1111/1468-0009.00223.

[6] Siegrist M. Trust and risk perception: a critical review of the literature. Risk Analysis 2021;41:480-90. https://doi.org/10.1111/risa.13325.

[7] Armstrong K, Rose A, Peters N, Long JA, McMurphy S, Shea JA. Distrust of the health care system and self-reported health in the United States. J Gen Intern Med 2006;21:292-7. https://doi.org/10.1111/j.1525-1497.2006.00396.x.

[8] Shea JA, Micco E, Dean LT, McMurphy S, Schwartz JS, Armstrong K. Development of a Revised Health Care System Distrust Scale. J Gen Intern Med 2008;23:727-32. https://doi.org/10.1007/s11606-008-0575-3.

[9] Dean LT, Moss SL, McCarthy AM, Armstrong K. Healthcare system distrust, physician trust, and patient discordance with adjuvant breast cancer treatment recommendations. Cancer Epidemiol Biomarkers Prev 2017;26:1745-52. https://doi.org/10.1158/1055-9965.EPI-17-0479.

[10] Greenaway KH, Cruwys T. The source model of group threat: Responding to internal and external threats. Am Psychol 2019;74:218-31. https://doi.org/10.1037/amp0000321.

[11] Sibley CG, Greaves LM, Satherley N, Wilson MS, Overall NC, Lee CHJ, et al. Effects of the COVID-19 pandemic and nationwide lockdown on trust, attitudes toward government, and well-being. Am Psychologist 2020;75:618-30. https://doi.org/10.1037/amp0000662.

[12] Falcone R, Colì E, Felletti S, Sapienza A, Castelfranchi C, Paglieri F. All we need is trust: how the COVID-19 outbreak reconfigured trust in Italian Public Institutions. Front Psychol 2020;11:561747. https://doi.org/10.3389/fpsyg.2020.561747.

[13] Han Q, Zheng B, Cristea M, Agostini M, Bélanger JJ, Gützkow B, Kreienkamp J; PsyCorona Collaboration; Leander NP. Trust in government regarding COVID-19 and its associations with preventive health behaviour and prosocial behaviour during the pandemic: a cross-sectional and longitudinal study. Psychol Med 2023;53:149-59. https://doi.org/10.1017/S0033291721001306.

[14] Larson HJ, Clarke RM, Jarrett C, Eckersberger E, Levine Z, Schulz WS, Paterson P. Measuring trust in vaccination: a systematic review. Hum Vaccin Immunother 2018;14:1599-609. https://doi.org/10.1080/21645515.2018.1459252.

[15] Gualano MR, Lo Moro G, Voglino G, Bert F, Siliquini R. Is the pandemic leading to a crisis of trust? Insights from an Italian nationwide study. Public Health 2022;202:32-34. https://doi.org/10.1016/j.puhe.2021.10.015.

[16] Soares P, Rocha JV, Moniz M, Gama A, Laires PA, Pedro AR, Dias S, Leite A, Nunes C. Factors Associated with COVID-19 Vaccine Hesitancy. Vaccines (Basel) 2021;9:300. https://doi.org/10.3390/vaccines9030300.

[17] Mouslim MC, Johnson RM, Dean LT. Healthcare system distrust and the breast cancer continuum of care. Breast Cancer Res Treat 2020;180:33-44. https://doi.org/10.1007/s10549-020-05538-0.

[18] Graffigna G, Palamenghi L, Savarese M, Castellini G, Barello S. Effects of the COVID-19 emergency and national lockdown on Italian Citizens' Economic Concerns, Government Trust, and Health Engagement: evidence from a Two-Wave Panel Study. Milbank Q 2021;99:369-92. https://doi.org/10.1111/1468-0009.12506.

[19] Campanozzi LL, Tambone V, Ciccozzi M. A Lesson from the Green Pass experience in Italy: a narrative review. Vaccines (Basel) 2022;10:1483. https://doi.org/10.3390/vaccines10091483.

[20] Decreto-Legge 7 gennaio 2022, n. 1, Misure urgenti per fronteggiare l'emergenza COVID-19, in particolare nei luoghi di lavoro, nelle scuole e negli istituti della formazione superiore. Gazzetta Ufficiale 2022;GU n. 4. Available at: https://www.gazzettaufficiale.it/eli/id/2022/01/07/22G00002/sg (Accessed on: 30/10/2022).

[21] De Caro W, Corvo E, Marucci AR, Mitello L, Lancia L, Sansoni J. eHealth Literacy Scale: an nursing analisys and Italian validation. Stud Health Technol Inform 2016;225:949.

[22] Diviani N, Dima AL, Schulz PJ. A Psychometric analysis of the Italian Version of the eHealth Literacy Scale using item response and classical test theory methods. J Med Internet Res 2017;19:E114. https://doi.org/10.2196/jmir.6749.

[23] An L, Bacon E, Hawley S, Yang P, Russell D, Huffman S, Resnicow K. Relationship between coronavirus-related ehealth literacy and COVID-19 knowledge, attitudes, and practices among US adults: Web-Based Survey Study. J Med Internet Res 2021;23:E25042. https://doi.org/10.2196/25042.

[24] Lorini C, Lastrucci V, Mantwill S, Vettori V, Bonaccorsi G. Measuring health literacy in Italy: a validation study of the HLS-EU-Q16 and of the HLS-EU-Q6 in Italian language, conducted in Florence and its surroundings. Ann Ist Super Sanita 2019;55:10-8. https://doi.org/10.4415/ANN_19_01_04.

[25] Cullati S, Bochatay N, Rossier C, Guessous I, Burton-Jeangros C, Courvoisier DS. Does the single-item self-rated health measure the same thing across different wordings? Construct validity study. Qual Life Res 2020;29:2593-604. https://doi.org/10.1007/s11136-020-02533-2.

[26] DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality prediction with a single general self-rated health question. A meta-analysis. J Gen Intern Med 2006;21:267-75. https://doi.org/10.1111/j.1525-1497.2005.00291.x.

[27] Lantian A, Muller D, Nurra C, Douglas KM. Measuring belief in conspiracy theories: validation of a French and English single-item scale. Int Rev Soc Psychol 2016;29:1-14. https://doi.org/10.5334/irsp.8.

[28] Lazarus JV, Ratzan S, Palayew A, Billari FC, Binagwaho A, Kimball S, Larson HJ, Melegaro A, Rabin K, White TM, El-Mohandes A. COVID-SCORE: a global survey to assess public perceptions of government responses to COVID-19 (COVID-SCORE-10). PLoS One 2020;15:E0240011. https://doi.org/10.1371/journal.pone.0240011.

[29] Armstrong K, Putt M, Halbert CH, Grande D, Schwartz JS, Liao K, Marcus N, Demeter MB, Shea J. The influence of health care policies and health care system distrust on willingness to undergo genetic testing. Med Care 2012;50:381-7. https://doi.org/10.1097/MLR.0b013e31824d748b.

[30] Armstrong K, Putt M, Halbert CH, Grande D, Schwartz JS, Liao K, Marcus N, Demeter MB, Shea JA. Prior experiences of racial discrimination and racial differences in health care system distrust. Med Care 2013;51:144-50. https://doi.org/10.1097/MLR.0b013e31827310a1.

[31] Devine D, Gaskell J, Jennings W, Stoker G. Trust and the coronavirus pandemic: what are the consequences of and for trust? An early review of the literature. Political Studies Review 2021;19:274-85. https://doi.org/10.1177/1478929920948684.

[32] Oneal JR, Bryan AL. The rally 'Round the Flag Effect in U.S. Foreign policy crises, 1950-1985. Polit Behav 1995;17:379-401.

[33] Bol D, Giani M, Blais A, Loewen PJ. The effect of COVID-19 lockdowns on political support: some good news for democracy? Eur J Polit Res 2021;60:497-505. https://doi.org/10.1111/1475-6765.12401.

[34] Ministero della Salute. Campagna di vaccinazione anti-COVID-19 2023. Available at: https://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?lingua=italiano&id=6110&area=nuovoCoronavirus&menu=vuoto (Accessed on: 30/10/2022).

[35] Giuffrida A. Italy braced for unrest as Covid pass becomes mandatory for all workers. The Guardian 2021. Available at: https://www.theguardian.com/world/2021/oct/14/italy-braced-for-unrest-as-covid-pass-becomes-mandatory-for-all-workers (Accessed on: 30/10/2022).

[36] Casiday R, Cresswell T, Wilson D, Panter-Brick C. A survey of UK parental attitudes to the MMR vaccine and trust in medical authority. Vaccine 2006;24:177-84. https://doi.org/10.1016/j.vaccine.2005.07.063.

[37] The COVID-19 Task force of the Department of Infectious Diseases and the IT Service Istituto Superiore di Sanità. COVID-19 integrated surveillance data in Italy. Istituto Superiore Di Sanità 2023. Available at: https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard (Accessed on: 30/10/2022).

[38] World Health Organization. Regional Office for Europe. Pandemic fatigue – reinvigorating the public to prevent COVID-19: policy framework for supporting pandemic prevention and management. Copenhagen: World Health Organization. Regional Office for Europe; 2020. Available at: https://iris.who.int/handle/10665/335820 (Accessed on:30/10/2022).

[39] Lazarus J V, Ratzan SC, Palayew A, Gostin LO, Larson HJ. A Global Survey of potential acceptance of a COVID-19 vaccine A Global Survey of potential acceptance of a COVID-19 vaccine. Nat Med 2020;27;225-8. https://doi.org/10.1038/s41591-020-1124-9.

[40] Blair RA, Morse BS, Tsai LL. Public health and public trust: Survey evidence from the Ebola Virus Disease epidemic in Liberia. Soc Sci Med 2017;172:89-97. https://doi.org/10.1016/j.socscimed.2016.11.016.

[41] Siegrist M, Zingg A. The role of public trust during pandemics: implications for crisis communication. Eur Psychol 2014;19:23-32. https://doi.org/10.1027/1016-9040/a000169.

[42] Ejelöv E, Nilsson A. Individual factors influencing acceptability for environmental policies: a review and research agenda. Sustainability (Switzerland) 2020;12. https://doi.org/10.3390/su12062404.

[43] Gilson L. Trust and the development of health care as a social institution. Soc Sci Med 2003;56:1453-68. https://doi.org/10.1016/s0277-9536(02)00142-9.

[44] Whetten K, Leserman J, Whetten R, Ostermann J, Thielman N, Swartz M, Stangl D. Exploring lack of trust in care providers and the government as a barrier to health service use. Am J Public Health 2006;96:716-21. https://doi.org/10.2105/AJPH.2005.063255.

[45] Wang H, Schlesinger M, Wang H, Hsiao WC. The flip-side of social capital: the distinctive influences of trust and mistrust on health in rural China. Soc Sci Med 2009;68:133-42. https://doi.org/10.1016/j.socscimed.2008.09.038.

[46] Oksanen A, Kaakinen M, Latikka R, Savolainen I, Savela N, Koivula A. Regulation and trust: 3-month follow-up study on COVID-19 mortality in 25 European countries. JMIR Public Health Surveill 2020;6:E19218. https://doi.org/10.2196/19218.

[47] Giacomini G, Elhadidy HSMA, Paladini G, Onorati R, Sciurpa E, Gianino MM, Borraccino A. Eating disorders in hospitalized school-aged children and adolescents during the COVID-19 pandemic: a cross-sectional study of discharge records in developmental ages in Italy. Int J Environ Res Public Health 2022;19:12988. https://doi.org/10.3390/ijerph192012988.

[48] CittadinanzAttiva. Liste di attesa post COVID-ritardi e scarsa trasparenza: la nostra indagine civica 2021. Available at: https://www.cittadinanzattiva.it/notizie/14417-liste-di-attesa-post-covid-ritardi-e-scarsa-trasparenza-la-nostra-indagine-civica.html (Accessed on: 30/10/2022).

[49] Connolly JM, Uscinski JE, Klofstad CA, West JP. Communicating to the public in the era of conspiracy theory. Public Integrity 2019;21:469-76. https://doi.org/10.1080/10999922.2019.1603045.

[50] Freeman D, Waite F, Rosebrock L, Petit A, Causier C, East A, Jenner L, Teale AL, Carr L, Mulhall S, Bold E, Lambe S. Coronavirus conspiracy beliefs, mistrust, and compliance with government guidelines in England. Psychol Med 2022;52:251-63. https://doi.org/10.1017/S0033291720001890.

[51] Pummerer L, Böhm R, Lilleholt L, Winter K, Zettler I, Sassenberg K. Conspiracy theories and their societal effects during the COVID-19 pandemic. Soc Psychol Personal Sci 2021;13:49-59. https://doi.org/10.1177/19485506211000217.

[52] Lo Moro G, Scaioli G, Bert F, Zacchero AL, Minutiello E, Siliquini R. Exploring the relationship between COVID-19 vaccine refusal and belief in fake news and conspiracy theories: a Nationwide Cross-Sectional Study in Italy. Int J Environ Res Public Health 2022;19:9350. https://doi.org/10.3390/ijerph19159350.

[53] Marietta M, Barker DC. Conspiratorial thinking and dueling fact perceptions. Conspiracy Theories and the People Who Believe Them 2018:0. https://doi.org/10.1093/oso/9780190844073.003.0014.

[54] Zanobini P, Lorini C, Lastrucci V, Minardi V, Possenti V, Masocco M, Garofalo G, Mereu G, Bonaccorsi G. Health Literacy, socio-economic determinants, and healthy behaviours: results from a large representative sample of Tuscany Region, Italy. Int J Environ Res Public Health 2021;18:12432. https://doi.org/10.3390/ijerph182312432.

[55] Nickel B, Pickles K, Cvejic E, Copp T, Dodd RH, Bonner C, Seale H, Steffens M, Meyerowitz-Katz G, McCaffery K. Predictors of confidence and trust in government and institutions during the COVID-19 response in Australia. Lancet Reg Health West Pac 2022;23:100490. https://doi.org/10.1016/j.lanwpc.2022.

[56] Sayón-Orea C, Santiago S, Bes-Rastrollo M, Martínez-González MA, Pastor MR, Moreno-Aliaga MJ, Tur JA, Garcia A, Martínez JA. Determinants of self-rated health perception in a sample of a physically active population: PLENUFAR VI Study. Int J Environ Res Public Health 2018;15:2104. https://doi.org/10.3390/ijerph15102104.

[57] Lastrucci V, Lorini C, Del Riccio M, Gori E, Chiesi F, Moscadelli A, Zanella B, Boccalini S, Bechini A, Puggelli F, Berti R, Bonanni P, Bonaccorsi G. The role of health literacy in COVID-19 preventive behaviors and infection risk perception: evidence from a population-based sample of essential frontline workers during the lockdown in the Province of Prato (Tuscany, Italy). Int J Environ Res Public Health 2021;18:13386. https://doi.org/10.3390/ijerph182413386.

[58] Gupta C, Bell SP, Schildcrout JS, Fletcher S, Goggins KM, Kripalani S. Predictors of health care system and physician distrust in hospitalized cardiac patients. J Health Commun 2014;19(Suppl 2):44-60. https://doi.org/10.1080/10810730.2014.934936.

[59] Bonds DE, Foley KL, Dugan E, Hall MA, Extrom P. An exploration of patients' trust in physicians in training. J Health Care Poor Underserved 2004;15:294-306. https://doi.org/10.1353/hpu.2004.0018.

[60] Cook TE, Gronke P. The Skeptical American: revisiting the meanings of trust in government and confidence in institutions. J Politics 2005;67:784-803. https://doi.org/10.1111/j.1468-2508.2005.00339.x.

[61] Lee C, Whetten K, Omer S, Pan W, Salmon D. Hurdles to herd immunity: distrust of government and vaccine refusal in the US, 2002-2003. Vaccine 2016;34:3972-8. https://doi.org/10.1016/j.vaccine.2016.06.048.

[62] Aassve A, Alfani G, Gandolfi F, Le Moglie M. Epidemics and trust: the case of the Spanish flu. Health Econ 2021;30:840-57. https://doi.org/10.1002/hec.4218.

[63] United Nations. Transforming our world: the 2030 Agenda for Sustainable Development 2015. Available at: https://sdgs.un.org/2030agenda (Accessed on: 30/10/2022).

Received on March 18, 2024. Accepted on June 19, 2024.

Correspondence: Gianmarco Giacomini, Department of Public Health Sciences and Pediatrics, University of Turin, via Santena 5 bis, 10126, Turin, Italy. E-mail: gianmarco.giacomini@unito.it

How to cite this article: Scacchi A, Lo Moro G, Giacomini G, Torchio F, Zotti Cm, Bert F, Siliquini R. Trust levels toward health care and government: insights from TrustMe, an Italian cross-sectional study. J Prev Med Hyg 2024;65:E125-E133. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3231

HEALTH PROMOTION

Longitudinal trends in physical activity levels and lifetime cardiovascular disease risk: insights from the ATTICA cohort study (2002-2022)

NIKOS DIMITRIADIS[1], THOMAS TSIAMPALIS[1,2,3], GIANNIS ARNAOUTIS[1], KONSTANTINOS D. TAMBALIS[4], EVANGELIA DAMIGOU[1], CHRISTINA CHRYSOHOOU[5], FOTIOS BARKAS[6], COSTAS TSIOUFIS[5], CHRISTOS PITSAVOS[5], EVANGELOS LIBEROPOULOS[7], PETROS P. SFIKAKIS[7], DEMOSTHENES PANAGIOTAKOS[1,3]

[1] Department of Nutrition and Dietetics, School of Health Sciences and Education, Harokopio University, Athens, Greece; [2] Department of Nutrition and Dietetics, School of Physical Education, Sports and Dietetics, University of Thessaly, Trikala, Greece; [3] Faculty of Health, University of Canberra, Canberra, Australia; [4] School of Physical Education and Sports Science, National and Kapodistrian University of Athens, Athens, Greece; [5] First Cardiology Clinic, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece; [6] Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece; [7] First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

Keywords

Physical activity trajectories • Lifetime CVD risk • ATTICA study • Socio-economic determinants

Summary

Objective. *To evaluate trends in physical activity levels and their associations with demographic characteristics, health status, and lifetime cardiovascular disease (CVD) risk.*

Methods. *A longitudinal analysis was conducted using data from 987 males and 1,001 females (45 ± 12 years old) participating in the ATTICA cohort study. Physical activity levels were assessed at baseline (2001-2002) and subsequent follow-ups (2006, 2012, and 2022). Four physical activity trajectories according to participants' physical activity tracking were defined, i.e., consistently active/inactive and changed from active/inactive. Twenty-year incidence of hypertension, hypercholesterolemia, and diabetes were evaluated in relation to physical activity trajectories; the life-table method was utilized to forecast the lifetime CVD risk (death without CVD was regarded as a competing event).*

Results. *in total, 47% of the participants were categorized as being consistently inactive, whereas only 9% of males and 15% of females sustained physical activity levels throughout the 20-year follow-up period ($p < 0.001$). Participants being consistently inactive were from lower socioeconomic backgrounds ($p = 0.002$). Transitioning to being physically active was associated with higher education level and being married ($p < 0.001$). Consistently active individuals had up to 35% reduced lifetime CVD risk, and lower 20-year incidence of hypertension, and hypercholesterolemia ($p < 0.01$); no association was observed regarding diabetes incidence.*

Conclusions. *Promoting and maintaining regular physical activity throughout lifespan is crucial for reducing lifetime CVD risk and related risk factors. Tailored interventions addressing demographic and socioeconomic factors may help enhance cardiovascular health outcomes.*

Introduction

Accumulating level of evidence during the past decades strongly suggest that even moderate physical activity levels are significant contributors for wellness, and longevity. The World Health Organization (WHO) has developed the "2018-2030 Action Plan for More Active People For A Healthier World", according to which physical activity is being recognized as a crucial lifestyle parameter across all ages, that can and should be integrated into people's everyday lives [1, 2]. This plan is also supported by several Organizations and medical societies suggesting that people of all ages should be engaged in regular physical activities to reduce morbidities and all-cause mortality [3-5].

Despite the plethora of health benefits presented in the scientific literature and supported by public health campaigns, a gradual shift towards a more sedentary lifestyle has been systematically observed over the past few years [6-8]. A combination of environmental, social, psychological, and physical factors can contribute to the adoption of a sedentary lifestyle. The current technological advancements and societal norms seem fostering a culture of prolonged sitting and reduced engagement in physical activities. For example, because of urbanization, limited access to safe outdoor spaces, sports facilities, or recreational areas is evident in many cities around the world, a fact that discourage engagement in physical activities [6]. Busy daily schedules and demanding workflow also make challenging for many people to prioritize physical activity in their daily life. Moreover, in some cultures, there may be less emphasis placed on physical activity, leading to a more sedentary lifestyle [7, 8].

However, the majority of evidence comes from ecological studies, and few observational studies have ventured into the assessment of long-term physical activity trajectories and their intersection with people's characteristics, leaving a void in our understanding of the dynamic interplay between lifestyle behaviors and

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3243

health over time. Therefore, it could be, at least partially explained, why prevention strategies, programs and population-based interventions have not been as efficient as expected so far.

Considering the gap in our understanding of the determinants of maintaining a physically active level throughout lifespan and its effect on health, the aim of the present study was to investigate the association of physical activity levels over a 20-year period of apparently healthy adults with various socio-demographic and clinical characteristics, as well as with cardiometabolic outcomes (*i.e.*, hypertension, hypercholesterolemia, and type II diabetes mellitus) and lifetime CVD risk. We hypothesize that individuals with consistently active lifestyles will exhibit lower incidence rates of hypertension, hypercholesterolemia, and diabetes mellitus, leading to a reduced lifetime risk of CVD compared to those with consistently sedentary behaviors.

Material and methods

Study design

The ATTICA study is a prospective epidemiological cohort study that aims to record the distribution and patterns of several socio-demographic, lifestyle, clinical, biochemical, and psychological factors related to CVD, and to investigate the relationships between these factors and long-term incidence of CVD.

Setting and participants

The study was carried out in the Attica region in Greece, with 78% coming from urban municipalities, including the capital city, Athens. The baseline participant sample consisted of 3,042 individuals (out of 4,056 who were initially invited, 75% participation rate), all free of CVD, cancer, and other chronic inflammatory diseases, as established by the physicians of the study during the baseline examination. The sampling procedure was random and stratified based on sex, age group, and region, in accordance with the 2001 census.

Detailed information about the objectives, design, sampling procedure, and methodology of the study can be found in previously published papers [9-11].

Bioethics

The ATTICA study adheres to the ethical guidelines of the Declaration of Helsinki and has been approved by the Ethics Committee of the First Cardiology Department of the National and Kapodistrian University of Athens (#017/01.05.2001), and the Ethics Committee of the Harokopio University (#38/29.03.2022). All participants were informed about the objectives and procedures of the study, and they provided their written consent to participate.

Follow-up examinations

The study performed 3 follow-up examinations, at 5-years (in 2006), 10-years (in 2012) and 20-years (in 2022), following the baseline assessment (in 2001-2002). Development of CVD or any other disease (including fatal events), as well as detailed clinical status, lifestyle characteristics (*i.e.*, dietary habits, physical activity level and smoking status), and psychological status, were repeatedly assessed in all follow-up periods following the same methodology [10, 11]. Specifically, in 2012, 2,583 participants were allocated and agreed to re-examined at the 10-year follow-up (85% participation rate), and in 2022, 2,169 participants were found and agreed to participate at the 20-year follow-up (participation rate of 71%). Among those who were lost to follow-up (n = 873 individuals), 771 could not be reached due to changes in their contact information or errors in their addresses or phone numbers, while 102 declined to participate in the screening. For deceased participants, information was gathered from relatives and death certificates.

When comparing the age and sex distribution of this sub-sample with the baseline group, no significant differences were found (p-values > 0.80).

Measurements

Physical activity status evaluation

The translated version of the validated into Greek population by Papathanasiou et al., International Physical Activity Questionnaire (IPAQ) of weekly energy expenditure was used [12]. The frequency (times per week), duration (in minutes) and intensity of leisure time physical activity (LTPA) during a usual week was recorded. Intensity was graded in qualitative terms, based on the metabolic equivalent of tasks (METmin/week), as: light (expended calories < 4 Kcal/min, *i.e.*, walking slowly, stationary cycling, light stretching *etc.*), moderate (expended calories 4-7 Kcal/min, *i.e.*, briskly walking, outdoor cycling, swimming with moderate effort *etc.*) and high (expended calories > 7 Kcal/min, *i.e.*, briskly walking uphill, long-distance running, cycling fast or racing, swimming fast crawl *etc.*).

For the present analysis, participants were classified as inactive (sedentary or light physical activity), and active (moderate or high physical activity) according to the METmin/week [13].

Four trajectories of physical activity were formed regarding the longitudinal tracking, 2002-2012, in the physical activity levels of the participants, *i.e.*, consistently inactive, became inactive from physically active, became active from physically inactive, consistently active.

Socio-demographic and behavioural characteristics

Demographic characteristics included, age (in years), sex (male, female), family status (single, married or cohabitated, divorced, widowed), financial status (average annual income during the past three years), occupational status (employed, unemployed, retired, housekeeping) and education level. Specifically, the educational level of the participants (as a proxy of social

status) was measured in years attending formal school, college and/or university.

A validated and reliable semi-quantitative food frequency questionnaire was utilized for dietary assessment, with habitual food intake expressed as servings per day or week [14]. Adherence to a Mediterranean-type diet was evaluated using the MedDietScore, an a-priori diet index comprising of 11 food group items traditionally consumed the region and has been found valid and reliable in measuring adherence to the Mediterranean dietary pattern [15]. The MedDietScore ranges from 0 to 55 points. Higher values of the MedDietScore signify enhanced adherence to the traditional Mediterranean diet. The median value of the MedDietScore was used to classify participants into a high (*i.e.*, MedDietScore > 27) and a low (*i.e.*, MedDietScore ≤ 27) adherence to the Mediterranean-type diet [15].

Clinical assessment

At baseline and at each follow-up examination, blood samples were collected after 12 hours of fasting and avoiding of alcohol. The biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories. According to the European Atherosclerosis Society and the European Society of Cardiology guidelines, participants with total serum cholesterol levels greater than 200 mg/dL or those taking lipid-lowering agents were classified as having hypercholesterolemia; participants with blood sugar > 125 mg/dL or the use of antidiabetic medication were classified as having diabetes mellitus. Arterial blood pressure was obtained with subjects in sitting position and calmed for 30 minutes. Participants whose average systolic/diastolic blood pressure levels were greater or equal to 140/90 mmHg or taking antihypertensive medication were classified as having hypertension. Body mass index (BMI) was calculated as weight (in kg) divided by standing height (in m squared). Obesity was defined as BMI > 29.9 kg/m^2. Details about the methods and definitions used may be found in previous publication of the study [9].

Follow-up assessment

Development of hypertension, hypercholesterolemia, diabetes melitus (type 2), as well as fatal or non-fatal CVD events (*i.e.*, coronary heart disease, stroke, or any other type of CVD) was assessed at all follow-up examinations, based on International Classification of Diseases (ICD)-10 version [16]. For individuals who suffered multiple events (*e.g.* individuals who might had first suffered from stroke and then had coronary heart disease) the first outcome was considered as the endpoint, and the consequent event was recorder as well for further testing of potential competing risks.

Statistical analysis

Continuous variables were expressed as mean values accompanied by their standard deviations. Categorical variables were presented as relative frequencies (percentages). The associations among categorical variables were assessed using Pearson's chi-squared test. Comparisons of mean values for continuous variables were conducted employing independent samples t-tests or Analysis of Variance (ANOVA), with Levene's test utilized to ensure equality of variances. In instances where variances were found to be unequal (Levene's test p-value < 0.05), the Welch's t-test was employed. Adjustment for multiple comparisons was performed using the Bonferroni correction method. The normality of continuous variables (*i.e.*, cholesterol and triglycerides levels) was assessed through P-P plots. Incidence rates were compared using 95% confidence intervals (CI) derived from the Normal approximation to the Poisson distribution, with p-values obtained from the 4-sample test for equality of proportions with continuity correction. The lifetime risk estimates for CVD were computed using age and sex-adjusted life-table techniques, considering the competing risk of mortality and projecting outcomes until the age of 85 years for the last participant in the cohort. Modified life-table techniques were utilized to account for the competing risk of mortality. To compare age and sex-adjusted lifetime risks across different physical activity trajectories, a two-tailed Z-test was employed. All reported p-values were based on two-sided hypotheses. Statistical analyses were conducted using STATA version 17 (STATA Corp, College Station, Texas, USA).

Results

Participants characteristics according to trajectories of physical activity levels

Thirty nine percent (39%) of males and 33% of females were classified as physically active at baseline examination (in 2002), 31% males and 26% females at 5-year follow-up (in 2005), 26% males and 19% females at 10-year follow-up (in 2012), and 30% males and 32% females at 20-year follow-up (in 2022). A progressive decrease in physical activity levels was observed (p < 0.001). In Figure 1 the distribution of physical activity levels at each time-point of the follow-up is illustrated, by sex and age group of the participants, while in Figure 2, the physical activity trajectories of participants are displayed, categorized by age, sex, and socioeconomic status. Specifically, this heatmap illustrates the predominant trajectory within each subgroup, determined by the highest probability of participant association. During the 20-year observation period, in total, 47% of the participants were classified as always inactive, 23% as became inactive from physically active, 18% as became active and, only 9% of males and 15% of females sustained physical activity levels (p < 0.001) (Tab. I). Moreover, participants who stopped being physically active during the follow-up period were older than those who were consistently active (43 ± 12 years *vs* 40 ± 12 years, p = 0.002), and participants who started physical activity were the

Fig. 1. Distribution of physical activity status at each time-point, by sex and age group of the participants; ATTICA study (2002-2022).

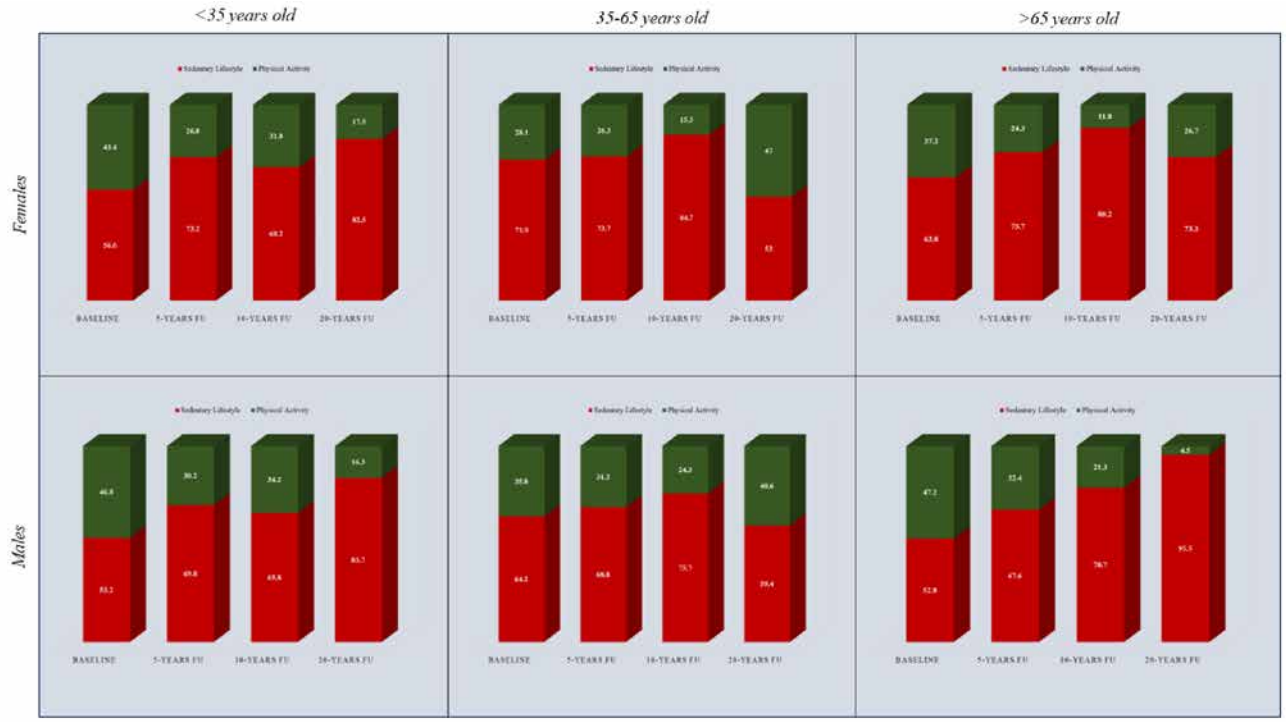
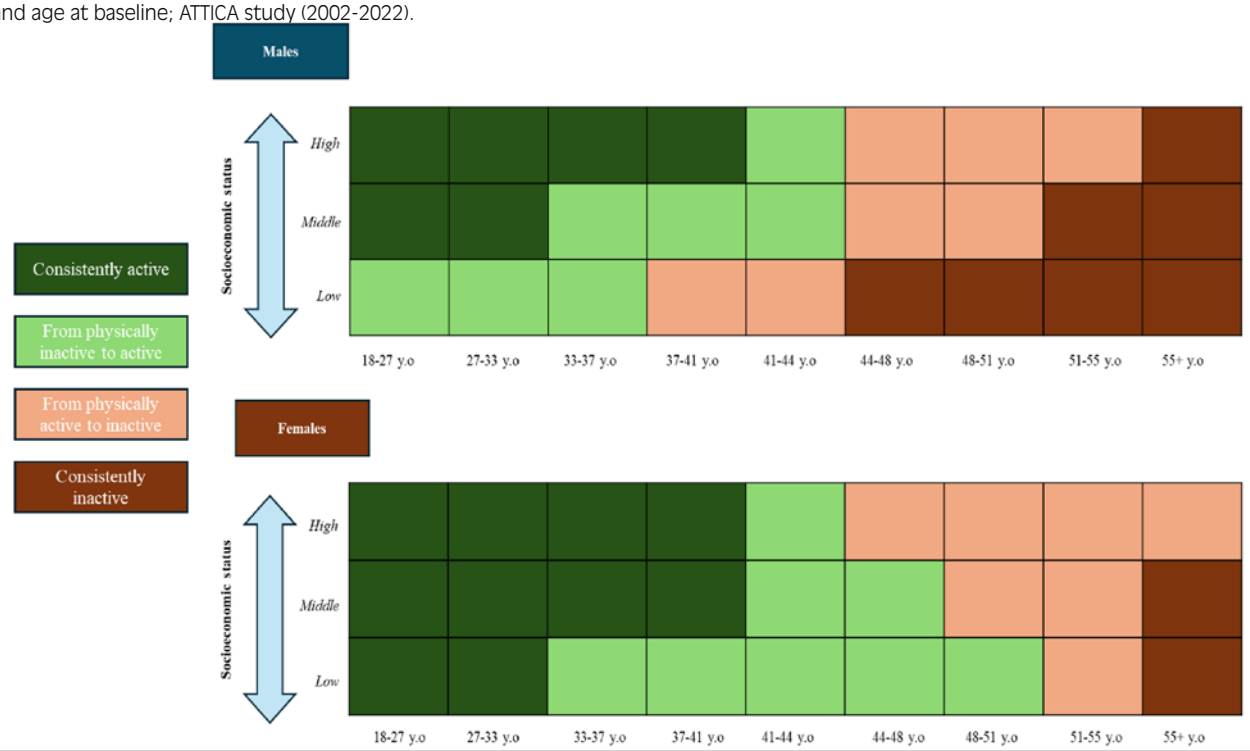


Fig. 2. Heatmap presenting the time trajectories of physical activity status in males and females, stratified by their socioeconomic status and age at baseline; ATTICA study (2002-2022).



youngest among all other trajectories (35 ± 13 years, $p < 0.01$).

The social and demographic characteristics of participants categorized by their physical activity trajectory during the follow-up period are presented in Table I. Participants identified as consistently physically inactive where from lower socioeconomic background (especially males) and had, particularly, lower education status. On the contrary, participants who transitioned to being physically active exhibited higher education level ($p < 0.001$ for both sexes) and were more likely of being married ($p < 0.05$ for both sexes).

Tab. I. Baseline sociodemographic characteristics of the ATTICA study participants, stratified according to their 20-year physical activity trajectory and sex; ATTICA study (2002-2022).

	Consistently inactive	From physically active to inactive	From physically inactive to active	Consistently active	p-value
Females (n = 1001)	472 (47%)	204 (20%)	181 (18%)	144 (15%)	
Age [in years; Mean (SD)]	38.5 (15.3)	31.1 (13.1)	41.9 (10.7)	42.7 (12.7)	< 0.001
Marrital status, %					
Never married	39.7	66.7	8.9	25.0	< 0.001
Married	52.1	33.3	82.1	68.2	
Divorced	3.4	0.0	7.1	6.8	
Widowed	4.8	0.0	1.8	0.0	
Years of education [Mean (SD)]	12.3 (3.2)	13.5 (2.6)	13.9 (4.1)	12.6 (3.7)	0.011
Socioeconomic status, %					
Low	12.9	2.1	6.1	16.7	0.002
Middle	68.8	66.0	39.4	53.3	
High	18.3	31.9	54.5	30.0	
Males (n = 987)	466 (47%)	245 (25%)	190 (19%)	86 (9%)	
Age [in years; Mean (SD)]	41.5 (14.9)	39.3 (15.1)	42.6 (8.2)	44 (11)	0.308
Marrital status, %					
Never married	30.1	41.8	16.4	20.0	0.015
Married	68.5	54.4	82.0	77.1	
Divorced	0.0	3.8	1.6	2.9	
Widowed	1.4	0.0	0.0	0.0	
Years of education [Mean (SD)]	11.9 (3.9)	12.4 (3.8)	14.2 (2.1)	13.6 (2.8)	< 0.001
Socioeconomic status, %					
Low	15.4	7.7	0.0	4.0	0.012
Middle	53.8	55.8	42.9	52.0	
High	30.8	36.5	57.1	44.0	

p-value was based on the Pearson chi- square test (categorical characteristics) and on the One-way ANOVA (continuous characteristics). Participants' physical activity level was assessed through the short-form International Physical Activity Questionnaire. DS: standard deviation.

Tab. II. Baseline clinical characteristics of the ATTICA study participants, stratified according to their 20-year physical activity trajectory and sex; ATTICA study (2002-2022).

	Consistently inactive	From physically active to inactive	From physically inactive to active	Consistently active	p-value
Females (N = 1001)	472 (47%)	204 (20%)	181 (18%)	144 (15%)	
Total serum cholesterol [Mean (SD); mg/dl]	182 (42)	175 (42)	188 (44)	181 (38)	0.424
Triglycerides [Mean (SD); mg/dl]	96 (68)	79 (50)	87 (42)	86 (51)	0.305
HDL-cholesterol [Mean (SD); mg/dl]	52 (12)	56 (12)	55 (19)	52 (13)	0.275
LDL-cholesterol [Mean (SD); mg/dl]	109 (32)	104 (41)	119 (43)	111 (33)	0.189
Hypertension (% Yes)	22.7	8.3	19.2	14.3	0.095
Hypercholesterolaemia (% Yes)	37.5	22.2	28.1	29.5	0.328
Type II diabetes (% Yes)	7.1	1.5	6.8	2.3	0.125
Obesity (% yes)	17	13	6	1	0.032
Males (N = 987)	466 (47%)	245 (25%)	190 (19%)	86 (9%)	
Total serum cholesterol [Mean (SD); mg/dl]	193 (42)	187 (44)	204 (46)	203 (48)	0.097
Triglycerides [Mean (SD); mg/dl]	128 (82)	111 (58)	140 (87)	122 (66)	0.194
HDL-cholesterol [Mean (SD); mg/dl]	44 (11)	45 (11)	43 (10)	46 (10)	0.446
LDL-cholesterol [Mean (SD); mg/dl]	122 (38)	120 (38)	130 (36)	138 (49)	0.149
Hypertension (% Yes)	43.3	29.6	33.3	34.8	0.608
Hypercholesterolaemia (% Yes)	54.3	41.8	42.0	48.3	0.507
Type II diabetes (% Yes)	9.1	6.3	3.3	5.7	0.489
Obesity (% Yes)	21	22	12	13	0.278

p-value was based on the Pearson chi- square test (categorical characteristics) and on the One-way ANOVA (continuous characteristics) Participants' physical activity level was assessed through the short-form International Physical Activity Questionnaire. HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; SD: Standard Deviation.

As shown in Table II, no significant differences were observed among the four physical activity level trajectories and the baseline levels of various biochemical markers and clinical status of the participants. However, it is noteworthy that both males and females who remained physically inactive throughout the entire period had a higher prevalence

Tab. III. Incidence rate of hypertension, hypercholesterolaemia and type II diabetes mellitus (95% Confidence Interval) of the ATTICA study participants, stratified according to their physical activity trajectory; ATTICA study (2002-2022).

Incidence rate (95% CI)	Consistently inactive	From physically active to inactive	From physically inactive to active	Consistently active	p-value
Females					
Incidence rate of (per 1,000 Person-years):					
Hypertension	19.7 (9.7, 29.7)	19.3 (8.8, 29.7)	15.3 (9.7, 20.8)	5.7 (1.1, 10.3)	0.015
Hypercholesterolaemia	35.9 (21.3, 50.6)	35.6 (19.2, 52.1)	26.7 (16.0, 37.3)	24.0 (17.2, 30.9)	0.147
Type II diabetes	16.0 (10.6, 21.5)	14.4 (6.9, 22.0)	14.1 (5.4, 22.8)	10.1 (3.1, 17.1)	0.622
Males					
Incidence rate of (per 1,000 Person-years):					
Hypertension	35.1 (13.3, 56.8)	25.4 (17.2, 33.6)	16.7 (7.2, 26.1)	11.0 (4.2, 17.9)	0.009
Hypercholesterolaemia	54.3 (33.1, 75.7)	41.9 (30.6, 53.2)	29.1 (18.5, 43.7)	28.6 (8.8, 48.4)	0.037
Type II diabetes	26.8 (16.1, 37.5)	25.8 (16.1, 35.6)	20.9 (14.4, 27.4)	17.0 (5.9, 28.1)	0.449

95% Confidence Interval was based on the Normal approximation to the Poisson distribution, as described by Rosner, Fundamentals of Biostatistics (5th Ed); p-value was based on the 4-sample test for equality of proportions with continuity correction. IR: Incidence Rate; CI: Confidence Interval.

Tab. IV. Lifetime risk estimates (and 95%CI) for fatal and nonfatal CVD, at selected index age, in males and females, according to their 20-year physical activity trajectory; ATTICA study (2002-2022).

	Females			Males		
	40 yrs	50 yrs	60 yrs	40 yrs	50 yrs	60 yrs
Consistently inactive	51 (45, 57)	62 (59, 65)	73 (38, 81)	63 (44, 82)	76 (73, 78)	68 (62, 74)
From physically active to inactive	49 (41, 57)	59 (54, 64)	61 (23, 72)	60 (55, 64)	74 (69, 79)	62 (55, 68)
From physically inactive to active	48 (46, 51)	58 (54, 63)	60 (56, 63)	58 (45, 71)	72 (68, 76)	62 (52, 71)
Consistently active	45 (43, 47)	57 (53, 61)	54 (18, 90)	57 (51, 62)	72 (68, 75)	52 (51, 59)
p-value	0.046	0.016	0.029	0.077	0.270	0.007

Lifetime risk estimates represent the proportion of ATTICA cohort participants projected to encounter a fatal or nonfatal cardiovascular disease (CVD) event from the index age until the end of follow-up, assuming the final participant in the cohort was to reach the age of 85 years. The lifetime incidence rate, was computed utilizing adjusted life-table techniques as recommended by Kaplan and Meier. Modified life-table techniques were employed to consider the competing risk of mortality. Lifetime risks across different physical activity trajectories were compared using a two-tailed Z-test. 95% CI: 95% confidence interval; CVD: Cardiovascular disease.

of hypertension, hypercholesterolemia, and type II diabetes mellitus, and females who were consistently physically active had the lowest prevalence of obesity compared to the other physical activity groups ($p < 0.001$).

20-year incidence of cardiometabolic disorders in relation to trajectories of physical activity levels

The 20-year incidence rates of hypertension, hypercholesterolemia, and type II diabetes in both males and females, categorized by their physical activity trajectory, are presented in Table III. Individuals who maintained a sedentary lifestyle throughout the studied period demonstrated a significantly higher incidence of hypertension, regardless of sex ($p < 0.05$ for both sexes). Moreover, females who were consistently physically active showed a significantly lower incidence of hypercholesterolemia [Incidence Rate (95% Confidence Interval): 11 (4.2, 17.9) cases per 1,000 person-years], whereas those adhering to a sedentary lifestyle had higher incidence rates [Incidence Rate (95% Confidence Interval): 54.3 (33.1, 75.7) cases per 1,000 person-years]. Turning from physically inactive to active during the studied period also conferred a significant cardiometabolic protection, through lowering the incidence of hypertension and hypercholesterolemia ($p < 0.001$), as compared to those who were consistently inactive or turned from active to inactive (Tab. III).

Lifetime CVD risk in relation to trajectories of physical activity levels

The lifetime risk of CVD among males and females at three distinct index ages (40, 50, and 60 years old), categorized by their trajectories of physical activity levels is presented in Table IV. Among women aged 40 years old, those who maintained a sedentary lifestyle throughout the studied period had higher lifetime risk of CVD compared to their counterparts who consistently engaged in regular physical activity [51% (95%CI 45%, 57%) among consistently inactive females versus 45% (95%CI 43%, 57%) among consistently active females]. This disparity persisted at ages 50 and 60. Similarly, males who adhered to regular physical activity throughout the entire study duration exhibited

a significantly reduced lifetime CVD risk compared to those adopting a sedentary lifestyle, particularly at the age of 60. This protective association of physical activity was apparent across all index ages (40 and 50 years old) as well.

Discussion

The present population-based study examined the trajectories of physical activity levels over a long-term period in relation to several demographic and clinical characteristics and health outcomes, of apparently healthy adults. A progressive decline in physical activity levels among both sexes was observed, as almost half of the cohort remained consistently inactive throughout the study period. Distinct patterns of physical activity trajectories emerged from our analysis, shedding light on the diverse pathways' individuals traverse in their physical activity behaviours. Profile analysis of those that were consistently inactive revealed that they had lower education and socio-economic status, but no other differences regarding their clinical status were observed. Furthermore, our study added to the compelling evidence of the impact of physical activity on cardiometabolic health across the lifespan. Participants who maintained a sedentary lifestyle throughout the study period had elevated lifetime CVD risk as compared to their consistently active counterparts.

Of the most important findings of our study is that almost half of the participants remained physically inactive through the entire 20-year studied period. This is in line with a body of previous research documenting in which a progressive decline in population physical activity levels over time has been reported. According to the World Health Organization, the latest global estimates show that 1.4 billion adults (*i.e.*, 27.5% of the world's adult population) do not meet the recommended level of physical activity to improve and protect their health [17]. Several longitudinal studies conducted in different regions around the world, have consistently reported similar to our findings, trends in reduced physical activity levels, in both adolescents and adults, illustrating the challenge of maintaining active lifestyles as individuals age [18, 19]. Specifically, the global age-standardized prevalence of insufficient physical activity was 23·4%, in men and 31·7%, in women [18]. The highest levels observed were in women in Latin America and the Caribbean (*i.e.*, 43·7%), south Asia (43·0%), and high-income Western countries (42·3%), whereas the lowest levels were in men from Oceania (12·3%), east and southeast Asia (17·6%), and sub-Saharan Africa (17·9%). Regarding younger people, globally, 81·0% of adolescents aged 11-17 years were insufficiently physically active (77·6% of boys and 84·7% of girls) [19].

Socio-demographic determinants in relation to physical activity trajectories

Our findings of socioeconomic disparities in physical activity trajectories resonates with a substantial body of existing literature documenting inequalities in activity levels among different socio-demographic groups [18-20]. In a global pooled analysis by Guthold et al., prevalence of inadequate physical activity was more than twice as high in high-income countries (36·8%) as in low-income countries (16·2%) [18]. Moreover, insufficient activity has increased in high-income countries during 2001-1016 (*i.e.*, 31·6 *vs* 36·8%). Concerning adolescents, the regions with the lowest prevalence were high-income western countries for boys (72·1%), and south Asia for girls (77·5%).

Numerous studies have highlighted the association between lower socioeconomic status and reduced engagement in physical activity, pointing to structural barriers, such as limited access to recreational facilities and resources as contributing factors [18-24]. In a large-scale epidemiological study in US, Wallace et al., examined how the rest-activity rhythms may mark development, aging, and physical and mental health in 12,526 participants from 3 to over 80 years old from the large-scale National Health and Nutrition Examination Survey (NHANES). They identified multiple trajectories of physical activity across adulthood, with factors such as age, sex, and socioeconomic status being as the most influential of these trajectories [21]. Stalling et al., analyzed data from 1507 participants (52.5% female), between 65-75 years old, residing in Germany, about physical activity participation (total, moderate and vigorous) and mean metabolic equivalents and found significant negative associations between physical activity and socioeconomic status [23]. In a review of Elhakeem et al. [24], the hypothesis that a lower childhood socioeconomic status is associated with less leisure-time physical activity during adulthood was strongly supported. All reviewed studies found that individuals with lower socioeconomic status were less likely to engage in leisure-time physical activity compared to those with higher socioeconomic status, even after accounting for individual-level factors. All these findings underscore the importance of considering the demographic dimension in interventions aimed at promoting active lifestyles and highlight the need for tailored approaches to address the diverse needs and preferences of various population groups.

Health-related outcomes in relation to physical activity trajectories

The link between physical activity and reduced CVD risk has been well-established in the literature through several studies [25-30]. In a previous analysis of our study it was revealed that participants being consistently physically active had lower CVD incidence during the 20-year follow-up period, as compared to those remained physically inactive or turned active/inactive [11]. A recent harmonised meta-analysis by Paluch et al., highlighted that adding even 1000 steps a day were associated with a 10% reduction in the risk of CVD events [29]. The present analysis also revealed that adopting a physically active lifestyle during lifespan was associated with substantially lower burden

of cardiometabolic disorders, *i.e.*, the development of hypertension, and hypercholesterolemia, as well as lower lifetime CVD risk, as compared to those remained or became physically inactive. These findings underscore the importance of promoting physical activity not only across all segments of the population, but also at any age, to effectively mitigate the lifetime burden of CVDs.

Potential mechanisms supporting the present findings

The observed associations between physical activity trajectories and CVD outcomes may be intermediated by various mechanistic pathways, as supported by extensive literature. Regular physical activity exerts beneficial effects on cardiovascular health through multiple physiological mechanisms, including improvements in lipid and triglycerides metabolism, blood pressure regulation, insulin sensitivity, and endothelial function. Additionally, physical activity enhances endothelial function by promoting nitric oxide production, leading to vasodilation and improved blood flow, thereby reducing hypertension, and enhancing vascular health [31-33]. Moreover, a plethora of research underscores the pivotal role of physical activity in glucose metabolism and insulin sensitivity, shedding light on its potential mechanisms [34]. Exercise stimulates glucose uptake by skeletal muscles, a process mediated by the translocation of glucose transporter proteins to the cell membrane, thereby lowering blood glucose levels and reducing the risk of insulin resistance and type II diabetes. A meta-analysis by Amanat et al., concluded that exercise interventions significantly improved glycaemic control and insulin sensitivity in individuals with type II diabetes [35]. However, in our study, none of the studied trajectories was associated with diabetes incidence, although, a clear trend towards engagement in physical activities was observed. This can be attributed in the relatively small number of people who developed diabetes during the studied period, lack of adequate confound, and not the absence of a true effect.

Furthermore, regular physical activity plays a crucial role in weight management and adiposity reduction, which are key factors in preventing metabolic disorders and reducing CVD risk. Exercise promotes energy expenditure, increases lean muscle mass, and decreases fat mass, thereby contributing to a healthy body composition and metabolic profile. Numerous studies have demonstrated the efficacy of exercise interventions in reducing visceral adiposity and improving cardio metabolic health outcomes [36, 37].

Limitations

The present study has several strengths, as it is one of the few in the literature that evaluated long-term trajectories of physical activity, their determinants, and relationships with cardiometabolic health, but also has several limitations that should be considered when interpreting the findings. The reliance on self-reported physical activity data through the International Physical Activity Questionnaire used may introduce recall bias and inaccuracies in assessing participants' true activity levels as compared to objective measures, like accelerometers; however, this tool has been found reliable and repeatable in previous studies and has been extensively used in epidemiologic assessment. Despite the efforts made, the dropout rate in follow-up examinations is significant (between 71 to 85%), but this is considered acceptable in epidemiological studies of long follow-up period, like the ATTICA study. Furthermore, the study took place only in Attica region, and therefore the homogeneity in terms of geographical location and ethnicity limits the generalizability of the findings to the broader Greek population, as well as other populations. However, it should be noted that in Attica region leaves 3,5 million people, *i.e.*, approximately 35% of the Greek population, in more than 50 urban and rural municipalities (including the capital city of Athens). Lastly, the inclusion of only baseline and follow-up assessments may not capture short-term fluctuations or intermittent changes in physical activity patterns and their impact on CVD outcomes.

Future research directions

Futur research in physical activity strategies could explore several key areas to further enhance our understanding and effectiveness in promoting physical activity. Investigate personalized approaches to physical activity promotion based on individual characteristics such as age, gender, fitness level, health status, and preferences. This could involve leveraging technology, such as wearable devices and mobile apps, to tailor interventions to individuals' needs and preferences. Moreover, future research could focus on the effectiveness of environmental and policy interventions in promoting physical activity at the community and population levels. This could include evaluating the impact of urban design, transportation policies, workplace wellness programs, and school-based interventions on physical activity levels. Sustainability in measures taken is a key for achieving good health. Future research should investigate strategies for promoting long-term maintenance of physical activity behaviors. Research could focus on identifying factors that contribute to sustained behavior change and developing interventions to support ongoing adherence to physical activity recommendations. An important issue is also to prioritize research on physical activity interventions that address health disparities and promote health equity. This could involve examining the effectiveness of interventions targeted towards underserved populations, including racial and ethnic minorities, low-income individuals, and people living in rural areas.

Conclusions

The findings of this comprehensive longitudinal study underscore the critical role of physical activity in

shaping CVD outcomes over the lifespan. The present findings highlight the importance of promoting and sustaining regular physical activity throughout the lifespan, as well as for shaping targeted interventions, tailored to demographic and socioeconomic characteristics of the referent population. Tailored physical activity interventions addressing demographic and socioeconomic factors may help reducing the burden of CVD-related outcomes. These interventions should consider the accessibility of physical activity resources. This includes ensuring that affordable facilities are available in neighborhoods, as well as providing transportation options for those who may not have easy access. Addressing socioeconomic factors involves providing education about the importance of physical activity for preventing CVD and managing risk factors. This education should be accessible and understandable to people from diverse socioeconomic backgrounds.

Acknowledgments

The authors would like to thank the ATTICA study group of investigators: Evrydiki Kravvariti, Elpiniki Vlachopoulou, Christina Vafia, Dimitris Dalmyras, Konstantina Kyrili, Petros Spyridonas Adamidis, Georgia Anastasiou, Amalia Despoina Koutsogianni, Asimina Loukina, Giorgos Metzantonakis, Evangelinos Michelis, Manolis Kambaxis, Kyriakos Dimitriadis, Ioannis Andrikou, Amalia Sofianidi, Natalia Sinou, Aikaterini Skandali, Christina Sousouni, for their assistance on the 20-year follow-up, as well as Ekavi N. Georgousopoulou, Natassa Katinioti, Labros Papadimitriou, Konstantina Masoura, Spiros Vellas, Yannis Lentzas, Manolis Kambaxis, Konstantina Palliou, Vassiliki Metaxa, Agathi Ntzouvani, Dimitris Mpougatsas, Nikolaos Skourlis, Christina Papanikolaou, Georgia-Maria Kouli, Aimilia Christou, Adella Zana, Maria Ntertimani, Aikaterini Kalogeropoulou, Evangelia Pitaraki, Alexandros Laskaris, Mihail Hatzigeorgiou and Athanasios Grekas, Efi Tsetsekou, Carmen Vassiliadou, George Dedoussis, Marina Toutouza-Giotsa, Konstantina Tselika and Sia Poulopoulou and Maria Toutouza for their assistance in the initial and follow-up evaluations.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

The ATTICA Study received funding from the Hellenic Cardiology Society (2002), and the Hellenic Atherosclerosis Society (2007). E.D. has received scholarship from the Hellenic Atherosclerosis Society (2022-2025).

Authors' contributions

ND, DP, TT: conceptualisation and writing the manuscript; TT: data analysis; ED, FB: investigation; DP, TT, YA, CT, ED: critical review of the manuscript; DP, CC, CP, CT, EL, PPS: methodology; DP: supervision and primary responsibility for final content. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Data described in the manuscript, code book, and analytic code will be made available upon request to the corresponding author.

References

[1] Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput J-P, Chastin S, Chou R, Dempsey PC, DiPietro L, Ekelund U, Firth J, Friedenreich CM, Garcia L, Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Wari V, Willumsen JF. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451-62. https://doi.org/10.1136/bjsports-2020-102955.

[2] Global action plan on physical activity 2018-2030: more active people for a healthier world. Geneva: World Health Organization 2018.

[3] Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-37. https://doi.org/10.1093/eurheartj/ehab484.

[4] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith Jr SC, Virani SS, Williams Sr KA, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:1376-414. https://doi.org/10.1161/CIR.0000000000000678.

[5] Patterson R, McNamara E, Tainio M, Hérick de Sá T, Smith AD, Sharp SJ, Edwards P, Woodcock J, Brage S, Wijndaele K. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol 2018;33:811-29. https://doi.org/10.1007/s10654-018-0380-1.

[6] Ammar A, Trabelsi K, Hermassi S, Kolahi AA, Mansournia MA, Jahrami H, Boukhris O, Boujelbane MA, Glenn JM, Clark CCT, Nejadghaderi A, Puce L, Safiri S, Chtourou H, Schöllhorn WI, Zmijewski P, Bragazzi NL. Global disease burden attributed to low physical activity in 204 countries and territories from 1990 to 2019: insights from the Global Burden of Disease 2019 Study. Biol Sport 2023;40:835-55. https://doi.org/10.1016/j.ajpc.2024.100633.

[7] Chastin SF, Buck C, Freiberger E, Murphy M, Brug J, Cardon G, O'Donoghue G, Pigeot I, Oppert J-M; DEDIPAC consortium. Systematic literature review of determinants of sedentary behaviour in older adults: a DEDIPAC study. Int J Behav Nutr

Phys Act 2015;12:127. https://doi.org/10.1186/s12966-015-0292-3.

[8] Gerovasili V, Agaku IT, Vardavas CI, Filippidis FT. Levels of physical activity among adults 18-64 years old in 28 European countries. Prev Med 2015;81:87-91. https://doi.org/10.1016/j.ypmed.2015.08.005.

[9] Pitsavos C, Panagiotakos DB, Chrysohoou C, Stefanadis C. Epidemiology of cardiovascular risk factors in Greece: aims, design and baseline characteristics of the ATTICA study. BMC Public Health 2003;3:32. https://doi.org/10.1186/1471-2458-3-32.

[10] Panagiotakos DB, Georgousopoulou EN, Pitsavos C, Chrysohoou C, Metaxa V, Georgiopoulos GA, Kalogeropoulou K, Tousoulis D, Stefanadis C; ATTICA Study group. Ten-year (2002-2012) cardiovascular disease incidence and all-cause mortality, in urban Greek population: the ATTICA Study. Int J Cardiol 2015;180:178-84. https://doi.org/10.1016/j.ijcard.2014.11.206.

[11] Damigou E, Kouvari M, Chrysohoou C, Barkas F, Kravvariti E, Pitsavos C, Skoumas J, Michelis E, Liberopoulos E, Tsioufis C, Sfikakis PP, Panagiotakos DB; ATTICA Study Group. Lifestyle trajectories are associated with incidence of cardiovascular disease: highlights from the ATTICA epidemiological cohort study (2002-2022). Life 2023;13:1142. https://doi.org/10.3390/life13051142.

[12] Papathanasiou G, Georgoudis G, Papandreou M, Spyropoulos P, Georgakopoulos D, Kalfakakou V, Evangelou A. Reliability measures of the short International Physical Activity Questionnaire (IPAQ) in Greek young adults. Hellenic J Cardiol 2009;50:283-94.

[13] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, Nieman DC, Swain DP; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334-59. https://doi.org/10.1249/MSS.0b013e318213fefb.

[14] Katsouyanni K, Rimm EB, Gnardellis C, Trichopoulos D, Polychronopoulos E, Trichopoulou A. Reproducibility and relative validity of an extensive semi-quantitative food frequency questionnaire using dietary records and biochemical markers among Greek schoolteachers. Int J Epidemiol 1997;S118-27. https://doi.org/10.1093/ije/26.suppl_1.s118.

[15] Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutr Metab Cardiovasc Dis 2006;16:559-68. https://doi.org/10.1016/j.numecd.2005.08.006.

[16] International Classification of Disease – 10. World Health Organization. Available at https://icd.who.int/browse10/2010/en (Accessed on: 1/10/2022).

[17] Global status report on physical activity 2022. Geneva: World Health Organization 2022.

[18] Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1.6 million participants. Lancet Child Adolesc Health 2020;4:23-35. https://doi.org/10.1016/S2352-4642(19)30323-2.

[19] Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob Health 2018;6:E1077-86. https://doi.org/10.1016/S2214-109X(18)30357-7.

[20] Voigt L, Ullrich A, Baumann S, Dörr M, John U, Ulbricht S. Do sociodemographic variables and cardiometabolic risk factors moderate the mere-measurement effect on physical activity and sedentary time? BMC Cardiovasc Disord 2020;20:272. https://doi.org/10.1186/s12872-020-01551-9.

[21] Wallace DA, Johnson DA, Redline S, Sofer T, Kossowsky J. Rest-activity rhythms across the lifespan: cross-sectional findings from the US representative National Health and Nutrition Examination Survey. Sleep 2023;46:zsad220. https://doi.org/10.1093/sleep/zsad220.

[22] Paudel S, Ahmadi M, Phongsavan P, Hamer M, Stamatakis E. Do associations of physical activity and sedentary behaviour with cardiovascular disease and mortality differ across socioeconomic groups? A prospective analysis of device-measured and self-reported UK Biobank data. Br J Sports Med 2023;57:921-29. https://doi.org/10.1136/bjsports-2022-105435.

[23] Stalling I, Albrecht BM, Foettinger L, Recke C, Bammann K. Associations between socioeconomic status and physical activity among older adults: cross-sectional results from the OUTDOOR ACTIVE study. BMC Geriatr 2022;22:396. https://doi.org/10.1186/s12877-022-03075-7.

[24] Elhakeem A, Cooper R, Bann D, Hardy R. Childhood socioeconomic position and adult leisure-time physical activity: a systematic review. Int J Behav Nutr Phys Act 2015;12:92. https://doi.org/10.1186/s12966-015-0250-0.

[25] Tambalis KD, Panagiotakos DB, Georgousopoulou EN, Mellor DD, Chrysohoou C, Kouli G-M, Tousoulis D, Stefanadis C, Pitsavos C; ATTICA Study Group. Impact of physical activity category on incidence of cardiovascular disease: results from the 10-year follow-up of the ATTICA Study (2002-2012). Prev Med 2016;93:27-32. https://doi.org/10.1016/j.ypmed.2016.09.023.

[26] Florido R, Daya NR, Ndumele CE, Koton S, Russell SD, Prizment A, Blumenthal RS, Matsushita K, Mok Y, Felix AS, Coresh J, Joshu CE, Platz EA, Selvin E. Cardiovascular disease risk among cancer survivors: the Atherosclerosis Risk In Communities (ARIC) Study. J Am Coll Cardiol 2022;80:22-32. https://doi.org/10.1016/j.jacc.2022.04.042.

[27] Ubago-Guisado E, Rodríguez-Barranco M, Ching-López A, Petrova D, Molina-Montes E, Amiano P, Barricarte-Gurrea A, Chirlaque M-D, Agudo A, Sánchez M-J. Evidence Update on the relationship between diet and the most common cancers from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: a systematic review. Nutrients 2021;13:3582. https://doi.org/10.3390/nu13103582.

[28] Mok A, Khaw KT, Luben R, Wareham N, Brage S. Physical activity trajectories and mortality: population based cohort study. BMJ 2019;365:l2323. https://doi.org/10.1136/bmj.l2323.

[29] Nemoto Y, Brown WJ, Mielke GI. Trajectories of physical activity from mid to older age in women: 21 years of data from the Australian Longitudinal Study on Women's Health. Int J Behav Nutr Phys Act 2024;21:4. https://doi.org/10.1186/s12966-023-01540-z.

[30] Paluch AE, Bajpai S, Ballin M, Bassett DR, Buford TW, Carnethon MR, Chernofsky A, Dooley EE, Ekelund U, Evenson KR, Galuska DA, Jefferis BJ, Kong L, Kraus WE, Larson MG, Lee I-M, Matthews CE, Newton Jr RL, Nordström A, Nordström P, Palta P, Patel AV, Pettee Gabriel K, Pieper CF, Pompeii L, Rees-Punia E, Spartano NL, Vasan RS, Whincup PH, Yang S, Fulton JE; Steps for Health Collaborative. Prospective Association of daily steps with cardiovascular disease: a harmonized meta-analysis. Circulation 2023;147:122-31. https://doi.org/10.1161/CIRCULATIONAHA.122.061288.

[31] Ross R, Arena R, Myers J, Kokkinos P, Kaminsky LA. Update to the 2016 American Heart Association cardiorespiratory fitness statement. Prog Cardiovasc Dis 2024:S0033-0620(24)00024-0. https://doi.org/10.1016/j.pcad.2024.02.003.

[32] Pagan LU, Gomes MJ, Okoshi MP. Endothelial Function and Physical Exercise. Arq Bras Cardiol 2018;111:540-1. https://doi.org/10.5935/abc.20180211.

[33] Hotta K, Behnke BJ, Arjmandi B, Ghosh P, Chen B, Brooks R, Maraj JJ, Elam ML, Maher P, Kurien D, Churchill A, Sepulveda JL, Kabolowsky MB, Christou DD, Muller-Delp JM. Daily muscle stretching enhances blood flow, endothelial function, capillarity, vascular volume and connectivity in aged skeletal muscle. J Physiol 2018;596:1903-17. https://doi.org/10.1016/j.carrev.2019.05.003.

[34] Sylow L, Kleinert M, Richter EA, Jensen TE. Exercise-stimulated glucose uptake – regulation and implications for glycae-

mic control. Nat Rev Endocrinol 2017;13:133-48. https://doi.org/10.1038/nrendo.2016.162.

[35] Amanat S, Ghahri S, Dianatinasab A, Fararouei M, Dianatinasab M. Exercise and type 2 diabetes. Adv Exp Med Biol 2020;1228:91-105. https://doi.org/10.1007/978-981-15-1792-1_6.

[36] Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H; Obesity Management Task Force of the European Association for the Study of Obesity. European Guidelines for Obesity Management in Adults. Obes Facts 2015;8:402-24. https://doi.org/10.1159/000442721.

[37] Recchia F, Leung CK, Yu AP, Leung W, Yu DJ, Fong DY, Montero D, Lee CH, Wong SHS, Siu PM. Dose-response effects of exercise and caloric restriction on visceral adiposity in overweight and obese adults: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med 2023;57:1035-41. https://doi.org/10.1136/bjsports-2022-106304.

Received on March 31, 2024. Accepted on May 30, 2024.

Correspondence: Demosthenes Panagiotakos, FRSPH, FACE, Harokopio University of Athens, 70 El. Venizelou, Kallithea, 17676, Athens, Greece. E-mail: dbpanag@hua.gr

How to cite this article: Dimitriadis N, Tsiampalis T, Arnaoutis G, Tambalis Kd, Damigou E, Chrysohoou C, Barkas F, Tsioufis C, Pitsavos C, Liberopoulos E, Sfikakis Pp, Panagiotakos D. Longitudinal trends in physical activity levels and lifetime cardiovascular disease risk: insights from the ATTICA cohort study (2002-2022). J Prev Med Hyg 2024;65:E134-E144. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3243

COVID-19

Impact of the COVID-19 pandemic on infectious diseases reporting

FABIO CONTARINO[1], FRANCESCA BELLA[2], ERMINIO DI PIETRO[1], CONCETTA RANDAZZO[1], MARIA LIA CONTRINO[3]
[1] Department of Public Health, Epidemiology Unit, Siracusa Local Health Authority, Italy; [2] Siracusa Cancer Registry, Siracusa Local Health Authority, Italy; [3] Head of Department of Public Health, Siracusa Local Health Authority, Italy

Keywords

Public health • Epidemiology • Notifiable diseases • Infectious disease • Surveillance • COVID-19 pandemic

Summary

Introduction. *COVID-19 pandemic had impacted the reporting of notifiable communicable diseases. Since the beginning of the pandemic and the introduction of relate public health measures, notifications for most notifiable diseases have declined compared to previous years. In this study, we aim to quantify the changes in the incidences of notifiable infectious diseases during and after the pandemic in Siracusa Local Health Authority, Italy.*
Methods. *We collected and analysed the infectious disease notifications made in two different three-years periods, 2017-2019 and 2020-2022 in Siracusa Local Health Authority, Italy. Descriptive statistics were used to find the percentages and the 95% confidence interval (CI). Exact "F-tests" was performed to compare the mean values between the studied periods to evaluate the hypothesis that the number of reported cases would not differ significantly between the two periods. Significance was assessed at the $p < 0.05$ level.*
Results. *The total number of notifications significantly decreased by 69.3% in the pandemic period compared to the pre-pandemic one, with the highest reduction of air-borne transmission diseases (-86.5%), followed by food-borne diseases (-68.2%) and sexually transmitted diseases (-39.3%). Conversely, an increase in number of notifications was found only for legionellosis.*
Conclusions. *The COVID-19 pandemic had the potential to influence communicable disease reporting at multiple points. While the effects could vary considerably, the results would be expected to reduce the number and the detection of notifiable cases. Included would be changes in exposures, diagnostic testing, reporting to public health agencies, and public health investigations.*

Introduction

The COVID-19 pandemic has had a fundamental impact on health services [1-3] and the epidemiology of other infectious diseases worldwide [4].
In response to the ongoing COVID-19 pandemic, a variety of public health interventions have been implemented worldwide to mitigate its impact, including nonpharmaceutical interventions (NPIs), as social distancing, mask-wearing, shelter-in-place, travel restrictions, school closure [5].
While pharmaceutical interventions generally target specific pathogens, NPIs can act on a broad spectrum of infectious pathogens. Tough these measures, initially specifically aiming for COVID-19, might have significant impact on other infectious diseases [4].
There is growing global evidence suggesting that NPIs are associated with decreased rates of COVID-19 and non–COVID-19 infectious diseases, and thus a decreased burden associated with seasonal influenza, other upper and lower respiratory infections, and food-borne diseases [6, 7].
Generally, those studies focused solely on respiratory pathogens such as influenza virus and respiratory syncytial virus. Although respiratory pathogens were likely affected the most by the NPIs, pathogens with other transmission modes, *e.g.,* gastrointestinal, sexually transmitted, or even vector-borne diseases, could have also been affected as the unprecedented changes in human movement and behavioral patterns might have changed exposure levels.
Surveillance of infectious diseases lays the foundation for their possible control [8]. In Italy, infectious disease surveillance is based on the Mandatory Reporting System, that pursuant to Ministerial Decree of 15 December 1990 - "Infectious and Transmissible Diseases Information System", involves the mandatory reporting by doctors of cases of the many infectious diseases [9]. The information flow for infectious diseases starts from the periphery and converge towards the centre for Regional, National and Supranational reporting. The infectious disease reporting system has been activated reporting of probable or confirmed cases of an infectious disease is made by local General Practitioners (GPs), Primary Care Pediatricians (PCPs), or hospital physicians. In addition to this general system, there are other specific surveillance systems at national level, such as those for legionellosis, influenza and viral hepatitis [10]. This mandatory notification system allows for a continuous analysis at a central and local level.
We have already analysed the impact of the pandemic on health services, such as vaccinations in Siracusa LHA different papers [11, 12]. In this paper, we aim to quantify the changes in the transmission, diagnosis and notifications of notifiable infectious diseases with different transmission modes before, during, and after the first wave of COVID-19 in Siracusa Local Health

Authority (LHA), Italy, by analysing the reported cases and their characteristics during the pandemic (2020-2022), in comparison to the pre-pandemic phase (2017-2019).

Methods

This study is a retrospective analysis of data previously generated from the infectious disease notifications in Siracusa LHA of two different three-year periods 2017-2019 (pre-pandemic period, from 1 January 2017 to 31 December 2019) and 2020-2022 (pandemic period, from 1 January 2020 to 31 December 2022). We compared annual case numbers and case characteristics in the pre-pandemic period and in the pandemic period.

Considering the average population, the resident population decreased by 1.8%, from 394,315 in the years 2017-2019 to 387,105 in the years 2020-2022. Just under a third of the residents lived in the city of Siracusa, provincial capital with about 116.635 residents. The territory is divided into four health districts.

The 29 infectious diseases examined are listed in Table I. We categorised the included notifiable diseases according to their main mode of transmission and vaccination availability. We included at least one disease per mode of transmission, considering public health relevance in Italy. Grouping the diseases according to their transmission modes, we evaluated the notification trend of the following groups of diseases (Tab. I): airborne/droplets/aerosol of contaminated water diseases (viral meningitis, herpes zoster-shingles, legionellosis, invasive bacterial diseases, measles, mumps, pertussis, rubella, scarlet fever, tuberculosis, chickenpox); fecal-oral/contaminated food or water diseases (brucellosis, hepatitis A, hepatitis E, typhoid fever and paratyphoid fever, non-typhoid salmonellosis, food poisoning, listeriosis); sexual/blood-borne/body fluids/transplacental diseases (hepatitis B, hepatitis C, HIV, syphilis, congenital syphilis); vector-borne diseases (visceral leishmaniasis, malaria, rickettsiosis); direct contact diseases (pediculosis, scabies); transmission through skin wound diseases (tetanus).

The diagnostic methods, that differ according to the category of infectious disease, such as polymerase

Tab. I. Main mode of transmission or acquisition and vaccination availability of notifiable infectious diseases included.

Disease/Infection	Main mode of transmission	Vaccination availability*	Compared to pre-COVID-19
Brucellosis	Fecal-oral transmission	No	Lower
Chickenpox	Airborne transmission	Yes	Lower
Congenital syphilis	Transplacental	No	Lower
Food poisoning	Contaminated food or water	No	Comparable
Hepatitis A	Fecal-oral transmission	Yes	Lower
Hepatitis B	Sexually transmitted and via body fluids	Yes	Comparable
Hepatitis C	Blood-borne	No	Lower
Hepatitis E	Fecal-oral transmission	No	Comparable
Herpes zoster-shingles	Airborne transmission	Yes	Comparable
HIV	Sexually transmitted and via body fluids	No	Lower
Invasive bacterial diseases (IBDs)	Airborne transmission	Yes	Lower
Legionellosis	Inhalation of contaminated aerosol	No	Higher
Listeriosis	Contaminated food or water	No	Comparable
Malaria	Vector-borne	No	Comparable
Measles	Airborne transmission	Yes	Lower
Mumps	Airborne transmission	Yes	Lower
Non-typhoid salmonellosis	Contaminated food or water	No	Comparable
Pediculosis	Direct contact	No	Comparable
Pertussis	Airborne transmission	Yes	Comparable
Rickettsiosis	Vector-borne	No	Lower
Rubella	Airborne transmission	Yes	Comparable
Scabies	Direct contact	No	Comparable
Scarlet Fever	Airborne transmission	No	Lower
Syphilis	Sexually transmitted and via body fluids	No	Comparable
Tetanus	Transmission through skin wound	Yes	Comparable
Tuberculosis	Airborne transmission	Yes	Lower
Typhoid and paratyphoid fever	Contaminated food or water	Yes	Comparable
Viral meningitis	Airborne transmission	No	Comparable
Visceral leishmaniasis	Vector-borne	No	Comparable

* Routinely administered in Italy.

chain reaction testing, antigen testing, or clinical diagnosis [13], did not change during the study period for each infectious disease included in the study.

All the notifications made by the local physicians are managed and insert into the IT platforms of the general and specifically dedicated national websites (PREMAL) by the Epidemiology Unit of the local Health Department. The notification data collected by these systems were used to obtain disease incidence values, considering the resident population per each year to make a difference between the pre-pandemic and the pandemic period. Resident population was obtained according to ISTAT data (Italian National Statistical Institute).

Descriptive statistics were used to find the percentages and the 95% confidence interval (CI). Exact "F-tests" was performed to compare the mean values between the studied periods to evaluate the hypothesis that the number of reported cases would not differ significantly between the two periods. Significance was assessed at the $p < 0.05$ level.

Results

Between January 2017 and December 2022, a total of 1,162 notifications of infectious diseases were reported: 273 cases were notified in the pandemic period (2020-2022), compared to 889 cases of the pre-pandemic one (2017-2019), with a percentage decrease of -69.3% ($p < 0.0001$) (Tab II).

We calculated the incidence rates (IR) based on resident population. Specifically, in the pre-pandemic period (2017-2019), the average IR was 75.2/100,000 ± 7.5 (95% CI: 67.7-82.7) while, in the pandemic period, the average IR was 23.5/100,000 ± 2.4 (95% CI: 21.1-25.9). Therefore, a significant percentage decrease of -68.8% between the average values of the two periods incidences was detected ($p < 0.00001$).

Of all diseases included in the study period, 25 of them (86.2%) reported a decrease in reported cases during the COVID-19 pandemic, and in 12 of them (41.4%) the decline was statistically significant. In contrast, 4 diseases (13.8%) reported an increase in reported

Tab. II. Comparison between the absolute numbers of the infectious disease notifications made in the pre-pandemic (2017-2019) and pandemic (2020-2022) periods, with corresponding absolute changes (Δ n), percentage changes (Δ %) and statistical significance.

Disease/Infection	Absolute number of reported cases		Δ n	Δ %	Fisher test
	2017-2019	2020-2022			
Brucellosis	36	0	-36	-100,0%	p < 0.00001
Chickenpox	54	20	-34	-63,0%	p < 0.0001
Congenital syphilis	12	0	-12	-100,0%	p < 0.0005
Food poisoning	3	9	6	+200,0%	ns
Hepatitis A	17	0	-17	-100,0%	p <.05
Hepatitis B	4	1	-3	-75,0%	ns
Hepatitis C	8	1	-7	-87,5%	p = 0.0391
Hepatitis E	2	0	-2	-100,0%	ns
Herpes zoster-shingles	2	1	-1	-50,0%	ns
HIV	62	40	-22	-35,5%	p = 0.0379
Invasive bacterial diseases (ibds)	12	2	-10	-83,3%	p = 0.013
Legionellosis	0	9	9	+100%	p = 0.0018
Listeriosis	1	1	0	0,0%	ns
Malaria	2	1	-1	-50,0%	ns
Measles	291	1	-290	-99,7%	p < 0.00001
Mumps	12	3	-9	-75,0%	p = 0.0353
Non-typhoid salmonellosis	22	12	-10	-45,5%	ns
Pediculosis	11	5	-6	-54,5%	ns
Pertussis	6	2	-4	-66,7%	ns
Rickettsiosis	32	6	-26	-81,3%	p < 0.05.
Rubella	1	0	-1	-100,0%	ns
Scabies	100	94	-6	-6,0%	ns
Scarlet fever	109	12	-97	-89,0%	p < 0.00001
Syphilis	21	23	2	+9,5%	ns
Tetanus	1	1	0	0,0%	ns
Tuberculosis	58	23	-35	-60,3%	p < 0.0001
Typhoid fever and paratyphoid fever	4	5	1	+25,0%	ns.
Viral meningitis	4	1	-3	0,0%	ns
Visceral leishmaniasis	2	0	-2	-100,0%	ns
Total	**889**	**273**	**-616**	**-69,3%**	**p < 0.00001**

cases, one of them (3.4%) with statistical significance (legionellosis) (Tab. I).
Grouping the diseases according to their transmission modes, those with the greatest reduction in reported cases were airborne/droplets/aerosol of contaminated water diseases (-86.5%, $p < 0.00001$), followed by fecal-oral/contaminated food or water diseases (-68.2%, $p < 0.00001$), sexual/blood-borne/body fluids/ transplacental diseases (-39.3%, $p = 0.0022$), and finally those transmitted by direct contact (-10.8%, ns).
Of the 12 infectious diseases with a significant decrease in the mean number of reported cases during the pandemic period, 6 diseases (50.0%) are characterized by airborne or droplets transmission (Tab. II). A significant increase in the number of reported cases during the pandemic was observed only for legionellosis, while an increase trend, but without statistical significance, was observed for food poisoning, syphilis, typhoid and paratyphoid fever.

Airborne/droplets/aerosol of contaminated water diseases

Measles was the disease with the most notified overall over the entire reporting period and by far the most notified among airborne diseases, with, however, a significant reduction of 99.7% from 2017-2019 to 2020-2022 ($p < 0.00001$).
Scarlet fever was the second most notified airborne disease; again, there was a significant reduction in incidence in the years 2020-2022 (-89.0%, $p < 0.00001$), compared to the previous.
Tuberculosis reported a highly significant decrease of -60.3% between the pre-pandemic period and the pandemic one ($p < 0.00001$), as the same for chickenpox (-63.0%; $p < 0.00001$).
Vaccine-preventable invasive bacterial diseases (caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*) had registered a decrease of -83.3% ($p < 0.05$) in the pandemic period.
Rubella was present with only 1 case in the pre-pandemic period and no case was notified in the pandemic one. In contrast, for legionellosis we recorded 9 cases in the years 2020-2022 *vs* no cases in the period 2017-2019 ($p = 0.0018$).

Fecal-oral/contaminated food or water diseases

The most notified foodborne disease was brucellosis (36 cases), for which no-one case was recorded in the years 2020-2022 ($p < 0.00001$). Hepatitis A ($p < 0.05$) and hepatitis E (ns) followed a similar trend, with 100.0% of reduction in the latter period. For Hepatitis A, an outbreak of 5 cases was reported in 2017 in a primary school affecting people coming back from Morocco.Non-typhoid salmonellosis cases were constantly notified, with a reduction from the first period to the second one (-45.5%, ns). Also, typhoid and paratyphoid fever cases were constantly notified (4 cases in pre-pandemic period and 5 cases in the pandemic one).

Sexual/blood-borne/body fluids/ transplacental diseases

HIV infection registered the largest number of cases in this group of diseases (102 cases), followed by syphilis. For HIV infection, there was a 35.5% reduction ($p = 0.0379$), while for syphilis there were 2 more cases in the 2020-2022 years compared to the 2017-2019 years (+9.5%, ns).
Both hepatitis B (-75.0%, ns) and hepatitis C (-87.5%, $p = 0.0391$) experienced a reduction in the post-pandemic period compared to pre-pandemic one.
Congenital syphilis (12 cases) experienced a 100% reduction in the post-pandemic period compared to the previous period ($p < 0.0005$).

Vector-borne diseases

Rickettsiosis, endemically present in this territory, has recorded a significant reduction comparing the 2020-22 period to the 2017-2019 period (-81.3%, $p < 0.05$). Two cases were notified for visceral leishmaniasis and malaria (all import cases for the latter) in the pre-pandemic period, while no case (-100%) and 1 case (-50%) was notified in the post-pandemic period, respectively.

Direct contact diseases

Pediculosis and scabies were constantly notified and the average number of cases of the two study periods remained overlapping for both the diseases. Overall, scabies was the second infection more notified after measles. Pediculosis recorded a percentage decrease of 54.5% from 2017-2019 to 2020-2022.

Transmission through skin wound diseases

During all the study period, two tetanus cases were overall notified, one in both periods, which interested the age group > 65 years old in both cases. One death was reported.

Vaccination availability

Comparing the two study periods, all the vaccine-preventable diseases (VPDs) showed an incidence decreased almost double compared to non VPDs (-87.2% *vs* -49.9%, $p < 0.00001$). In more details: measles -290 cases (-99.7%), chickenpox -34 cases (-63.0%), hepatitis A -17 cases (-100%), invasive bacterial diseases (IBDs) -10 cases (-83.3%), mumps -9 cases (-75.0%), pertussis -4 cases (-66.7%); hepatitis B -3 cases (-75%).

Discussion

In this study, we reported the impact of the COVID-19 pandemic on the endemic status of other 29 infectious diseases in Siracusa Local Health Authority, Italy. Specifically, we observed an abrupt decline in the number of many reported infectious diseases.
As already reported, infectious disease with airborne route of transmission experienced the greatest reduction between the two different three-year study

periods. Airborne infectious diseases and COVID-19 share similar routes of transmission; therefore, the widespread of NPIs, such as restrictions on gatherings and international travel, physical distancing, mandatory mask wearing and school closures, implemented to prevent COVID-19 are likely to have prevented other infectious diseases circulation as well. During 2017–2019 period, a resurgence of measles was being observed both in the EU/EEA, during which Italy accounted for almost 30% of the over 18,000 reported cases [14]. As a result, mandatory vaccination for measles (and other diseases such as mumps, rubella and chickenpox) was introduced in Italy for all newborns from 2017 [15]. Given the above, however, we can rule out the possibility that this reduction is entirely due to the pandemic, as a decline in the incidence of the disease was observed in Italy as early as the third quarter of 2019, thus well before the onset of the pandemic [16]. Our data are in line with the national data; indeed, we recorded 19 cases in 2017, 269 cases in 2018 and only 3 cases in 2019, while only one case was recorded in pandemic period (2020).

Some infectious diseases have had a rebound outbreak in 2022 after decreased incidence in 2020. It's the case of food poisoning infections, that showed outbreaks in 2022 after decreased incidences in 2020 (9 cases *vs* no case; $p = 0.0019$). A similar trend was observed for scabies and pediculosis, although without any statistical significance.

No (routinary) vaccinations are available for the diseases with a higher number of cases during the pandemic period; conversely, none of the 12 vaccine-preventable diseases included in the study showed increased incidences during the COVID-19 pandemic. Our findings indicate a sustainable suppression of VPDs also beyond the lifting of restrictions. This included measles, mumps, rubella, pertussis, meningococcal and pneumococcal diseases.

Pandemic containment measures, instead, have play a more important role in reducing the notifications of varicella, scarlet fever and IBDs infections. For the latter, we can also assume an important role played by the drastic decrease of influenza cases occurred in Italy during the 2020-2021 season [17], given that some bacterial diseases, including Streptococcus pneumoniae, can occur as complication of influenza, especially in the elderly and fragile people [18].

Regarding food-borne diseases, the closure of restaurants and food service providers in schools, hotels, and catering businesses has resulted in more eating at home than away from home. Such shift resulted in lower rates of foodborne illnesses, especially the pathogens associated with restaurant settings [19]. Furthermore, international travel restrictions have decreased infections associated with such activities. These policies and regulations and changes in hygiene behaviours, such as increased handwashing, likely reduced exposure to foodborne pathogens. Studies have shown that washing hands before preparing food increased by at least 20% during the COVID-19 pandemic [20].

COVID-19 pandemic and NPIs likely modulated the incidences of vector-borne diseases in at least two more ways in addition to altering healthcare-seeking behaviour. The restrictions on human mobility inevitably reduced people's outdoor activities and hence lowered their exposure to vectors and animal hosts of vector-borne or zoonotic diseases. Meanwhile, restrictions and screening of international travellers dramatically reduced the number of imported cases.

Less variation of sexually transmitted or bloodborne diseases was observed in comparison with respiratory diseases and gastrointestinal or enteroviral diseases, possibly due to the difference in their transmission modes. However, sexually transmitted infections remain a significant public health concern, even in the face of a pandemic. The syphilis has been constantly present in our territory during the last years. This is in line with data from different countries where syphilis has been a resurgent disease especially in some particularly at-risk group of population [21, 22].

A separate mention has to be made for scabies, which experienced the smallest decrease in notifications compared to the pre-pandemic period (-6.0%). Generally, scabies has been thought to occur only sporadically, but in the last two decades, there has been an increase in published papers indicating that disease is occurring more frequently [23]. It's possible that the pandemic could have exacerbated an already existing situation characterized by a general increasing trend linked to various variable. This situation is in line with what reported by other countries where an analogous increase was detected in last years [23-27].

Legionellosis was the only infection with a significant increase in reported cases in the pandemic period compared with the previous one in our study. These data are in line with national data: in Italy, in 2022 the incidence of legionellosis increased from previous years, returning to pre-pandemic incidence values [26, 27]. In Europe, the reporting rate of legionellosis cases also increased in 2021 compared to 2020, reaching the highest level ever recorded by ECDC surveillance. Italy, France, Spain and Germany account for 75% of all reported cases [28]. The cause of the recent increase in the reporting rate in Europe remains unknown. It is possible that it is associated with the lifting of COVID-19 restrictions, as travel-associated infections decreased significantly in 2020 compared to the years before the COVID-19 pandemic. Changes in building occupancy and water use altered the demand on public water systems during the COVID-19 pandemic, potentially impacting the risk of Legionella growth in areas with reduced water flow or loss of disinfectant residuals [29]. When buildings are reopened after the lockout, it is essential that water systems are not put back into operation without considering the risks of Legionnaires' disease. The risk of the presence of waterborne pathogens, such as legionella bacteria, increases due to conditions that may have been created during the shutdown. In addition, as a result of the pandemic, the possibility exists that more people may be susceptible to Legionnaires' disease due to a compromised respiratory system during or after infection with COVID-19.

Our findings of a remarkable and significant decrease of notifications of infectious diseases in the pandemic

period are in line with what reported by previous evidence [30-43]. Such reports suggest that the COVID-19 strategy has led to similar control of other infectious diseases, mainly comprising those transmitted by airborne/droplets or contact, in many countries.

The COVID-19 pandemic has led to lifestyle changes worldwide. Individual and public health measures against COVID-19 are considered to have contributed to the control of many infectious diseases [44-49].

The reasons for these observations are likely to be multifactorial, and our analyses of surveillance data cannot determine with certainty to which extent decreases in disease reporting were due to a true decrease in transmission or whether the decrease was only due to a decrease in diagnosis. While the effects could vary considerably, the results would be expected to reduce the number and the detection of notifiable cases. Included would be changes in exposures, diagnostic testing, reporting to public health agencies, and public health investigations. However, by assessing diseases with different modes of transmission, we can derive hypotheses regarding the reasons for the reduction in case numbers. There may have been a decrease in transmission, and thus a true decrease of cases, for several notifiable diseases as a consequence of the COVID-19 NPIs as indicated by the decrease in chickenpox, IBDs, mumps, scarlet fever cases in pandemic period. These diseases are mainly transmitted via direct close contact, *i.e.* airborne, via droplets. Hence, as described, NPIs such as increased hand and cough hygiene, physical distancing, contact restrictions and the closure of schools and daycare centres, probably also reduced infections caused by transmission via direct close contact [4].

The COVID-19 pandemic had the potential to influence communicable disease reporting at multiple points. First, decreasing the viral circulation following to a lower people movement, specifically during the lockdown. Individuals restricting their activities could result in fewer exposures to communicable diseases. Closure of schools and public areas could reduce the risk of exposure to respiratory diseases such as influenza and pertussis. Closure of restaurants could reduce large foodborne disease outbreaks. Reduced domestic and international travel could in turn reduce a wide range of exposures. The pandemic led to in fewer in-person visits to healthcare facilities including for non-respiratory symptoms. Secondly, public health measures put in place to control the pandemic, such as physical distancing, international and local travel restrictions, lockdowns, mask-wearing and handwashing, would have also affected the spread of other infectious diseases, particularly respiratory viruses [50]. As already reported, many infectious diseases, especially air-borne infectious diseases, and COVID-19 share similar routes of transmission; therefore, the widespread of NPIs implemented to prevent COVID-19 are likely to have prevented other infectious diseases circulation as well.

However, despite strong and valid evidences highlight the key role played by the pandemic and by the counter measures in the reduction of infectious disease notifications, we cannot exclude a possible role of the widespread phenomenon of underreporting, a well-known malpractice present in ordinary situations [50, 51], that it could be stressed in the extraordinary situation given by the pandemic. Another impact was suspension of Public Health Laboratories' capacity for strain typing for a while, interfering with the ability to detect outbreaks [51, 52]. Without laboratory testing, the cause of any possible infection would remain undetermined and unreported. Finally, people may have been less likely than usual to seek medical care for relatively minor illnesses, leading to under-diagnosis and under-reporting for some diseases. It is difficult to determine the relative contribution of these various factors to the declines [53].

Surveillance is the backbone of any disease control program [54]. Surveillance is "the ongoing systematic collection, analysis, interpretation and dissemination of data regarding a health-related event; for doing actions" [55]. It is essential for evaluating the impact of an intervention, such as mass vaccination, on a population. It can also act as a fairly sensitive system for the early detection of outbreaks. The importance of an organized notification system coordinating the surveillance of infectious diseases has been widely shown by the COVID-19 pandemic, when surveillance systems have been widely used worldwide as cornerstone in the fight against COVID-19 pandemic [56, 57, 58]. The pandemic highlighted the need for strengthened surveillance data to accurately track the distribution of infectious diseases for informing public health responses to improve infection prevention and control.

The COVID-19 pandemic has brought both challenges and opportunities in surveillance [59, 60]. Yet, gaps in surveillance, from the local to the global, continue to leave the world vulnerable to infectious hazards. The COVID-19 pandemic revealed that various healthcare systems in the world are fundamentally weak. Compared with many developed countries, the ability of less developed countries to tackle a pandemic seems to be much lower and the medical system in those nations is frequently grossly inadequate. Some disease outbreaks, if not detected and controlled at an early stage, have the potential to turn into an epidemic or even a pandemic, which can disrupt the commercial growth of the nation and the health of human resources. The health and well-being of people around the world continue to be challenged by infectious hazards. The progression of COVID-19 has proven that "no one is safe until everyone is safe" in this interconnected world.

This study has several limitations that should be kept in mind. First, this is an observational study; thus, our results should be interpreted as associations of COVID-19 pandemic and NPIs with, rather than causal effect on, reducing transmission of non-COVID-19 infectious diseases. Second, the assessment of just two time periods (pre-pandemic and pandemic) could represent a simplified approach of assessing effects of the pandemic. During the pandemic period, there were various, sometimes overlapping COVID-19-related

developments (new variants, newly introduced vaccines or vaccination recommendations, new NPIs and changing perception of the pandemic in the population), that, probably, had different impacts on the healthcare system and on healthcare-seeking behaviour, and consequently on the diagnosis and notification of other infectious diseases. As it is difficult to disentangle these effects, we chose the pragmatic approach of assessing only one pandemic period. Third, this study did not include all the infectious diseases, but only those and for which there were a sufficient number of notifications to allow appropriate statistical analysis, to avoid that the small numbers of reported cases could have been affected by the sporadic outbreaks. Other study limitations include the omission of data on incidence of influenza and other data such as seasonal trends, effect of vaccination, and changes in the sensitivity of surveillance due to insufficient data availability.

With our study we hope to contribute to a better understanding and interpretation of the local epidemiology of infectious diseases other than COVID-19 during and after pandemics. To the best of our knowledge, very few publications have analysed the "new" endemic status of infectious diseases considering the changes brought by the pandemic at the local level. Generally, those studies focused solely on respiratory pathogens such as influenza virus and respiratory syncytial virus. Although respiratory pathogens were likely affected the most by the NPIs, pathogens with other transmission modes, *e.g.,* gastrointestinal, sexually transmitted, or even vector-borne diseases, could have also been affected as the unprecedented changes in human movement and behavioral patterns might have changed exposure levels. In our opinion, the local level analysis is very useful to understand the "new endemic status" of the other infectious diseases after the pandemic in our territory.

These findings could be used to inform scientific decisions about possible future epidemics and to organize appropriate public health responses, such as vaccinations or other measures.

Conclusions

In conclusion, we comprehensively describe the epidemiological characteristics of infectious diseases and analyse the difference before and after the epidemic of COVID-19 in Siracusa LHA.

The study showed that during the COVID-19 pandemic, particularly in 2020 and in 2021 and to a lesser extent also in 2022, there were significantly fewer cases of notifiable diseases other than COVID-19 in Siracusa LHA. This decrease was particularly marked for airborne infectious diseases, but it involved almost every infectious disease. Various factors should be considered when evaluating possible reasons for this decline, including under diagnosis, under-reporting and decreased transmission. The magnitude of the observed decrease in incidence and its temporal coincidence with the introduction of national lockdown measures suggest that our findings represent a real decline of infectious diseases, but besides a real decrease in transmission, there may have been under-detection for some diseases, which might have been due by such extraordinary situation given by the pandemic, due to the huge load of healthcare professionals involved, for the most part, in managing the pandemic.

Acknowledgements

The authors would like to thank all the health professionals involved in the routine collection of infectious diseases in Siracusa Local Health Authority.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, FC; methodology, FC; acquisition of data, FC, EDP, CR; formal analysis and interpretation of data, FC, FB; writing - original draft preparation, FC; writing - review and editing, FC, FB; statistical analysis, FC; supervision and project administration, FC, EDP, MLC. All authors have read and agreed to the submitted version of the manuscript.

References

[1] World Health Organization (WHO). Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report, 27 August 2020 Geneva: WHO 2020. Available at: https://www.who.int/publications/i/item/ WHO-2019-nCoV-EHS_continuity-survey-2020.1 (Accessed on: 30/01/2024).

[2] World Health Organization (WHO). The impact of the COVID-19 pandemic on noncommunicable disease resources and services: results of a rapid assessment. Geneva: WHO 2020. Available at: https://www.who.int/publications/i/item/9789240010291 (Accessed on: 30/01/2024).

[3] World Health Organization (WHO). COVID-19 continues to disrupt essential health services in 90% of countries. Geneva: WHO 2021. Available at: https://www.who.int/news/ item/23-04-2021-COVID-19-continues-to-disrupt-essentialhealth- services-in-90-of-countries (Accessed on: 30/01/2024).

[4] Oh KB, Doherty TM, Vetter V, Bonanni P. Lifting non-pharmaceutical interventions following the COVID-19 pandemic - the quiet before the storm? Expert Rev Vaccines 2022;21:1541-53. https://doi.org/10.1080/14760584.2022.2117693.

[5] Mader S, Rüttenauer T. The effects of non-pharmaceutical interventions on COVID-19 mortality: a generalized synthetic control approach across 169 countries. Front Public Health 2022;10:820642. https://doi.org/10.3389/fpubh.2022.820642. Erratum in: Front Public Health 2023;11:1186935.

[6] Sacri AS, De Serres G, Quach C, Boulianne N, Valiquette L, Skowronski DM. Transmission of acute gastroenteritis and respiratory illness from children to parents. Pediatr Infect Dis J 2014;33:583-8. https://doi.org/10.1097/INF.0000000000000220.

[7] Oh DY, Buda S, Biere B, Reiche J, Schlosser F, Duwe S, Wedde M, von Kleist M, Mielke M, Wolff T, Dürrwald R. Trends in respiratory virus circulation following COVID-19-targeted

nonpharmaceutical interventions in Germany, January - September 2020: analysis of national surveillance data. Lancet Reg Health Eur 2021;6:100112. https://doi.org/10.1016/j.lanepe.2021.100112.

[8] Noah N. Surveillance of infectious diseases. Encyclopedia of Virology 2021:247-255. https://doi.org/10.1016/B978-0-12-814515-9.00068-0.

[9] Ministero della Salute. Decreto Ministeriale 15 dicembre 1990-Sistema informativo delle malattie infettive e diffusive. 1990. Available at: https://www.esteri.it/mae/resource/doc/2020/03/decreto_9_marzoeng.pdf (Accessed on: 20/11/2023).

[10] Il sistema di sorveglianza routinario per le malattie infettive (Sistema informativo malattie infettive, Simi). Available at: https://www.epicentro.iss.it/infettive/sorveglianza (Accessed on: 20/11/2023).

[11] Contarino F, Di Pietro E, Randazzo C, Bella F, Contrino ML. Effectiveness of a vaccine recovery plan after the COVID-19 pandemic in the Siracusa Local Health Authority, Italy. Results of one year follow-up. J Prev Med Hyg 2023;64:E289-97. https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3001.

[12] Contarino F, Di Pietro E, Bella F, Randazzo C, Contrino ML. Childhood immunization coverage during the COVID-19 pandemic in the province of Siracusa, Italy. J Prev Med Hyg 2022;63:E513-9. https://doi.org/10.15167/2421-4248/jpmh2022.63.4.2587.

[13] Istituto Superiore di Sanità. Infectious Diseases Department. Available at: https://www.iss.it/web/iss-en/infectious-diseases (Accessed on: 29/01/2024).

[14] European Centre for Disease Prevention and Control. Measles. In: ECDC. Annual epidemiological report for 2019. Stockholm: ECDC 2020.

[15] Ministero della Salute. Conversione in legge, con modificazioni, del decreto-legge 7 giugno 2017, n. 73, recante disposizioni urgenti in materia di prevenzione vaccinale. 2017. Available at: https:// www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=60201 (Accessed on: 28/01/2024).

[16] Filia A, Bella A, Del Manso M, Baggieri M, Marchi A, Bucci P, Magurano F, Nicoletti L, Rota MC. Morbillo & Rosolia News, N. 58 gennaio 2020. Available at: http://www.epicentro.iss.it/problemi/morbillo/bollettino.asp (Accessed on: 28/01/2024).

[17] Istituto Superiore di Sanità (ISS). Rapporto della sorveglianza integrata dell'influenza. 2021. Available at: https://www.epicentro. iss.it/influenza/flunews20-21 (Accessed on: 28/01/2024).

[18] Siegel SJ, Roche AM, Weiser JN. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. Cell Host Microbe. 2014;16:55-67. https://doi.org/10.1016/j.chom.2014.06.005.

[19] Akil L, Ahmad HA. Socioeconomic impacts of COVID-19 pandemic on foodborne illnesses in the United States. Eur J Environ Public Health 2023;7:em0128. https://doi.org/10.29333/ejeph/12585.

[20] Görür N, Topalcengiz Z. Food safety knowledge, hygiene practices, and eating attitudes of academics and university students during the coronavirus (COVID-19) pandemic in Turkey. J Food Saf 2021;41:e12926. https://doi.org/10.1111/jfs.12926.

[21] Ukai T, Kakimoto K, Kawahata T, Miyama T, Iritani N, Motomura K. Resurgence of syphilis in 2022 amongst heterosexual men and women in Osaka, Japan. Clin Microbiol Infect 2023;29:396-7. https://doi.org/10.1016/j.cmi.2022.11.010.

[22] Amerson EH, Castillo Valladares HB, Leslie KS. Resurgence of Syphilis in the US-USPSTF Reaffirms Screening Guidelines. JAMA Dermatol. 2022;158:1241-3. https://doi.org/10.1001/jamadermatol.2022.3499.

[23] Ažđajić MD, Bešlić I, Gašić A, Ferara N, Pedić L, Lugović-Mihić L. Increased Scabies Incidence at the Beginning of the 21st Century: What Do Reports from Europe and the World Show? Life 2022;12:1598. https://doi.org/10.3390/life12101598.

[24] van Deursen B, Hooiveld M, Marks S, Snijdewind I, van den Kerkhof H, Wintermans B, Bom B, Schimmer B, Fanoy E. Increasing incidence of reported scabies infestations in the Netherlands, 2011-2021. PLoS One 2022;17:e0268865. https://doi.org/10.1371/journal.pone.0268865.

[25] Redondo-Bravo L, Fernandez-Martinez B, Gómez-Barroso D, Gherasim A, García-Gómez M, Benito A, Herrador Z. Scabies in Spain? A comprehensive epidemiological picture. PLoS One. 2021;16:e0258780. https://doi.org/10.1371/journal.pone.0258780.

[26] Rota MC, Caporali MG, Bella A, Scaturro M, Giannitelli S, Ricci ML. I risultati del sistema di sorveglianza della legionellosi nel 2021. Boll Epidemiol Naz 2022;3:30-7. https://doi.org/10.53225/BEN_045. Errata corrige in: Boll Epidemiol Naz 2022;3:30-7. https://doi.org/10.53225/BEN_047.

[27] Rota MC, Caporali MG, Bella A, Scaturro M, Giannitelli S, Ricci ML. I risultati del sistema di sorveglianza della legionellosi nel 2021. Boll Epidemiol Naz 2023;4:25-32. https://doi.org/10.53225/BEN_062.

[28] European Centre for Disease Prevention and Control. Legionnaires' disease. In: ECDC. Annual Epidemiological Report for 2021. Stockholm: ECDC 2023. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/legionnaires-disease-annual-epidemiological-report-2021.pdf (Accessed on: 02/02/2024).

[29] Kunz JM, Hannapel E, Vander Kelen P, Hils J, Hoover ER, Edens C. Effects of the COVID-19 pandemic on legionella water management program performance across a United States lodging organization. Int J Environ Res Public Health 2023;20:6885. https://doi.org/ 10.3390/ijerph20196885.

[30] Chen B, Wang M, Huang X, Xie M, Pan L, Liu H, Liu Z, Zhou P. Changes in Incidence of Notifiable Infectious Diseases in China Under the Prevention and Control Measures of COVID-19. Front Public Health 2021;9:728768. https://doi.org/10.3389/fpubh.2021.728768.

[31] Geng MJ, Zhang HY, Yu LJ, Wang T, Che TL, Xu Q, Jiang BG, Chen JJ, Hay SI, Li ZJ, Gao GF, Wang LP, Yang Y, Fang LQ, Liu W. Changes in notifiable infectious disease incidence in China during the COVID-19 pandemic, Nat Commun 2021;12:6923. https://doi.org/10.1038/s41467-021-27292-7.

[32] Ullrich A, Schranz M, Rexroth U, Hamouda O, Schaade L, Diercke M, Boender TS; Robert Koch's Infectious Disease Surveillance Group. Impact of the COVID-19 pandemic and associated non-pharmaceutical interventions on other notifiable infectious diseases in Germany: An analysis of national surveillance data during week 1-2016 - week 32-2020. Lancet Reg Health Eur 2021;6:100103. https://doi.org/10.1016/j.lanepe.2021.100103.

[33] Sohail A, Cheng AC, McGuinness SL, Leder K. The epidemiology of notifiable diseases in Australia and the impact of the COVID-19 pandemic, 2012–2022. BMC Global and Public Health 2024;2:1. https://doi.org/10.1186/s44263-023-00029-y.

[34] Redlberger-Fritz M, Kundi M, Aberle SW, Puchhammer-Stöckl E. Significant impact of nationwide SARS-CoV-2 lockdown measures on the circulation of other respiratory virus infections in Austria. J Clin Virol 2021;137:104795. https://doi.org/10.1016/j.jcv.2021.104795.

[35] Nash K, Lai J, Sandhu K, Chandan JS, Shantikumar S, Ogunlayi F, Coleman PC. Impact of national COVID-19 restrictions on incidence of notifiable communicable diseases in England: an interrupted time series analysis. BMC Public Health 2022;22:2318. https://doi.org/10.1186/s12889-022-14796-0.

[36] Li H, Ling F, Zhang S, Liu Y, Wang C, Lin H, Sun J, Wu Y. Comparison of 19 major infectious diseases during COVID-19 epidemic and previous years in Zhejiang, implications for prevention measures. BMC Infect Dis 2022;22:296. https://doi.org/10.1186/s12879-022-07301-w.

[37] van de Berg S, Charles T, Dörre A, Katz K, Böhm S. Epidemiology of common infectious diseases before and during the COVID-19 pandemic in Bavaria, Germany, 2016 to 2021: an analysis of routine surveillance data. Euro Surveill 2023;28:2300030. https://doi.org/10.2807/1560-7917.ES.2023.28.41.2300030.

[38] Hayes LJ, Uri H, Bojkova D, Cinatl J Jr, Wass MN, Michaelis M. Impact of the COVID-19 pandemic on the circulation

of other pathogens in England. J Med Virol 2023;95:e28401. https://doi.org/10.1002/jmv.28401.

[39] Komori A, Mori H, Naito T. The impact of the COVID-19 pandemic on other infections differs by their route of transmission: A retrospective, observational study in Japan. J Infect Chemother 2022;28:1700-3. https://doi.org/10.1016/j.jiac.2022.08.02.

[40] Hirae K, Hoshina T, Koga H. Impact of the COVID-19 pandemic on the epidemiology of other communicable diseases in Japan. International Journal of Infectious Diseases 2023;128: 265-271. https://doi.org/10.1016/j.ijid.2023.01.013.

[41] Facciolà A, Laganà A, Genovese G, Romeo B, Sidoti S, D'Andrea G, Raco C, Visalli G, DI Pietro A. Impact of the COVID-19 pandemic on the infectious disease epidemiology. J Prev Med Hyg 2023;64:E274-82. https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2904.

[42] Rotulo GA, Percivale B, Molteni M, Naim A, Brisca G, Piccotti E, Castagnola E. The impact of COVID-19 lockdown on infectious diseases epidemiology: The experience of a tertiary Italian Pediatric Emergency Department. Am J Emerg Med 2021;43:115-7. https://doi.org/10.1016/j.ajem.2021.01.065.

[43] Facchin G, Bella A, Del Manso M, Rota MC, Filia A. Decline in reported measles cases in Italy in the COVID-19 era, January 2020 - July 2022: The need to prevent a resurgence upon lifting non-pharmaceutical pandemic measures. Vaccine 2023;41:1286-9. https://doi.org/10.1016/j.vaccine.2023.01.021.

[44] Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, Guedj R, Soussan-Banini V, Basmaci R, Lefevre-Utile A, Brun-Ney D, Beaujouan L, Skurnik D. Coronavirus Disease 2019 Pandemic: impact caused by school closure and national lockdown on pediatric visits and admissions for viral and nonviral infections-a time series analysis. Clin Infect Dis 2021;72:319-22. https://doi.org/10.1093/cid/ciaa710.

[45] Hatoun J, Correa ET, Donahue SMA, Vernacchio L. Social Distancing for COVID-19 and diagnoses of other infectious diseases in children. Pediatrics 2020:146. https://doi.org/10.1542/peds.2020-006460.

[46] Xiao J, Dai J, Hu J, Liu T, Gong D, Li X, Kang M, Zhou Y, Li Y, Quan Y, He G, Zhong R, Zhu Z, Huang Q, Zhang Y, Huang J, Du Q, Li Y, Song T, Hu W, Zhong H, Ma W. Co-benefits of nonpharmaceutical intervention against COVID-19 on infectious diseases in China: A large population-based observational study. Lancet Reg Health West Pac 2021;17:100282. https://doi.org/10.1016/j.lanwpc.2021.100282.

[47] Lai CC, Chen SY, Yen MY, Lee PI, Ko WC, Hsueh PR. The impact of the coronavirus disease 2019 epidemic on notifiable infectious diseases in Taiwan: S database analysis. Travel Med Infect Dis 2021;40:101997. https://doi.org/10.1016/j.tmaid.2021.101997.

[48] Bright A, Glynn-Robinson AJ, Kane S, Wright R, Saul N. The effect of COVID-19 public health measures on nationally notifiable diseases in Australia: preliminary analysis. Commun Dis Intell 2020;44. https://doi.org/10.33321/cdi.2020.44.85.

[49] Sullivan SG, Carlson S, Cheng AC, Chilver MB, Dwyer DE, Irwin M, Kok J, Macartney K, MacLachlan J, Minney-Smith C, Smith D, Stocks N, Taylor J, Barr IG. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. Euro Surveill 2020;25:2001847. https://doi.org/10.2807/1560-7917.ES.2020.25.47.2001847.

[50] Gibbons CL, Mangen MJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, Peterson KL, Stuurman AL, Cassini A, Fèvre EM, Kretzschmar ME; Burden of Communicable diseases in Europe (BCoDE) consortium. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC Public Health 2014;14:147. https://doi.org/10.1186/1471-2458-14-147.

[51] Charlton CL, Hull N, Sloma CR, Bonifas M, Johnson M, Strain AK, Wolford T, Staley S, Perkins C, Razzaque R, Courtney C, Bind EP. How To Prepare for the Unexpected: a Public Health Laboratory Response. Clin Microbiol Rev 2021;34:e00183-20. https://doi.org/10.1128/CMR.00183-20.

[52] A Monthly Bulletin on Epidemiology and Public Health Practice in Washington. epiTRENS 2021:26. Available at: https://doh.wa.gov/sites/default/files/legacy/Documents/5100//420-002-epitrends2021-01.pdf (Accessed on: 28/01/2024).

[53] Australian Institute of Health and Welfare (2022) Infectious and communicable diseases, AIHW, Australian Government. Available at: https://www.aihw.gov.au/reports/australias-health/infectious-and-communicable-diseases (Accessed on: 28/01/2024).

[54] Simonsen L, Gog JR, Olson D, Viboud C. Infectious disease surveillance in the big data era: towards faster and locally relevant systems. J Infect Dis 2016;214:S380-5. https://doi.org/10.1093/infdis/jiw376.

[55] Ibrahim NK. Epidemiologic surveillance for controlling COVID-19 pandemic: types, challenges and implications. J Infect Public Health 2020;13:1630-8. https://doi.org/10.1016/j.jiph.2020.07.019.

[56] de Lusignan S, Lopez Bernal J, Zambon M, Akinyemi O, Amirthalingam G, Andrews N, Borrow R, Byford R, Charlett A, Dabrera G, Ellis J, Elliot AJ, Feher M, Ferreira F, Krajenbrink E, Leach J, Linley E, Liyanage H, Okusi C, Ramsay M, Smith G, Sherlock J, Thomas N, Tripathy M, Williams J, Howsam G, Joy M, Hobbs R. Emergence of a Novel Coronavirus (COVID-19): Protocol for Extending Surveillance Used by the Royal College of General Practitioners Research and Surveillance Centre and Public Health England. JMIR Public Health Surveill 2020;6:e18606. https://doi.org/10.2196/18606.

[57] Sakib MN, Butt ZA, Morita PP, Oremus M, Fong GT, Hall PA. Considerations for an individual-level population notification system for pandemic response: a review and prototype. J Med Internet Res 2020;22:e19930. https://doi.org/10.2196/19930. Erratum in: J Med Internet Res 2020;22:e21634.

[58] Adebisi YA, Rabe A, Lucero-Prisno Iii DE. COVID-19 surveillance systems in African countries. Health Promot Perspect 2021;11:382-92. https://doi.org/10.34172/hpp.2021.49.

[59] Future surveillance for epidemic and pandemic diseases: a 2023 perspective. Geneva: World Health Organization 2023. Available at: https://iris.who.int/bitstream/handle/10665/374992/9789240080959-eng.pdf?sequence=1 (Accessed on: 07/02/2024).

[60] World Health Organization. Rapid review of WHO COVID-19 surveillance: External review, 27 October 2021. Geneva: WHO 2021. Available at: https://cdn.who.int/media/docs/default-source/2021-dha-docs/rapid-review-of-who-COVID-19-surveillance.pdf?sfvrsn=a640902c_1&download=true (Accessed on: 07/02/2024).

Received on February 9, 2024. Accepted on May 20, 2024.

Correspondence: Fabio Contarino, Epidemiology Unit, Department of Public Health, Siracusa Local Health Authority, Traversa la Pizzuta snc, Siracusa, 96100, Italy. E-mail: fabio.contarino@asp.sr.it

How to cite this article: Contarino F, Bella F, Di Pietro E,, Randazzo C, Contrino ML. Impact of the COVID-19 pandemic on infectious diseases reporting. J Prev Med Hyg 2024;65:E145-E153. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3197

COVID-19

The impact of SARS-CoV-2 on emergency health care demand: inverse relationship between COVID-like illnesses and ED accesses in Genoa, Italy

ALLEGRA FERRARI[1], GIOVANNA IUDICA[1], MARTINA PORRETTO[1], CAROLA MINET[1], MATILDE OGLIASTRO[1], DAVIDE SIMONETTA[1], STEFANO MOSCA[2], GIANCARLO ICARDI[1,2,3], ANDREA ORSI[1,2,3]
[1] Department of Health Sciences (DISSAL), University of Genoa; [2] Interuniversity Research Centre on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy; [3] IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Keywords

SARS-CoV-2 • COVID-19 • ARI • Syndromic surveillance • Epidemiological surveillance • Emergency department • ED

Summary

Introduction. *SARS-CoV-2 has changed the demand for in-person health care. The aim of this study was to retrospectively analyzed data on access to San Martino Hospital Emergency Department (ED), Genoa, Italy, during the COVID-19 pandemic.*
Methods. *Descriptive statistics for 180,117 records of patients accessing the ED between 2019 and 2021 were reported. A linear regression model was built to evaluate the relationship between the weekly number of COVID-like illness cases and ED attendances.*
Results. *In comparison to pre-pandemic levels, the median number of ED visits declined by 41.6% in 2020 and by 27.4% in 2021. The period of maximum drop in access (-61.9%) was the 2020 12-16th calendar weeks and coincided with the highest rates of COVID-like illness cases (+360%; 22.8% of total ED attendances). About 20% of the variation of the weekly number of ED attendances was explained by the number of COVID-like illness cases. In 2020 and 2021 non-urgent ED codes decreased (-6.7%; -7.3%) and both urgent and emergency ED codes increased (+4.8% and +3.9% the first; +1.9% and +3.5% the second). However, the absolute number of ED access fell drastically for all codes. In particular, the highest increase was registered in 2020 for acute respiratory infections (ARI), including COVID-19 (+3.28%), while traumas and eye diseases saw the highest decrease (-1.02%; -3.80%).*
Conclusions. *While the reduction in non-urgent visits suggests avoidable pre-pandemic access levels, the decline in non-COVID-19 urgent accesses potentially points to an increase in delayed and missed care.*

Introduction

Over the past two decades, the number of visits to emergency departments (ED) has increased overall in almost all the Organization for Economic Co-operation and Development (OECD) countries, switching from 29.3 visits per 100 population in 2001 to 30.8 visits per 100 population in 2011 (+5.2%). Even so, a year-on-year analysis, reveals no consistent growth trend [1]. For instance, while between 2009 and 2010 the number of ED visits increased by 4% in France and 2% in Australia, it also decreased by 12% in Ireland and 1.5% in Italy [1, 2]. More recently, also a report of the United States (US) Department of Health & Human Services indicated that between 2009 and 2018, the proportion of ED visits in the American hospitals remained relatively stable [3].
Variability in ED visits across and within countries over time is associated with various factors. Any occurrence that disrupts normal living conditions within a community (*e.g.* extremely cold or hot weather conditions, floods, earthquakes, conflicts) has the power to modify people health needs. Likewise, the seasonal circulation of microbes (*e.g.* epidemic and pandemic influenza) can impact emergency care. Since its first appearance at the end of 2019, the COVID-19 pandemic, caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has drastically transformed the demand for healthcare services. As of May 2023, when the World Health Organization (WHO) has declared the end of the COVID-19 pandemic as a public health emergency, SARS-CoV-2 had caused over 750 million cases of respiratory infections and 6.5 million deaths worldwide [4]. Of these, over 25 million cases of respiratory infections and 190.000 deaths occurred in Italy [5].
Contradicting previous observations of ED overcrowding during seasonal influenza epidemics [6], a systematic review of 81 studies estimated that, in comparison with pre-pandemic levels, health services worldwide have reported a median 37% reduction in services overall. These comprised median reductions for visits of 42%, admissions of 28%, diagnostics of 31%, and therapeutics of 30% [7]. The use of emergency healthcare services, in particular, decreased significantly, with reports of drop in ED admissions up to 50% in England [8] and Italy [9], 42% in USA [10], 41% in Greece [11] and 38% in Germany [12].
Especially during the first wave of the pandemic, Italy was one of the most hard-hit countries [13]. IRCCS San Martino Hospital, Genoa, Liguria Region (Northwest Italy) is the referral tertiary acute-care center in its

 https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3279

region. Although, during the pandemic, San Martino Hospital did not undergo major organizational changes (*e.g.* only limited numbers of healthcare workers were hired or fired; no additional ED opened or closed), except for those necessary for the safe admission of patients with COVID-19 (*e.g.* partition of COVID-19 wards and COVID-19 free wards) the number of ED visits and admissions fell drastically, especially during the months of full lockdown (March-June 2020).

Decline in access to emergency care services can result in missed and delayed diagnoses that, in addition to deaths from COVID-19, have translated, since the beginning of the pandemic, in higher rates of all-cause excess mortality worldwide [14]. An increase in out-of-hospital cardiac arrests, as well as a relative reduction in the execution of primary percutaneous coronary interventions, have been reported in many affected countries [15-17]. Cancer deaths are also expected to increase substantially in the upcoming years [18].

Since the decline in access to in-person health care implies elevated health, social and economic costs, it is vital to describe the effect of the pandemic trends on emergency care services and quantify their impact. To this end, in this study, over 180,000 records of patients accessing San Martino Hospital ED between 2019 and 2021 were analyzed and evaluated.

Materials and methods

Study design, setting and population

In this study we retrospectively analyzed electronic medical records (EMRs) collected at the emergency department (ED) of IRCCS San Martino Hospital between 2019 (pre-pandemic reference year) and 2020-2021 (two consecutive pandemic years).

San Martino Hospital is a IRCCS or "Scientific Hospital and Care Institute" of national importance with high standards for both scientific production activities and specialized clinical care services. Being the referral tertiary acute-care center in the Liguria region, San Martino Hospital has the largest catchment area in the metropolitan area of Genoa where over 675,000 individuals live. Hosting more than 1,200 beds and 70 medical wards, the average number of accesses to the emergency department is about 78,000 people (range of 56,000-87,000 between 2014 and 2021) per year.

With regards to the pediatric age, San Martino Hospital has a birth center, however, it is not the referral hospital for children. As a consequence, only a small number of individuals under the age of 18 years old are treated here.

Data source and study variables

EMRs of emergency room visits occurred between January 1st, 2019 and December 31th, 2021 and collected through the hospital information system (HIS) were manually extracted and analyzed. 202,578 records of patients that, during the study period, visited the ED were retrieved. Records of patients which abandoned or were removed from the ED before receival of an International Classification of Diseases - 9th revision (ICD-9) code diagnosis (14,429), those diagnosed with either an E or V (external causes of injury and supplemental classification) ICD-9 code (5,087), and those with either an incomplete or incorrect ICD-9 code (2,945) were excluded. Finally, 180,117 records were analyzed.

Each EMR contains demographic, administrative and clinical information (presenting symptoms, medical history, emergency color code, diagnosis and inpatient ward).

Attendances were counted by week, year and stratified by several variables: sex (male, female, not known), age group (0-17,18-64, ≥ 65), triage severity (non-urgent, urgent, emergency), primary diagnosis and ward of admission.

It should be noted that the triage severity categories (non-urgent, urgent, emergency), were established based on the actual color codes used during triage at San Martino Hospital's Emergency Department. These categories correspond to specific colors: white and green (non-urgent and minor urgency, respectively), orange and blue (urgency and deferrable urgency, respectively), and red (emergency).

Furthermore, considering the communal clinical features among different causes of illness, primary diagnoses identified by ICD-9 codes were grouped into clinically meaningful disease categories during a brainstorming session between four medical residents in Hygiene and Preventive medicine (AF, GI, MP, DS). Finally, 13,844 ICD-9 codes, including special codes later introduced to identify COVID-19 cases (04311, 04312, 04321, 04322, 04331, 04332, 48041, 48042, 51971, 51972, 51891, 51892) were grouped into 23 disease categories. In order to analyze inpatient admissions, 117 hospital units were grouped into 26 main medical wards.

Because of the initial absence, during the first months of 2020, of readily available laboratory diagnostic tests for SARS-CoV-2, as well as specific ICD-9 diagnostic codes for COVID-19, COVID-like illness cases – defined as either influenza-like illness (ILI) or lower respiratory tract infection (LRTI) cases identified through an operator dependent syndromic surveillance system – were preferred to ICD-9 codes as the most accurate proxy to evaluate the pandemic trends.

In the pre-pandemic time, an annual average of 430 cases of ILI and 1200 cases of LRTI were identified at San Martino Hospital through the syndromic surveillance system. This system is based on a two-steps screening procedure: the first is automated and uses catchment keywords such as "cough", "sore throat", "fever", "cold", "nasal congestion", "respiratory distress", "dyspnea" to select potential records of patients presenting with an acute respiratory infection (ARI); the second is carried out, on a daily basis, by a medical provider that by reading the complete ED record, including radiology reports, classifies the event as either "ILI", "LRTI" or "other".

Tab. I. Characteristics of emergency department visits across considered years (2019-2021).

	2019 (ref.)	2020	2021
Number of visits, n	76269	50053	53795
Visits per day, n (range)	209 (151-278)	143 (20-246)	151 (36-215)
Visits per week, n (range)	1465 (1371-1623)	1007 (402-1485)	1059 (290-1299)
Number of admissions, n	18290	14833	14294
Sex, n (%)			
Female	40060 (52.52)	25367 (50.68)	27720 (51.52)
Male	36209 (47.47)	24686 (49.31)	26073 (48.46)
Not known	0 (0)	0 (0)	2 (0.003)
Age group, n (%)			
0-17	2394 (3.13)	1150 (2.29)	1579 (2.93)
18-64	43542 (57.09)	28926 (57.79)	31814 (59.13)
≥ 65	30333 (39.77)	19977 (39.91)	20402 (37.92)
Severity at triage, n (%)			
Not urgent	3858 (5.05)	3502 (6.99)	4584 (8.52)
Urgent	47509 (62.29)	27824 (55.58)	29429 (54.70)
Emergency	24902 (32.65)	18727 (37.41)	19578 (36.39)

In our study, we present data related to both the syndromic surveillance of COVID-like illness cases (Section "COVID-like illness") and data related to ICD-9 codes assigned to patients accessing the ED (Section "Clinical diagnosis").

Statistical Analysis

Descriptive statistics were reported as median and range for continuous variables, and proportion and percentage for categorical variables.

A linear regression model with the weekly number of COVID-like illness cases as the independent variable and the weekly number of overall ED visits as dependent variable was performed. The results are presented as adjusted R squared (R^2) and p values. When the p-value was < 0.05, the difference was regarded as statistically significant.

Statistical analyses and data cleaning were performed using KNIME Analytics Platform version 4.6.0 (University of Konstanz, Zurich, Switzerland) and Microsoft Excel version 16.52 (Microsoft Corporation, USA).

Results

In comparison to 2019 (ref.), 2020 e 2021 saw a substantial reduction in the number of ED visits. This reduction in attendances was also seen in subgroups based on sex, age group, triage severity and inpatient admission (Tab. I).

COVID-like illness

Following the introduction of social distancing measures (March 9th-11th calendar week), in comparison with the pre-pandemic era - during which the median number of ED visits was 208 per day (range of 82-278) - the median number of ED visits declined by 41.6% [median ED visits 121.5 per day (range of 20-214)] in 2020 and by 27.4% [median ED visits 151 per day (range of 36-215)] in 2021.

The period of maximum drop in accesses (-61.9%) [median ED visits 79 per day (range of 50-110)] corresponded to the 2020 12-16th calendar weeks and coincided with the highest rates of COVID-like illness – defined as either ILI or LRTI cases – identified through an operator dependent syndromic surveillance system (+360%; 22.8% of total ED attendances) [median COVID-like illness cases 18 per day (range of 4-46)].

Figure 1 shows the trends of ED attendances with respect to the total number of ED episodes (blue line), the total number of COVID-like illness cases (orange line) and the proportion of COVID-like illness cases (grey line) registered between November 1st, 2019 and December 31th, 2021.

ILI in particular, rose from a median of 2 to 3 cases per day (range 1-14) (+150%), and LRTI rose from a median of 4 to 16 cases per day (range 2-37) (+400%).

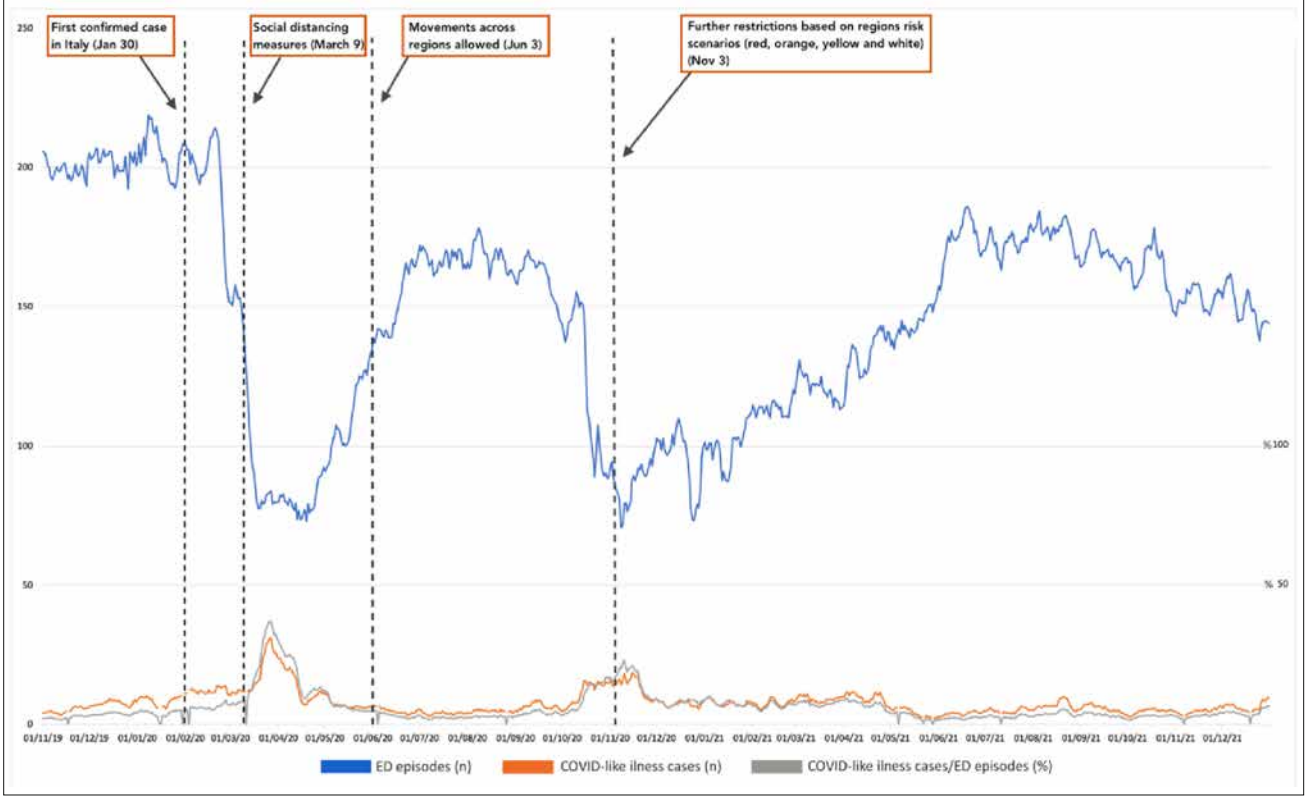
Table II shows the characteristics of COVID-like patients that were evaluated as either ILI or LRTI cases during the study period.

In order to describe the relationship between the number of people presenting with COVID-like illness and ED attendances, a linear regression was performed. The model showed that when COVID-like illness cases increased, the overall number of ED visits at San Martino Hospital decreased (negative gradient). Adjusted R squared (R^2) was 0.20 [standard error (SE) 282.09; p value < 0.001]. In other words, about 20% of the variation of the weekly number of ED attendances (dependent variable Y) was explained by the number of COVID-like illness cases (independent variable X) (Fig. 2).

Triage severity codes

In terms of relative impact, compared with the total number of ED accesses in 2019, in 2020 and 2021 non-urgent ED codes decreased (-6.7% and -7.3%)

Fig. 1. Trends of ED attendances between November 1st, 2019 and December 31th, 2021 (moving average).



Tab. II. COVID-like illness (ILI and LRTI) cases stratified by sex and age group, n (%).

COVID-like illness	Sex	Age group	2019 (ref.) (n, %)	2020 (n, %)	2021 (n, %)
ILI	F	0-17	3 (0.15)	2 (0.05)	1 (0.04)
		18-64	210 (10.86)	323 (9.65)	183 (8.20)
		≥ 65	540 (27.93)	712 (21.27)	544 (24.39)
	M	0-17	6 (0.31)	4 (0.11)	2 (0.08)
		18-64	236 (12.20)	479 (14.31)	314 (14.08)
		≥ 65	555 (28.71)	863 (25.79)	604 (27.08)
LRTI	F	0-17	9 (0.46)	11 (0.32)	7 (0.31)
		18-64	139 (7.19)	280 (8.36)	203 (9.10)
		≥65	58 (3.00)	165 (4.93)	78 (3.49)
	M	0-17	7 (0.36)	14 (0.41)	7 (0.31)
		18-64	120 (6.20)	302 (9.02)	209 (9.37)
		≥65	50 (2.58)	191 (5.70)	78 (3.49)
Tot.			1993 (100)	3346 (100)	2230 (100)

and both urgent and emergency ED codes increased (+4.8% and +3.9% the first; +1.9% and +3.5% the second). Even so, the overall absolute number of ED access fell drastically, especially for non-urgent and urgent codes. The former, in particular, experienced the most severe decrease, shifting from a pre-pandemic value of 47,509 to 27,824 (-19,685) in 2020 and 29,429 (-18,080) in 2021. The latter decreased by 6,175 in 2020 and 5,324 in 2021. Emergency codes decreased by 356 in 2020 and increased by 726 in 2021.

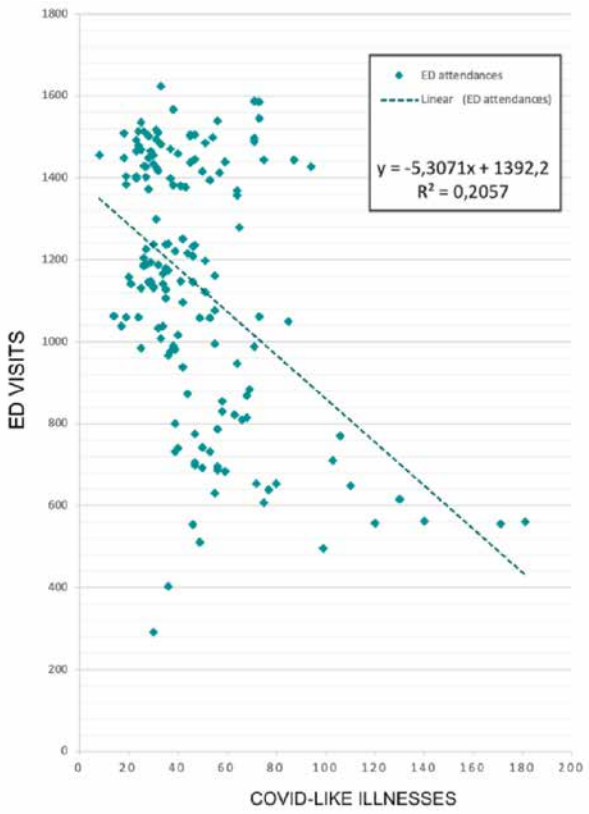
Figure 3 shows the trend of ED attendances with respect to different triage severity codes registered between 2019 and 2021 at San Martino Hospital.

Table III shows the characteristics of patients that, during the study period, were assigned a triage code.

With regards to patients' characteristics, in 2020 and 2021, elderly aged ≥ 65 and males visiting the ED tended to be assigned more often with severity codes that identify severe conditions.

In particular, in 2020, the rate of urgent codes rose by about 1.60% among both males aged 18-64 and ≥ 65. This trend was partially maintained in 2021, which saw a continuous rise in the proportion of adult males (age 18-

Fig. 2. Relationship between the number of people presenting with COVID-like illness and ED attendances on a weekly basis.



64) assigned with an urgent code (+1.69%). With regards to emergency codes, during the study period their rate saw a considerable increase among both male and female elderly (+0.60% in 2020 and +1.10% in 2021).

Clinical diagnosis

With regards to ICD-9 diagnoses, in 2020, acute respiratory infections (ARI), including COVID-19, saw the highest increase (+3.28%) while traumas and eye diseases saw the highest decrease (-1.02% and -3.80%, respectively).

The rise in ARI was maintained in 2021, during which the percentage of people who received this diagnosis was 1.52% higher than in 2019.

In terms of absolute numbers, ARI went from 1,664 in 2019 to 2,736 in 2020 and 1,995 in 2021. Among them, 1,468 and 1,254 persons, in 2020 and 2021 respectively, were diagnosed with a COVID-19 code.

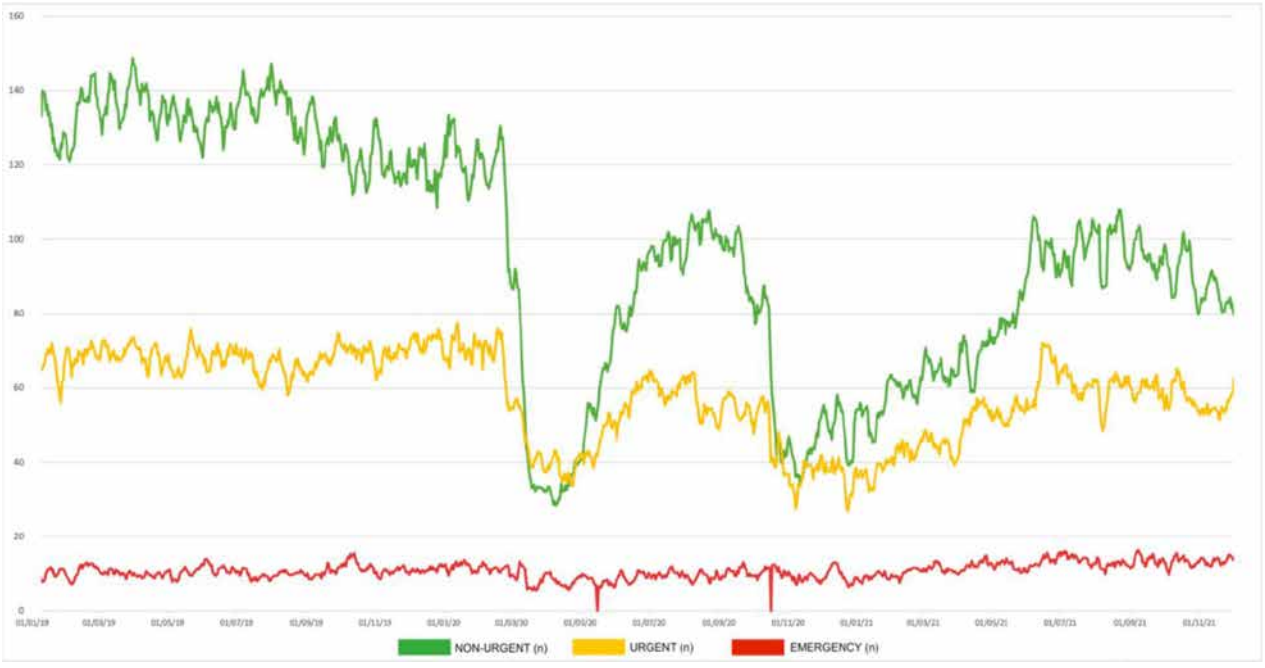
Interestingly, despite not being a referral care center for the pediatric age, the second largest relative increase was observed in the percentage of complications of pregnancy, congenital and growth disease (+1.50% in 2020 and 1.49% in 2021).

A rise was also noticed in the rates of unspecified malaise and fatigue (+1.47% in 2020 and 1.02% in 2021) and thromboembolic and cerebrovascular events (+1.04% in 2020 and 0.60% in 2021).

Being San Martino Hospital an IRCCS with special attention to oncological care, it is interesting to note a slight relative increase in access for oncological conditions of +0.22% in 2020 and +0.25% in 2021. Furthermore, with regards to accesses for mental health, there was a slight increase of +0.09% in access for mental disorders and +0.04% for substance use in 2020, which was not maintained in 2021.

Although the admissions of the elderly, in comparison to adults, being routinely lower, this category experienced the greatest increase in accesses for ARI. Over the total number of patients diagnosed with an acute respiratory infection, in 2020 and 2021, respectively, the rate of ARI

Fig. 3. Trend of ED attendances with respect to the proportion of different triage codes (moving average).



Tab. III. ED attendees stratified by triage severity, sex and age group.

Triage severity	Sex	Age group	2019 (ref.) (n, %)	2020 (n, %)	2021 (n, %)
Non-urgent	F	0-17	809 (1.06)	362 (0.72)	431 (0.80)
		18-64	16582 (21.74)	10042 (20.06)	10934 (20.40)
		≥ 65	7890 (10.34)	4057 (8.10)	3988 (7.44)
	M	0-17	1074 (1.40)	467 (0.93)	754 (1.40)
		18-64	15156 (19.87)	9578 (19.13)	10140 (18.92)
		≥ 65	5998 (7.86)	3318 (6.62)	3182 (5.93)
Urgent	F	0-17	221 (0.28)	137 (0.27)	134 (0.25)
		18-64	5157 (6.76)	3796 (7.58)	4448 (8.29)
		≥ 65	7619 (9.98)	5368 (10.72)	5548 (10.35)
	M	0-17	238 (0.31)	142 (0.28)	202 (0.37)
		18-64	5380 (7.05)	4353 (8.69)	4686 (8.7)
		≥ 65	6287 (8.24)	4931 (9.85)	4558 (8.50)
	NA	≥ 65	0 (0)	0 (0)	2 (0.01)
Emergency	F	0-17	17 (0.02)	15 (0.02)	27 (0.05)
		18-64	485 (0.63)	446 (0.89)	564 (1.05)
		≥ 65	1280 (1.67)	1144 (2.28)	1542 (2.87)
	M	0-17	35 (0.04)	27 (0.05)	29 (0.05)
		18-64	782 (1.02)	711 (1.42)	927 (1.72)
		≥65	1259 (1.65)	1159 (2.31)	1495 (2.78)
Tot.			76269 (100)	50053 (100)	53591 (100)

rose by 6.44% and 3.11% among males ≥65, and by 2.68% and 2.04% among females ≥ 65.

Hospital admissions

Out of 180,117 individuals accessing the ED between 2019 and 2021, 47,417 were admitted as inpatients. In comparison with 2019, hospital admissions went from 18646 to 14972 in 2020 and 14308 in 2021 (-19.7% and -23.3% in 2020 and in 2021, respectively).

The most significant reduction was observed in the rate of patients admitted to the emergency medicine ward (-12.05% in 2020 and 18.74% in 2021), which can likely be explained by the overall reduction in the number of people visiting the ED. By contrast, a larger proportion of patients was admitted to the wards of internal medicine (+6.11% in 2020 and 5.95% in 2021), orthopedics and traumatology (+2.13% in 2020 and 1.31% in 2021), obstetrics and gynecology (+1.97% in 2020 and 1.73% in

Fig. 4. Proportion of diagnoses in each disease category between 2019 and 2021.

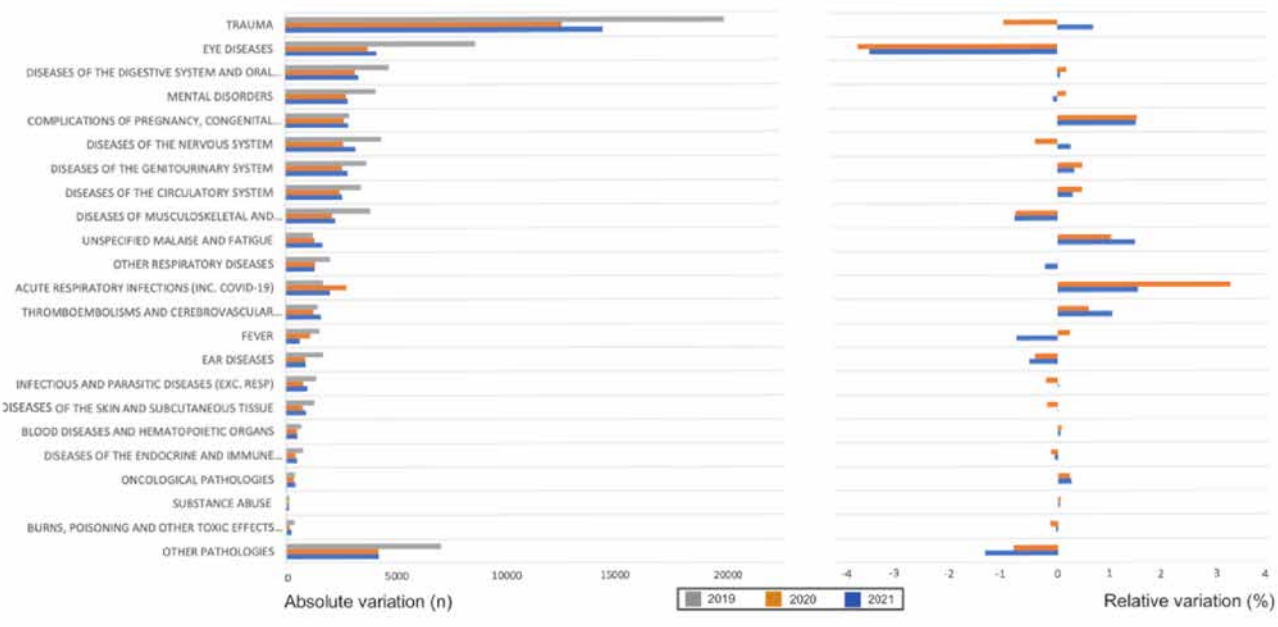
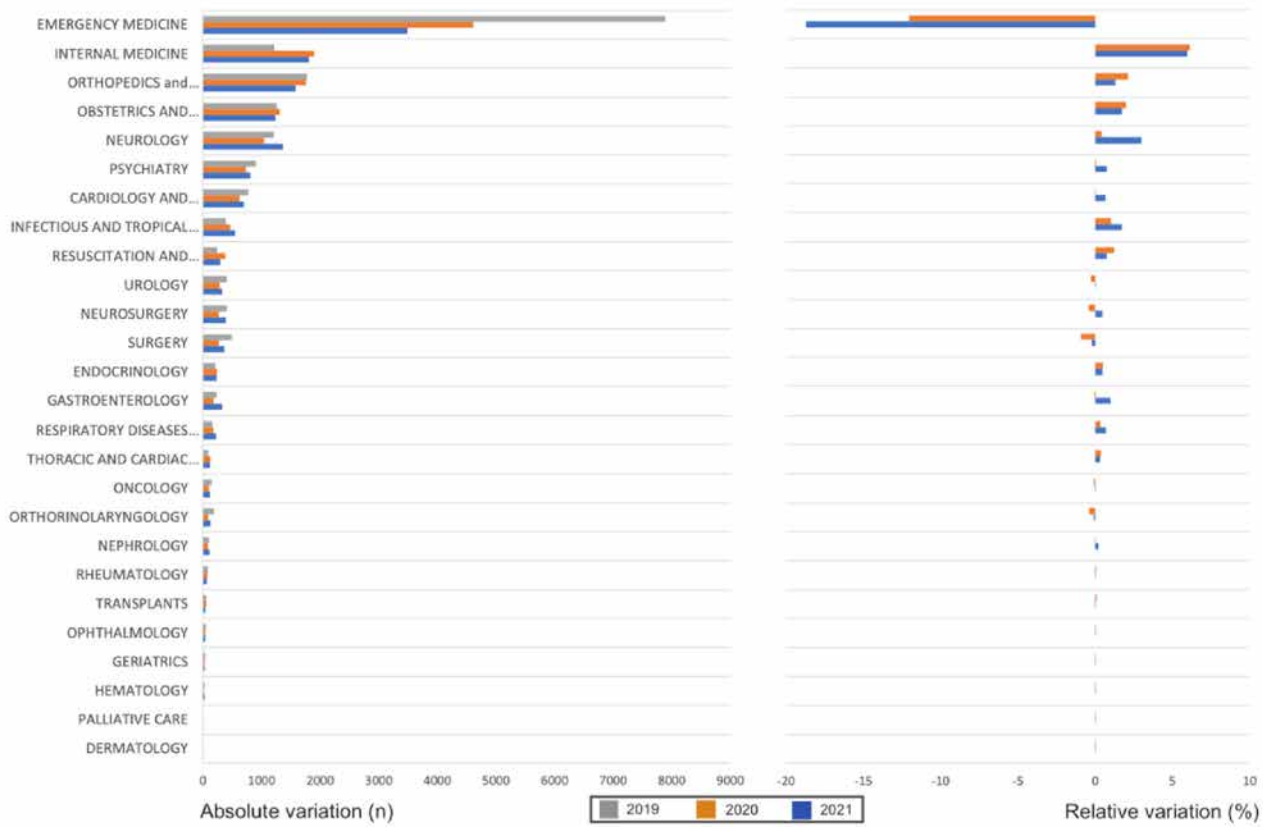


Fig. 5. Proportion of patients admitted to different hospital wards between 2019 and 2021.



2021). Notably, in 2021, the neurology ward recorded a significant increase in the proportion of hospitalizations (+2.96%).

Admissions at infectious and tropical diseases, where a large proportion of COVID-19 patients were treated, increased by 1.03% in 2020 and 1.72% in 2021. Finally, admissions to the resuscitation and intensive care unit grew by 0.31% in 2020 and 1.42% in 2021.

Figure 5 shows the variation in the proportion of patients that, during the study period, were admitted to a hospital ward. The extended figures for Figure 5 are reported in supplementary materials.

Discussion

Principal results

In comparison with the pre-pandemic era, ED visits at San Martino Hospital declined by 41.6% and 27.4% in 2020 and 2021, respectively. During the period of maximum drop in accesses, COVID-like illness cases accounted for 22.8% of total ED attendances. The linear regression model showed that about 20% of the decline in the weekly number of ED attendances was explained by the rise of COVID-like illness cases.

Overall, there were fewer ED visits across all triage severity codes, with non-urgent ED codes decreasing the most. In terms of relative impact, however, non-urgent codes decreased (-6.7% and -7.3%, respectively), while both urgent and emergency codes increased (+4.8% and +3.9% the former; +1.9% and +3.5% the latter). Elderly and males tended to be assigned more often with triage severity codes that identify severe conditions (urgent and emergency).

In 2020 and 2021, 1,468 and 1,254 individuals were diagnosed with a COVID-19 code. Overall, acute respiratory infections increased by 3.28% in 2020 and 1.52% in 2021 and admissions at infectious and tropical diseases increased by 1.03% in 2020 and 1.72% in 2021.

Comparison with previous studies

Our results substantiate with those of several authors [8–10, 12, 19, 20. For example, Slagman et al. reported that, in 43 emergency departments in Germany, in 2020, calendar week 14th was the period of maximum drop in accesses (-38%) and coincided with the highest number of COVID-19 cases [12]. At San Martino Hospital, the period between the 12th and the 16th calendar week of 2020 represented the period of maximum drop in accesses (-61.9%) and coincided with the highest number of COVID-like illness cases (+360%). A reduction in non-urgent triage codes, in most cases complemented by a shift towards higher priority triage codes, was observed in Northen Italy by Bellan et al. [20] and Giostra et al. [9], in UK by Wyatt et al. [8] and Reschen et al. [19] and in Germany by Slagman et al. [12]. We observed an overall reduction in all severity

triage categories which, in relative terms, translated in a substantial decline in non-urgent codes and a raise in urgent and emergency codes. Analogously to our findings, Reschen et al. observed that traumatic causes of ED visits saw a consistent decline, while respiratory diseases (including COVID-19) were the only clinical category to not fall significantly during the first wave of the pandemic [19]. A substantial decline in traumatic causes of ED visits was also reported by Slagman et al. [12] and Giostra et al. [9]. The overall reduction in ED accesses during the COVID-19 pandemic may partially be explained by fear of acquiring COVID-19 whilst in hospital. This hypothesis is supported by the results of surveys conducted by the Irish Cardiac Society and the British Heart Foundation indicating that fear of being exposed to COVID-19 was the reason mostly frequently reported for the decrease in acute coronary syndromes admissions, followed by concerns of burdening the healthcare system, as well as lockdown measures and movement restrictions [17].

In Italy, during the first wave of the pandemic, strict emergency measures including the closing of all non-essential businesses and industries and the restriction of people's movement have been in place since March 9th and only gradually eased until June 3rd, when movement across regions and other European countries was restored.

In autumn, the second wave of the pandemic also brought the Italian government to introduce further restrictions on movement and social life, which were gradually lifted in mid-2021. These forced changes in lifestyle may also have concurred to a decline in the number of medical emergencies, explaining the reduction in ED visits for non-COVID-19 causes of illness [21].

For instance, it is generally known that unusual physical exertion can frequently lead to myocardial infarction [22]. Occasions for extraordinary physical efforts, however, have appreciably been reduced because of the social distancing measures. Moreover, restrictions of travel reduced road traffic movements. It should also be noted that Liguria is a touristic region, and the pandemic led to a sharp decline in tourist flow [23]. Fewer tourists meant fewer instances of travel-related incidents and health issues requiring emergency attention. In this regard, a recent review on the effects of the pandemic on road traffic collisions (RTCs) has shown that the drop of traffic volume was associated with a significant drop in RTCs globally and a reduction of road deaths up to 50% [24].

On the other hand, it should be considered that the overall reduction in the absolute number of people presenting with severe non-COVID-19 related diseases potentially points to an increase in delayed or missed opportunities to treat conditions leading to avoidable morbidity and mortality. In fact, along with the sudden drop of ED visits and hospitalizations, there was an increase out-of-hospital all-cause mortality, mainly driven by an increase in deaths for neoplasms, cardiovascular diseases and endocrine, nutritional and metabolic diseases [25]. As others have suggested [7], our findings provide compelling evidence in favor of giving priority to initiatives that cater to the unmet needs of people with non-COVID-19 illnesses. Finally, the important reduction in ED attendances for non-urgent complaints indicates that the high pre-pandemic access levels may have partially been avoidable. This evidence provides an opportunity to inform and implement new paradigms of care that maximize the appropriateness of future ED visits while simultaneously preventing overdiagnosis and overtreatment [26]

Strengths and limitations

This study presents some limitations. First, while for this analysis two pandemic years were considered, these were compared with only one pre-pandemic year. Second, our study is largely based on ICD-9 code diagnoses. Often, the complete diagnosis comprises more than one code. However, for each record only the first code, considered to be the main one, was extracted. Secondly, although other authors have employed laboratory confirmed SARS-CoV-2 to estimate the impact of COVID-19 on emergency care trends, especially during the first wave of the pandemic this information was not available nor complete in a relevant number of ED records. For this reason, we decided to employ a clinical proxy measure, COVID-like illness rates. In general, this is an analysis of aggregated routine administrative data extracted from San Martino Hospital HIS. Even though it is impossible to completely rule out reporting errors or inaccuracies in the filling/reporting of records, given the volume of cases, these can probably be overlooked. In fact, the large number of records considered (over 180,000) represents a strength of our study. In addition, we were able to show directly, by means of a linear regression model, the existence of an inverse relationship between COVID-19 cases and ED accesses. It should also be considered that, because of the employment of a clinical proxy measure for COVID-19 cases (COVID-like illness cases – defined as either ILI or LRTI cases – identified through an operator dependent syndromic surveillance system), the estimation of figures related to our study outcome was not affected by the limitations posed, in early-2020, by the lacking of readily available laboratory diagnostic tests for SARS-CoV-2, as well as specific ICD-9 diagnostic codes for COVID-19. Finally, the utilization of a clinical proxy measure allowed for an accurate comparison with the reference pre-pandemic year.

Conclusions

Further research will be necessary to fully understand the causes and effects of the changes in emergency care utilization described in this article. For example, qualitative studies aimed at assessing the reasons why people seek or neglect to receive care are necessary to comprehend how the pandemic may have differentially affected treatment among vulnerable groups. This information will be crucial to guide systematic changes

in the healthcare systems aimed at reducing unnecessary ED visits and promoting high-value care.

Supplementary materials

The following supporting information can found below: TabS1- Proportion of diagnoses in each disease category between 2019 and 2021; TabS2 - Proportion of patients admitted to different hospital wards between 2019 and 2021.

Funding

This research received no external funding.

Conflict of interest statement

The authors declare no conflicts of interest.

Authors' contributions

Conceptualization, AF; SM; AO; methodology, AF; SM; AO; formal analysis, AF; SM; investigation, AF; MO; GI; MP; CM; DS; SM; AO; resources, GI; AO; data curation, AF; SM; AO; writing-original draft preparation, AF; AO; writing-review and editing, AF; GI; MO; MP; CM; DS; SM; AO; GI; visualization, AF; GI; MO; MP; CM; DS; SM; AO; GI; supervision, AO. All authors have read and agreed to the published version of the manuscript.

References

[1] Berchet C. Emergency Care Services: Trends, Drivers and Interventions to Manage the Demand. OECD Health Working Papers, No. 83. Paris: OECD Publishing 2015. https://doi.org/10.1787/5jrts344crns-en.

[2] The Italian National Institute of Statistics (ISTAT). Available at: http://dati.istat.it/ (Accessed on: 8 January 2022).

[3] Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health & Human Ser-vices. Trends in the Utilization of Emergency Department Services, 2009-2018, 2021. Available at: https://aspe.hhs.gov/pdf-report/utilization-emergency-department-services (Accessed on: 8 January 2022).

[4] United Nations (UN). WHO chief declares end to COVID-19 as a global health emergency Johns Hopkins Coronavirus Resource Center. Available at: https://news.un.org/en/story/2023/05/1136367 (Accessed on: 20 December 2023).

[5] Bollettini Giornalieri Protezione Civile. Dashboards Coronavirus. Available at: https://mappe.protezionecivile.gov.it/it/mappe-e-dashboards-emergenze/dashboards-coronavirus/ (Accessed on: 8 July 2024).

[6] Casalino E, Choquet C, Bouzid D, Peyrony O, Curac S, Revue E, Fontaine JP, Plaisance P, Chauvin A, Ghazali DA. Analysis of Emergency Department Visits and Hospital Activity during Influenza Season, COVID-19 Epidemic, and Lockdown Periods in View of Managing a Future Disaster Risk: A Multicenter Observational Study. Int J Environ Res Public Health 2020;17:8302. https://doi.org/10.3390/ijerph17228302.

[7] Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, Jones M, Kitchener E, Fox M, Johansson M, Lang E, Duggan A, Scott I, Albarqouni L. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ Open 2021;11:e045343. https://doi.org/10.1136/bmjopen-2020-045343.

[8] Wyatt S, Mohammed MA, Fisher E, McConkey R, Spilsbury P. Impact of the SARS-CoV-2 pandemic and associated lockdown measures on attendances at emergency departments in English hospitals: A retrospective database study. Lancet Reg Health Eur 2021;2:100034. https://doi.org/10.1016/j.lanepe.2021.100034.

[9] Giostra F, Mirarchi MG, Farina G, Paolillo C, Sepe C, Benedusi F, Bellone A, Ghiadoni L, Barbieri G, Santini M, Guiddo G, Riccardi A, Lerza R, Coen D. Impact of COVID-19 Pandemic and Lockdown on Emergency Room Access in Northern and Central Italy. Emerg Care J 2021;17(2). https://doi.org/10.4081/ecj.2021.9705.

[10] Adjemian J, Hartnett KP, Kite-Powell A, DeVies J, Azondekon R, Radhakrishnan L, van Santen KL, Rodgers L. Update: COVID-19 Pandemic-Associated Changes in Emergency Department Visits - United States, December 2020-January 2021. MMWR Morb Mortal Wkly Rep 2021;70:552-6. https://doi.org/10.15585/mmwr.mm7015a3.

[11] Kastritis E, Tsitsimpis K, Anninos E, Stamatelopoulos K, Kanakakis I, Lampropoulos C, Chatzidou S, Michopoulos S, Papamichail C, Kostis E, Manios E, Kontogiannis S, Paraskevaidis I, Terpos E, Mitrakou A, Dimopoulos MA. Significant reduction in the visits to the emergency room department during the COVID-19 pandemic in a tertiary hospital in Greece: Indirect victims of the pandemic? Medicine (Baltimore) 2020;99:e23845. https://doi.org/10.1097/MD.0000000000023845.

[12] Slagman A, Behringer W, Greiner F, Klein M, Weismann D, Erdmann B, Pigorsch M, Möckel M; AKTIN Emergency Department Registry; German Forum of University Emergency Departments (FUN) in the Society of University Clinics of Germany E.V. Medical Emergencies During the COVID-19 Pandemic. Dtsch Arztebl Int 2020;117:545-52. https://doi.org/10.3238/arztebl.2020.0545.

[13] Italian National Institute of Statistics (ISTAT). Impatto dell'epidemia COVID-19 sul sistema ospedaliero italiano. Available at: https://www.istat.it/it/files//2022/07/Impatto-covid-su-ricoveri-ospedalieri-Istat-Agenas.pdf (Accessed on: 8 July 2024).

[14] COVID-19 Excess Mortality Collaborators. Estimating Excess Mortality Due to the COVID-19 Pandemic: A Systematic Analysis of COVID-19-Related Mortality, 2020-21. Lancet 2022;399:1513-36. https://doi.org/10.1016/S0140-6736(21)02796-3.

[15] Marijon E, Karam N, Jost D, Perrot D, Frattini B, Derkenne C, Sharifzadehgan A, Waldmann V, Beganton F, Narayanan K, Lafont A, Bougouin W, Jouven X. Out-of-hospital cardiac arrest during the COVID-19 pandemic in Paris, France: a population-based, observational study. Lancet Public Health 2020;5:e437-43. https://doi.org/10.1016/S2468-2667(20)30117-1.

[16] Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, Dixon S, Rade JJ, Tannenbaum M, Chambers J, Huang PP, Henry TD. Reduction in ST-Segment Elevation Cardiac Catheterization Laboratory Activations in the United States During COVID-19 Pandemic. J Am Coll Cardiol 2020;75:2871-2. https://doi.org/10.1016/j.jacc.2020.04.011.

[17] Pessoa-Amorim G, Camm CF, Gajendragadkar P, De Maria GL, Arsac C, Laroche C, Zamorano JL, Weidinger F, Achenbach S, Maggioni AP, Gale CP, Poppas A, Casadei B. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. Eur Heart J Qual Care Clin Outcomes 2020;6:210-6. https://doi.org/10.1093/ehjqcco/qcaa046.

[18] Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, Rachet B, Aggarwal A. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in Eng-

land, UK: a national, population-based, modelling study. Lancet Oncol 2020;21:1023-34. https://doi.org/10.1016/S1470-2045(20)30388-0. Erratum in: Lancet Oncol2021;22:e5.

[19] Reschen ME, Bowen J, Novak A, Giles M, Singh S, Lasserson D, O'Callaghan CA. Impact of the COVID-19 pandemic on emergency department attendances and acute medical admissions. BMC Emerg Med 2021;21:143. https://doi.org/10.1186/s12873-021-00529-w.

[20] Bellan M, Gavelli F, Hayden E, Patrucco F, Soddu D, Pedrinelli AR, Cittone MG, Rizzi E, Casciaro GF, Vassia V, Landi R, Menegatti M, Gastaldello ML, Beltrame M, Labella E, Tonello S, Avanzi GC, Pirisi M, Castello LM, Sainaghi PP. Pattern of Emergency Department referral during the COVID-19 outbreak in Italy. Panminerva Med 2021;63:478-81. https://doi.org/10.23736/S0031-0808.20.04000-8.

[21] Di Renzo L, Gualtieri P, Pivari F, Soldati L, Attinà A, Cinelli G, Leggeri C, Caparello G, Barrea L, Scerbo F, Esposito E, De Lorenzo A. Eating habits and lifestyle changes during COVID-19 lockdown: an Italian survey. J Transl Med 2020;18:229. https://doi.org/10.1186/s12967-020-02399-5.

[22] Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA 3rd, Fulton JE, Gordon NF, Haskell WL, Link MS, Maron BJ, Mittleman MA, Pelliccia A, Wenger NK, Willich SN, Costa F; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Heart Association Council on Clinical Cardiology; American College of Sports Medicine. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation 2007;115:2358-68. https://doi.org/10.1161/CIRCULATIONAHA.107.181485.

[23] Della Corte V, Doria C, Oddo G. The impact of COVID-19 on international tourism flows to Italy: Evidence from mobile phone data. World Econ 2023:10.1111/twec.13380. https://doi.org/10.1111/twec.13380.

[24] Yasin YJ, Grivna M, Abu-Zidan FM. Global impact of COVID-19 pandemic on road traffic collisions. World J Emerg Surg 2021;16:51. https://doi.org/10.1186/s13017-021-00395-8.

[25] Santi L, Golinelli D, Tampieri A, Farina G, Greco M, Rosa S, Beleffi M, Biavati B, Campinoti F, Guerrini S, Ferrari R, Rucci P, Fantini MP, Giostra F. Non-COVID-19 patients in times of pandemic: Emergency department visits, hospitalizations and cause-specific mortality in Northern Italy. PLoS ONE 2021;16:e0248995. https://doi.org/10.1371/journal.pone.0248995.

[26] Radogna A, Bolcato V, Carelli C, Bini G, Braga P, Quaiotti J, Tronconi LP. Italian National Health Service immunized by COVID-19? J Prev Med Hyg 2022;63:E4-5. https://doi.org/10.15167/2421-4248/jpmh2022.63.1.1858.

Received on May 20, 2024. Accepted on July 9, 2024.

Correspondence: Allegra Ferrari, via Antonio Pastore, 16122 Genova, Italy. E-mail: allegraferrari@virgilio.it

How to cite this article: Ferrari A, Iudica G, Porretto M, Minet C, Ogliastro M, Simonetta D, Mosca S, Icardi G, Orsi A. The impact of SARS-CoV-2 on emergency health care demand: inverse relationship between COVID-like illnesses and ED accesses in Genoa, Italy. J Prev Med Hyg 2024;65:E154-E165. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3279

Supplementary Materials

The impact of SARS-CoV-2 on emergency health care demand: inverse relationship between COVID-like illnesses and ED accesses.

Tab. S1. Proportion of diagnoses in each disease category between 2019 and 2021.

Diagnoses, n (%)	2019	2020	2021
Burns, poisoning and other toxic effects (*e.g.* substance abuse)	240 (0.48)	167 (0.33)	372 (0.44)
Substance abuse	116 (0.18)	116 (0.23)	144 (0.21)
Oncological pathologies	404 (0.5)	361 (0.72)	385 (0.75)
Diseases of the endocrine and immune system, nutrition and metabolism	485 (0.97)	420 (0.83)	742 (0.9)
Blood diseases and hematopoietic organs	509 (0.9)	486 (0.97)	692 (0.94)
Diseases of the skin and subcutaneous tissue	896 (1.67)	737 (1.47)	1281 (1.66)
Infectious and parasitic diseases (exc. Resp)	957 (1.76)	768 (1.53)	1343 (1.77)
Ear diseases	877 (2.17)	873 (1.74)	1658 (1.63)
Fever	634 (1.96)	1093 (2.18)	1495 (1.17)
Thromboembolisms and cerebrovascular diseases	1565 (1.87)	1237 (2.47)	1429 (2.9)
Acute respiratory infections (inc. COVID-19)	1995 (2.18)	2736 (5.46)	1664 (3.7)
Other respiratory diseases	1291 (2.64)	1320 (2.63)	2017 (2.4)
Unspecified malaise and fatigue	1642 (1.58)	1303 (2.6)	1210 (3.05)
Diseases of musculoskeletal and connective tissues	2234 (4.97)	2090 (4.17)	3796 (4.15)
Diseases of the circulatory system	2540 (4.43)	2452 (4.89)	3384 (4.72)
Diseases of the genitourinary system	2805 (4.75)	2538 (5.07)	3623 (5.21)
Diseases of the nervous system	3151 (5.61)	2599 (5.19)	4279 (5.85)
Complications of pregnancy, congenital and growth disease	2835 (3.77)	2644 (5.28)	2881 (5.27)
Mental disorders	2815 (5.32)	2745 (5.48)	4059 (5.23)
Diseases of the digestive system and oral cavity	3293 (6.07)	3126 (6.24)	4631 (6.12)
Eye diseases	4099 (11.19)	3698 (7.38)	8538 (7.62)
Trauma	14260 (25.82)	12412 (24.79)	19697 (26.51)
Other pathologies	4146 (9.1)	4128 (8.24)	6942 (7.7)
Total	76262 (100)	50049 (100)	53789 (100)

Tab. S2. Proportion of patients admitted to different hospital wards between 2019 and 2021.

Hospital wards, n (%)	2019	2020	2021
Dermatology	1 (0)	0 (0)	2 (0.01)
Palliative care	0 (0)	6 (0.04)	2 (0.01)
Hematology	34 (0.18)	18 (0.12)	23 (0.16)
Geriatrics	30 (0.16)	49 (0.32)	24 (0.16)
Ophthalmology	42 (0.22)	37 (0.24)	34 (0.23)
Transplants	51 (0.27)	56 (0.37)	39 (0.27)
Rheumatology	79 (0.42)	73 (0.48)	67 (0.46)
Nephrology	102 (0.54)	81 (0.54)	109 (0.76)
Orthorinolaryngology	182 (0.97)	86 (0.57)	124 (0.86)
Oncology	145 (0.77)	99 (0.66)	119 (0.83)
Thoracic and cardiac surgery	92 (0.49)	130 (0.86)	119 (0.83)
Respiratory diseases and allergology	183 (0.98)	176 (1.17)	219 (1.53)
Gastroenterology	232 (1.24)	177 (1.18)	322 (2.25)
Endocrinology	207 (1.11)	243 (1.62)	228 (1.59)
Surgery	582 (3.12)	263 (1.75)	357 (2.49)
Neurosurgery	410 (2.19)	269 (1.79)	385 (2.69)
Urology	407 (2.18)	286 (1.91)	320 (2.23)
Resuscitation and intensive care	327 (1.75)	476 (3.17)	294 (2.05)
Infectious and tropical diseases	387 (2.07)	467 (3.11)	548 (3.83)
Cardiology and vascular surgery	855 (4.58)	624 (4.16)	697 (4.87)
Psychiatry	945 (5.06)	735 (4.9)	808 (5.64)
Neurology	1206 (6.46)	1042 (6.95)	1369 (9.56)
Obstetrics and gynecology	1257 (6.74)	1312 (8.76)	1230 (8.59)
Orthopedics and Traumatology	1776 (9.52)	1757 (11.73)	1585 (11.07)
Internal medicine	1229 (6.59)	1902 (12.7)	1801 (12.58)
Emergency medicine	7885 (42.28)	4608 (30.77)	3483 (24.34)
Total	18646 (100)	14972 (100)	14308 (100)

Infectious disease

Environmental Surveillance of *Legionella spp*. in an Italian University Hospital: results of 7 years of analysis

LUCIA MASSOLO[1], MATILDE OGLIASTRO[1], PETER POSTMA[1], ORIANA FERRANTE[1], ROSA AMATO[1], ELVIRA MASSARO[1], DOROTEA BELLINA[2], ROBERTO ZIFERRO[2], ALBERTO BORNETO[3], ALESSANDRA MORANDO[4], ANDREA ORSI[1,2]

[1] Department of Health Sciences, University of Genoa, Genoa, Italy; [2] Hygiene Unit, IRCCS Policlinico San Martino Hospital, Genoa, Italy; [3] Technical Activities Operational Unit, IRCCS Policlinico San Martino Hospital, Genoa, Italy; [4] Medical Direction, IRCCS Policlinico San Martino Hospital, Genoa, Italy

Keywords

Legionella • Hospital surveillance • Water safety plan

Summary

Introduction. *Nosocomial structures pose a high risk of* Legionella spp. *contamination due to complex water systems with challenging disinfection; moreover, the risk of severe legionellosis as a consequence of nosocomial exposure is very high in settings characterized by vulnerable patient conditions.*

Methods. *In the present work, we described the results of 7 years of environmental surveillance in a reference hospital in Liguria, in which a specific water safety plan (WSP) has been implemented in 2017, including data collected during the COVID-19 pandemic.*

Results. *During the study period, 1190 water samples were collected, of which 277 (23.3%) tested positive for* Legionella spp. *Positive samples with concentration values above 1,000 CFU/l were 184 (66.4%). Based on the new structure categorization contained in the WSP, hospital buildings classified as at "very high" risk resulted the most affected structures over the entire study period; however, the absolute number of positive samples greatly decreased over time, from 61 contaminated water samples in 2017 to only 9 in 2023.*

Conclusions. *Our findings prompted the reinforcement of control and prevention measures, affirming the appropriateness of risk-category classification. Indeed, the majority of contamination cases were associated with the water networks of buildings classified as "very high" risk.*

Introduction

Legionella spp. is a pathogen identified in 1976 during an outbreak of atypical pneumonia at an American Legion conference in Philadelphia and subsequently named *Legionella pneumophila* [1, 2].

Legionella pneumophila, responsible for most human infections, has 16 serogroups, with serogroup 1 being predominant [3]. *Legionella spp*. colonizes natural aquatic environments, artificial water tanks and pipelines, evaporative cooling systems and various facilities like water networks of buildings [1, 3, 4]. Factors contributing to water network contamination involve temperature, amoebae/protozoa presence, stagnant water, low biocide concentration, poor flow, and biofilm/scale presence [1, 3]. Humans can contract *Legionella* infections through aerosol inhalation or contaminated water suction. Risk factors include age over 50, male gender, smoking or intravenous drug use, chronic diseases, and immunosuppression [3, 5-7].

In accordance with Italian guidelines, cultural methods are considered the gold standard for environmental surveillance. The diagnosis of human cases is supported by numerous laboratory methods, such as the isolation of the bacterium by culture, detection of antibodies in sera during the acute and convalescent phases of the disease, detection of urinary antigen, detection of the bacterium in tissues or body fluids by immunofluorescence testing, and detection of bacterial DNA using PCR [3, 8-9].

Nosocomial structures pose a high risk of *Legionella spp*. contamination due to complex water systems with challenging disinfection, including blind-bottomed branches, water stagnation, and biofilms. Moreover, although it is not a problem to achieve high water temperatures at the source of the distribution system, maintaining these high temperatures throughout the entire network, especially in its terminal parts, is challenging [10-13]. The risk of severe legionellosis as a consequence of nosocomial exposure is very high in settings characterized by vulnerable patient conditions and high number of respiratory care practices [3, 7, 14].

In Italy the first national guidelines for legionellosis prevention and control were issued in 2000 and then updated in 2015, with a particular focus on surveillance and control activities in the hospital setting [3].

Current *Legionella* monitoring in hospitals follows 2015 guidelines, considering patient types, high-risk practices, and facility history for risk assessment. The goal is to minimize colonization risk rather than complete elimination, often unachievable in the long term. This does not apply to wards housing profoundly immunocompromised patients; in this case, the inability of the immune system to respond to any exposure makes interventions to ensure the absence of *Legionella*

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3195

(undetectability) necessary. Risk classification mandates various preventive measures and remediation strategies once contamination occurs [3, 14, 15].
In the present work, we described the results of 7 years of environmental surveillance in a reference hospital in Liguria, in which a specific water safety plan (WSP) has been implemented in 2017, including data collected during the COVID-19 pandemic.

Materials and methods

A retrospective study was conducted at the IRCCS Ospedale Policlinico San Martino, a historical university reference hospital for adult care located in Genoa, in the Liguria region of northern Italy. The hospital covers a vast urban area and consists of 31 buildings that host all the nosocomial services and clinical wards, including 1200 beds, built between 1910 and 1923; adult patients at high risk of legionellosis due to their clinical conditions, such as transplant, oncology, haematology, intensive care and infectious disease patients, are hospitalized in six buildings, representing 70% of total beds. Each building is supplied by separate water tanks. Structural and organizational preventive measures against *Legionella* contamination used in the hospital include absolute filters in specific high-risk areas, a chlorine dioxide system in most of buildings hosting patients, a program of environmental sampling involving all the hospital buildings and an alert surveillance system based on laboratory results on human samples.
In 2017, a WSP was adopted, introducing a systematic monitoring of *Legionella* presence in water network and a new classification of risk levels of all buildings. Water Safety Planning is an international framework developed by the World Health Organization in 2004 that utilizes local system knowledge and risk management strategies to continuously improve water quality. The WSP is a cyclical and adaptive framework built on proactive hazard identification, risk mitigation, and operator knowledge [16].
The Hygiene Unit manages and implements the WSP through activities carried out by a multidisciplinary working group. This group includes specialized staff in infection control, biologists, laboratory technicians, health and safety manager, filter suppliers, and plumbers. The main critical issues encountered were related to structural problems, various renovations that have taken place over the years, and the absence of a map of the water network.
The first activity was the introduction of a risk classification for all the hospital buildings: they are categorized in four risk levels (very high, high, intermediate, and low), according to 2015 national guidelines [3].
Buildings hosting transplant centres, oncology, haematology, intensive care and infectious disease wards are considered among very high risk structures (6 buildings): in these buildings the aim of the WSP is to maintaining zero colonization/presence of *Legionella*.
Other 5 buildings host patients considered at risk for *Legionella* infection due to their clinical condition or other individual risk factors: these 5 buildings are classified as high risk structures.
Other 10 buildings are considered at intermediate risk because mainly host outpatient services or clinical wards with a limited patient presence.
The remaining 10 buildings host administrative or other services, with scarce or no presence of patients, presenting minimal risk of legionellosis, comparable to the community.
Sampling is conducted every six months in very high-risk departments and annually in others, with biennial frequency for departments considered at higher risk than general population. Additional sampling can be performed in case of unexpected events. The collected hot water samples, obtained from the points of sampling identified for each department of the Hospital, are transported and processed at the laboratories of the Hygiene Unit, according to national indications. In case of colony growth, agglutination tests are performed for serogroup identification.
During the study period, there were deficiencies of reagents for the execution of the agglutination test for the identification of *Legionella* serogroup 3 and serogroup 6: in this case, after exclusion of serogroup 1, the identified *Legionella* serogroup was generically expressed as "serogroup 2-14".
The environmental samples considered for the purposes of our study included routine sampling and extraordinary sampling following contamination detection.
We calculated the prevalence of *Legionella spp*. contamination for each year investigated and the cumulative incidence in the period between January 2017 and November 2023.
Then, we described in absolute numbers the distribution of isolates for serogroups of *Legionella spp*.; subsequently, we calculated the prevalence of each serogroup annually and over the total period. The results of the sampling were divided into the following ranges of values: < 100 colony-forming units/litre (CFU/l), 100-1,000 CFU/l, 1,001-10,000 CFU/l and more than 10,000 CFU/l.
In addition, we evaluated the distribution of positive samples based on the sampling points and their location in the hospital; therefore, we calculated the prevalence of contamination in individual buildings annually and in the overall period. Chi square for trend was calculated from Epitools - Epidemiological Calculators (Sergeant, ESG, 2018. Epitools Epidemiological Calculators. Ausvet. Available at: http://epitools.ausvet.com.au.).

Results

From January 2017 to November 2023, 1190 water samples were collected and processed, of which 277 (23%) tested positive for *Legionella spp*. Positive samples with concentration values above 1,000 CFU/l were 184 (66%).
Figure 1 shows the prevalence of positive hospital water network samples for *Legionella spp*. from January 2017

Fig. 1. Prevalence of positive sampling found in the sampling of the hospital water network of the IRCCS San Martino Polyclinic Hospital, Genoa (January 2017-November 2023).

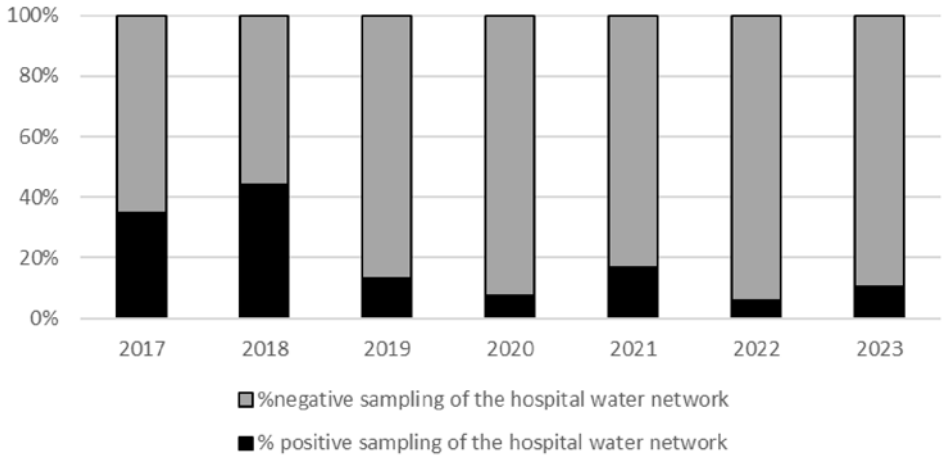
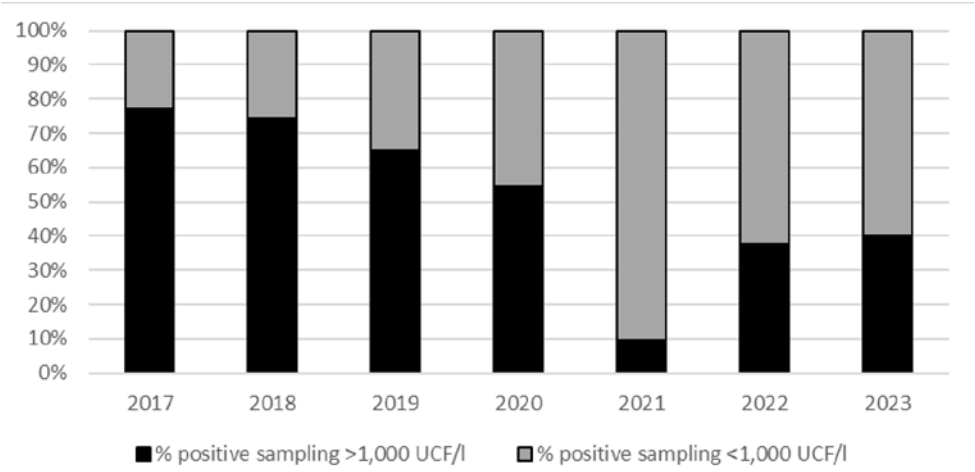


Fig. 2. Prevalence of hospital water network sampling positive results with *Legionella spp.* concentration above 1,000 UCF/l (January 2017-November 2023).



to November 2023; Figure 2 shows the prevalence of positive sampling with *Legionella spp*. concentration above 1,000 UCF/l in the same period. We observed a steadily decreasing trend for both rates during the study period (chi square for trend $p < 0.0001$).

Legionella pneumophila was the only isolated species: serogroup 3 was the most identified serogroup (80% of all positive samples), followed by serogroup 1 (13%) and serogroup 6 (1%); the remaining positive samples (7%) were classified as serogroup 2-14 after exclusion of serogroup 1.

Figure 3 shows the absolute numbers of *Legionella pneumophila* identification by serogroup and year of analysis.

We evaluated the distribution of the contaminated samples according to the sampling points and their location in the hospital. Figure 4 shows the prevalence of *Legionella* contamination of the hospital buildings in relation to the risk category to which they belong in each year of the survey: those classified as "at very high risk" resulted the most affected structures by contamination over the entire study period; however, the absolute number of positive samples greatly decrease over time, from 61 contaminated water samples in 2017 to only 9 in 2023.

Discussion

We observed a dramatic decrease in *Legionella* contamination among water samples collected at IRCCS Ospedale Policlinico San Martino during the study period, after the implementation of a WSP in 2017. One of the main elements of this plan is the scheduling of periodic checks [17]: therefore, a systematic monitoring was introduced with a sampling frequency indicated based on the level of risk. Furthermore, the WSP included mapping of water terminals as part of a larger project to map the water network, which is currently not yet completed.

The decrease was observed for all the *Legionella* serogroup identified, in particular for serogroup 3, that was the most represented serogroup, which is more

Fig. 3. Histogram showing the absolute numbers of *Legionella pneumophila* Ser. 1, Ser. 3, Ser 6 and Ser 2-14 detected in each year of our investigation.

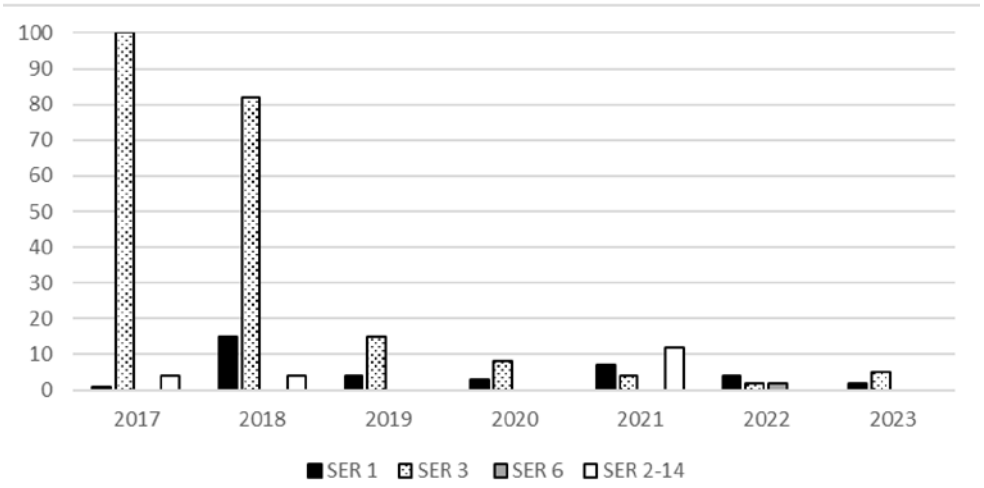
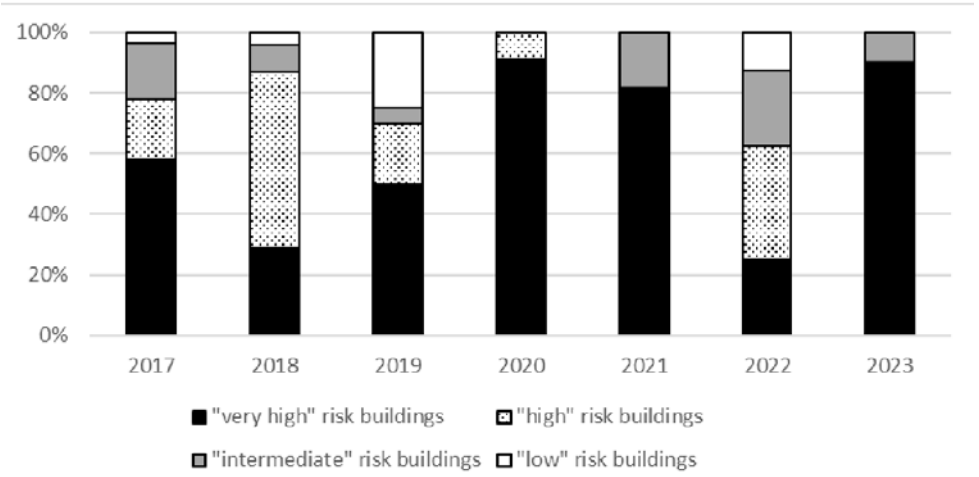


Fig. 4. Prevalence of contamination of the water network of the buildings analyzed in relation to the risk category to which they belong in each year of our survey (January 2017-November 2023).



difficult to diagnose in the case of human contagion since it is not detectable by the search for common urinary antigen tests.

Regarding the risk classification of hospital buildings, structures categorized as "very high" and "high" risk consistently exhibited the highest contamination levels throughout the entire study period. Nevertheless, there was a notable decrease in the absolute number of positive samples in these structures.

Our findings prompted the reinforcement of control and prevention measures, affirming the appropriateness of risk-category classification. Indeed, the majority of contamination cases were associated with the water networks of buildings classified as "very high" risk.

Analyzing the higher presence of positive samples in buildings categorized as high risk, this phenomenon may be partially attributed to a more extensive sampling frequency in these structures. The sustained detection of positivity could also be linked to challenges that can be effectively addressed only through structural interventions, as detailed in [18], because the old water network of the hospital, increases the risk of contamination by *Legionella spp*.

Regarding serogroups in our sample a significant prevalence of serogroups 2-14 has been observed, particularly serogroup 3. These serogroups are less frequently sought, and therefore more challenging to diagnose, as described in other Italian studies such as [19-21]. Consequently, in the fight against hospital-acquired legionellosis, it is essential to ensure correct and effective information and training of the staff to lead to the correct application of the indications for the prevention and control of the infection. Clinicians must be aware of the potential contamination of the hospital water network by *Legionella* and the associated risk of disease occurrence. This is crucial to prevent underdiagnosis and to always consider *Legionella* pneumonia possibly associated with care practices, especially in patients at high risk, using appropriate diagnostic tests. It is therefore essential to train the person responsible for infection control and the person responsible for the management and maintenance of the facilities on the

measures to control legionellosis associated with care practices, to inform the departments of the results of the risk assessment and to ensure the traceability of the activities carried out through appropriate records.
Our study is subject to certain limitations. The surveillance started in 2017, and there are no available systematically collected data for previous years and lack of data on water pipe temperatures hampers the assessment of correlation with *Legionella spp*. contamination.
The COVID-19 pandemic introduces a confounding factor, as it resulted in a decrease in the execution of sampling in the wards. Furthermore, there have been significant changes in the organization of hospital departments, including the conversion of some units into intensive or sub-intensive care facilities for the treatment of severe cases. Consequently, in the years 2020-2021, there was a structural reorganization of the hospital, temporarily modifying the categorization of buildings based on the level of risk.

Conclusions

Our work highlights the importance of an adequate surveillance of legionellosis in a nosocomial environment to implement, effectively and promptly, the planned disinfection and prevention measures, reducing the likelihood of hospital infections. Based on our results, it is important to make all healthcare professionals in the hospital aware of the potential infectious risk in wards, especially those at increased risk of contamination, so that a possible case of legionellosis related to assistance can be timely recognized.

Acknowledgments

The authors thank all the staff of the Hygiene Unit of the IRCCS Ospedale Policlinico San Martino for their work.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions:

LM, AO: conceptualisation; LM, MO, AO: methodology; MO, AO: formal analysis; MO, PP, OF, RA, EM, DB, RZ: investigation; AM, AO: resources; LM, RA: data analysis; LM, RA: writing – original draft preparation,; MO, AB, AM, AO: writing – review and editing; MO, EM, AO: visualisation; AO: supervision.
All authors have read and agreed to the current version of the manuscript.

References

[1] Barbuti S, Fara GM, Giammanco G. Hygiene – Preventive Medicine – Public Health. EdiSES 2022.

[2] Fraser DW. The challenges were legion. Lancet Infect Dis 2005;5:237-41. https://doi.org/10.1016/S1473-3099(05)70054-2.

[3] Ministry of Health. Line and guide for the prevention and control of legionellosis (2015). Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2362_allegato.pdf (Accessed on: 09/09/2023).

[4] Diederen BM. *Legionella spp*. and Legionnaires' disease. J Infect 2008;56:1-2. https://doi.org/10.1016/j.jinf.2007.09.010.

[5] Cunha BA, Burillo A, Bouza E. Legionnaires' disease. Lancet 2016;387:376-85. https://doi.org/10.1016/S0140-6736(15)60078-2.

[6] Phin N, Parry-Ford F, Harrison T, Stagg HR, Zhang N, Kumar K, Lortholary O, Zumla A, Abubakar I. Epidemiology and clinical management of Legionnaires' disease. Lancet Infect Dis 2014;14:1011-21. https://doi.org/10.1016/S1473-3099(14)70713-3.

[7] Signorelli. Hygiene and public health. III ed. Universo Publishing Company 2021.

[8] Girolamini L, Brattich E, Marino F, Pascale MR, Mazzotta M, Spiteri S, Derelitto C, Tositti L, Cristino S. Cooling towers influence in an urban environment: a predictive model to control and prevent *Legionella* risk and Legionellosis events. Build Environ 2023;228:109891. https://doi.org/10.1016/j.buildenv.2022.109891.

[9] European Society of Clinical Microbiology and Infectious Diseases Study Group for Legionella Infections. European Technical Guidelines for the Prevention, Control and Investigation of Infections Caused by *Legionella* Species. Basel: ESCMID; 2017. Available at: https://www.escmid.org/fileadmin/src/media/PDFs/3Research_Projects/ESGLI/ESGLI_European_Technical_Guidelines_for_the_Prevention_Control_and_Investigation_of_Infections_Caused_by_Legionella_species_June_2017.pdf (Accessed on: 09/09/2023).

[10] Coniglio MA, Ferrante M, Yassin MH. Preventing healthcare-associated legionellosis: results after 3 years of continuous disinfection of hot water with monochloramine and an effective water safety plan. Int J Environ Res Public Health 2018;15:1594. https://doi.org/10.3390/ijerph15081594.

[11] Orsi GB, Vitali M, Marinelli L, et al. *Legionella* control in the water system of antiquated hospital buildings by shock and continuous hyperchlorination: 5 years experience. BMC Infect Dis 2014;14:1-10. https://doi.org/10.1186/1471-2334-14-394.

[12] Vincenti S, De Waure C, Raponi M, Teleman AA, Boninti F, Bruno S, Boccia S, Damiani G, Laurenti P. Environmental surveillance of *Legionella spp*. colonization in the water system of a large academic hospital: analysis of the four-year results on the effectiveness of the chlorine dioxide disinfection method. Sci Total Environ 2019;657:248-53. https://doi.org/10.1016/j.scitotenv.2018.12.036.

[13] Gavaldà L, Garcia-Nuñez M, Quero S, Gutierrez-Milla C, Sabrià M. Role of hot water temperature and water system use on *Legionella* control in a tertiary hospital: an 8-year longitudinal study. Water Res 2019;149:460-6. https://doi.org/10.1016/j.watres.2018.11.032.

[14] Wenzel RP. Health care-associated infections: major issues in the early years of the 21st century. Clin Infect Dis 2007;45(Suppl 1):S85-8. https://doi.org/10.1086/518136.

[15] Lucentini L, Marchiafava C, Mattei D, Nigro Di Gregorio F, De Giglio O, Montagna MT, ed. Water and health: elements of risk analysis in new environmental and climate scenarios. Rome: Istituto Superiore di Sanità 2020. (ISTISAN Reports 20/19). Available at: https://www.iss.it/documents/20126/0/20-19+web.pdf/5b18b48c-a6f4-4bdf-cba4-e1a22877e0bd?t=1602579117495 (Accessed on: 09/09/2023).

[16] Lane K, Fuller M, Dyment T, Gagnon G. Co-development of a risk assessment tool for use in First Nations water supply systems: a key step to water safety plan implementation. Int J Hyg Environ Health 2022;240:113916. https://doi.org/10.1016/j.ijheh.2021.113916.

[17] Cristina ML, Sartini M, Schinca E, Ottria G, Casini B, Spagnolo AM. Evaluation of multidrug-resistant P. aeruginosa in healthcare facility water systems. Antibiotics 2021;10:1500. https://doi.org/10.3390/antibiotics10121500.

[18] Arrigo I, Galia E, Fasciana T, Diquattro O, Tricoli MR, Serra N, Palermo M, Giammanco A. Four-year environmental surveillance program of *Legionella spp*. in one of Palermo's largest hospitals. Microorganisms 2022;10:764. https://doi.org/10.3390/microorganisms10040764.

[19] Felice A, Franchi M, De Martin S, Vitacolonna N, Iacumin L, Civilini M. Environmental surveillance and spatio-temporal analysis of *Legionella spp*. in a region of northeastern Italy (2002–2017). PLos One 2019;14:E0218687. https://doi.org/10.1371/journal.pone.0218687.

[20] Triassi M, Di Popolo A, D'Alcalà GR, Albanese Z, Cuccurullo S, Montegrosso S, Crispino M, Borella P, Zarrilli R. Clinical and environmental distribution of *Legionella pneumophila* in a university hospital in Italy: efficacy of ultraviolet disinfection. J Hosp Infect 2006;62:494-501. https://doi.org/10.1016/j.jhin.2005.09.029.

[21] Borella P, Montagna MT, Stampi S, Stancanelli G, Romano-Spica V, Triassi M, Marchesi I, Bargellini A, Tato D, Napoli C, Zanetti F. *Legionella* contamination in hot water of Italian hotels. Appl Environ Microbiol 2005;71:5805-13. https://doi.org/10.1128/AEM.71.10.5805-5813.200.

Received on February 6, 2024. Accepted on June 14, 2024.

Correspondence: Matilde Ogliastro, Dipartimento di Scienze della Salute, Università degli Studi di Genova, via Antonio Pastore, 16132 Genoa, Italy. E-mail: matilde.ogliastro.doc@gmail.com

How to cite this article: Massolo L, Ogliastro M, Postma P, Ferrante O, Amato R, Massaro E, Bellina D, Ziferro R, Borneto A, Morando A, Orsi A. Environmental Surveillance of *Legionella spp*. in an Italian University Hospital: results of 7 years of analysis. J Prev Med Hyg 2024;65:E166-E171. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3195

Infectious disease

First real-world data on universal respiratory syncytial virus prophylaxis with Nirsevimab in infants

ANDREA ORSI[1,2], MARIANNA SCARPALEGGIA[1], VINCENZO BALDO[2,3], FABIO BARBONE[2,4], MARIA CHIRONNA[2,5], SANDRO GIUFFRIDA[6], EMANUELE MONTOMOLI[2,7], ELENA PARIANI[2,8], CATERINA RIZZO[9], DONATELLA PANATTO[1,2], GIANCARLO ICARDI[1,2]

[1] Department of Health Sciences, University of Genoa, Genoa, Italy; [2] Interuniversity Research Centre on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy; [3] Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy; [4] Department of Medicine, Surgery and Health Sciences, University of Trieste, Ospedale di Cattinara, Trieste, Italy; [5] Interdisciplinary Department of Medicine, University of Bari, Bari, Italy; [6] Department of Prevention, Azienda Sanitaria Provinciale, Reggio Calabria, Italy; [7] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy; [8] Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; [9] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Keywords

Respiratory syncytial virus (RSV) • Nirsevimab • Effectiveness • Infants • Prophylaxis

Summary

Introduction. *Respiratory Syncytial Virus (RSV) predominantly affects young children, with a peak incidence in temperate regions of the northern hemisphere from October to May. Children under 24 months of age are particularly vulnerable because of the immaturity of their lungs and immune systems, often leading to severe respiratory infections. The World Health Organization (WHO) recognizes RSV as a global health priority. Recently, Nirsevimab, a long-acting monoclonal antibody (mAb), was authorised to prevent RSV disease in infants.*

Methods. *Our narrative review brings together the effectiveness data of Nirsevimab available in the literature, highlighting the strengths and weaknesses of the published studies and the prevention opportunities represented by the new preparation.*

Results. *All reviewed studies provide evidence for the effectiveness of immunisation with Nirsevimab in real-world settings, beyond the controlled conditions of clinical trials, and highlight its safety and feasibility. Nirsevimab significantly reduces RSV hospitalisations and Intensive Care Unit (ICU) admissions. High coverage and high efficacy of immunisation have been reported, although supply issues and variability in studies present challenges.*

Conclusions. *Continued research and surveillance are critical to understanding the long-term effectiveness of Nirsevimab. Overall, available data provide valuable insights into the efficacy, safety, and impact of immunisation with Nirsevimab in preventing severe RSV infections in infants, highlighting its potential to reduce the burden of RSV-related hospitalisations and improve paediatric health outcomes.*

Introduction

Respiratory Syncytial Virus (RSV) is a single-stranded RNA virus belonging to the Paramyxoviridae family, with two main antigenic subtypes (A and B). RSV is a seasonal virus with epidemiology that strongly depends on the climatic zone concerned; in temperate regions of the Northern Hemisphere, it generally circulates from October to early May, with a typical peak between December and February [1].

RSV appears to be the most common etiological agent identified in respiratory infections among young children, with greater severity in infants up to 24 months, probably due to incomplete lung and immune system development. RSV disease is often not self-limiting and may have long-term consequences, as suggested by the fact that approximately 30-40% of children with previous bronchiolitis-related hospitalisations are likely to experience recurrent episodes of bronchospasm and asthma as long-term complications [2, 3].

All newborns are at risk of developing Lower Respiratory Tract Infection with RSV (RSV-LRTI), mainly due to seasonality and being under one year of age. Other risk factors include prematurity, congenital heart malformations/diseases (CHD), chronic lung disease (CLD), bronchopulmonary dysplasia (BPD), and other severe conditions that compromise the immune and neuromuscular systems [2, 4]. However, research conducted by the Centers for Disease Control and Prevention (CDC) in the United States, confirmed by recent studies conducted in Italy, revealed that almost 90% of infants hospitalised for RSV and up to 90% of infants with a lower respiratory tract infection seen on an outpatient basis were born at term and in apparently normal health [5, 6].

Globally, RSV causes a significant burden of respiratory disease annually, with 33 million cases of Lower Respiratory Tract Infections (LRTIs) requiring outpatient medical care and 3.6 million hospital admissions, causing more than 100,000 deaths, including more than 26,000 in hospital settings [7].

In Europe, RSV causes, on average, about 250,000 hospitalisations in children under five years of age, with most cases occurring in children under one year

 https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3329

of age. Epidemiological studies conducted in Italy have shown an increased incidence of RSV infections and an increased need for Paediatric Intensive Care (PICU), especially in infants ≤ 3 months [8, 9]. According to the Italian RespiVirNet surveillance network, during the 2022-2023 influenza season, RSV caused 49.1% and 22.3% of influenza-like illnesses in children under 2 years of age and between 2 and 4 years of age [10].

A recent study conducted in the winter season 2022-2023, described a baseline of the RSV disease burden in primary care in Italy prior to the introduction of upcoming immunization strategies. Specifilly, fifty-five paediatricians from five Italian regions collected nasal swabs from 650 children under 5 years of age with acute respiratory infections (ARI). The results showed 37.8% of ARI cases were RSV-positive, with subtype B comprising 65.4%. RSV-positive children were younger and had symptoms lasting 11.47 ± 6.27 days. RSV-A cases required more paediatric visits than RSV-B. The impact included 53% of children missing school, 46% of parents losing workdays, and 25% of families facing extra costs [11].

In the 2023-2024 season, the total number of RSV-positive samples corresponded to 4,341 on a total of 15,684 ARI positive samples, with a clear prevalence in the 0-2 age group [12].

Given the substantial clinical burden in terms of morbidity and mortality, RSV disease is recognised by the World Health Organisation (WHO) as a global public health priority [13]. In 2016, the WHO Strategic Advisory Group on Immunisation recommended that efforts be made to identify and address gaps in evidence needed for regulation, pre-qualification, and policy guidance for RSV prevention interventions, including maternal and paediatric immunisation with RSV vaccines and passive childhood immunisation with long-acting RSV monoclonal antibodies (mAb) [14].

Palivizumab, the first mAb approved in 1999, requires monthly injections at a dose of 15 mg/kg body weight to provide protection during the typical 5-month RSV season. This drug is only recommended for high-risk infants in a limited age group, leaving most children vulnerable to RSV infection [6, 15].

Between 2022 and 2023, two novel products received authorisation to prevent RSV disease in neonates: Nirsevimab and a bivalent recombinant vaccine.

Nirsevimab, a long-acting mAb, was licensed to prevent lower respiratory tract disease caused by RSV in infants and children during their first RSV season [16, 17]. The recombinant bivalent RSVpreF vaccine has been approved for administration during pregnancy to prevent lower respiratory tract disease in children from birth to 6 months of age [18, 19].

European Centre for Disease prevention and Control (ECDC), WHO and the Italian Guidelines on the Management of RSV Bronchiolitis identified Nirsevimab as a promising preventive strategy that could soon be included in routine immunisation programs to protect all infants and children during their first RSV season [2].

This narrative review describes the available effectiveness data of Nirsevimab, highlighting the strengths and weaknesses of the published studies and the prevention opportunities represented by the new preparation.

Methods

This narrative review is structured into three main sections: the characteristics of the Nirsevimab (MEDI8897) and available efficacy studies, real-world effectiveness data and trials in Progress.

In the first section, we reported the main technological characteristics and some clinical practice aspects (dosage, administration, and usage recommendations). Moreover, we synthetically described the available efficacy studies, identified through the same search performed for effectiveness studies and described below.

The second section represents the core of our work and summarises all the available evidence on the real-world effectiveness of Nirsevimab.

The references for this article were identified through PubMed, GoogleScholar and Clinicaltrials.gov with the search terms: “effectiveness”, “efficacy”, “real-world”, “Nirsevimab”, “Beyfortus”, “Respiratory Syncytial Virus” and “RSV”, over the period from 2000 until the end of June 2024.

In the third section, we discussed ongoing clinical trials evaluating the efficacy and effectiveness of Nirsevimab: the search was performed on Clinicaltrials.gov with the methodology described above.

Results and discussion

Nirsevimab (MEDI8897)

Nirsevimab, marketed under the brand name Beyfortus® and manufactured by AstraZeneca, is distributed by Sanofi Pasteur, Inc [16, 20, 21].

It is indicated for infants and children up to 12 months of age and for children at increased risk of RSV up to 24 months. Safety and efficacy in children over 24 months have not been established.

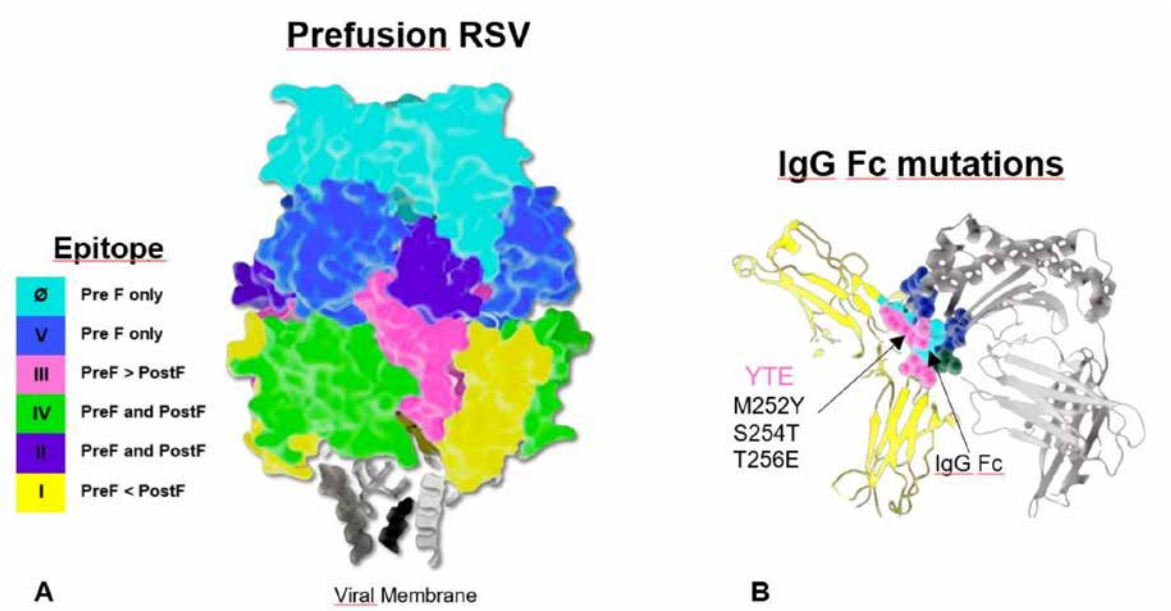
Nirsevimab is not indicated for pregnant or lactating individuals or those with reproductive potential. Clinical studies have shown that neither race nor increased susceptibility to severe RSV significantly affects the pharmacokinetics of Nirsevimab [16, 20].

Structure

Nirsevimab is a human G1 kappa-type monoclonal antibody (IgG1κ) produced in animal cells using recombinant DNA technology and designed to have sustained action [22].

It provides passive immunity against RSV infections by binding to a highly conserved epitope within the Ø site of the pre-fusion conformation (PreF) of the RSV fusion protein (F) inhibiting viral fusion and thus preventing virus entry into the host cell.

Fig. 1. Mechanism of action of Nirsevimab. **A)** Ø site of the PreF of the RSV fusion protein (F). **B)** The addition of the triple amino acid substitution M252Y/S254T/T256E (YTE) to the crystallisable region of the fragment (Fc).



The enhanced neutralising activity of Nirsevimab is due to the addition of the triple amino acid substitution M252Y/S254T/T256E (YTE) to the crystallisable region of the fragment (Fc). This modification extends the serum half-life in vivo approximately 3-fold (average 71 days), allowing a single intramuscular injection of Nirsevimab to provide protection for an entire RSV season [23, 24] (Fig. 1).

Dosage, administration, and usage recommendations

Nirsevimab is available in sterile prefilled syringes of 50 mg/0.5 ml or 100 mg/ml, without preservatives, for intramuscular injection. The dosage is weight-based: for infants and children weighing < 5 kg, the recommended dose is 50 mg; for children weighing > 5 kg, the recommended dose is 100 mg [20].

The Advisory Committee on Immunisation Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend 1 dose of Nirsevimab for all children <8 months of age during or entering their first RSV season [25, 26]. The same recommendations are also suggested by the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) [16, 17].

Children born shortly before or during the RSV season are recommended to receive their initial dose of Nirsevimab within the first week of life, either before hospital discharge or during their first outpatient visit. For those eligible by age who have not yet received a dose, administration is advised at any point during the season [25, 27].

The AAP also recommends administering Nirsevimab to children between 8 and 19 months of age during their second RSV season. However, providers may decide to administer the drug up to 24 months of age for those children considered to be at higher risk. Children who received less than five doses of Palivizumab during the season should switch to one dose of Nirsevimab, and those entering the second RSV season after receiving Palivizumab in the first season should receive Nirsevimab, otherwise continue with Palivizumab. A child receiving Nirsevimab should not concurrently receive Palivizumab in the same season [26].

For children at increased risk of severe RSV disease entering their second RSV season (up to 24 months of age) or children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of 200 mg (two 100 mg IM injections administered simultaneously) is recommended [20]. The AAP defines children at consistently increased risk as severely immunocompromised children, those with cystic fibrosis, children with severe or chronic premature lung disease (for which they required medical support in the 6 months preceding the RSV season) or those at increased risk of developing severe RSV disease because they live in communities in remote areas [26-28] (Tab. I).

Potential adverse effects

Nirsevimab may cause common adverse effects such as pain, swelling, hardness, or redness at the injection site and rashes in the first 7-14 days after administration. Rare adverse effects include hypersensitivity reactions, such as anaphylaxis, and thrombocytopenia. Severe allergic reactions observed with other mAb products may manifest with symptoms such as malaise, headache, arthralgias, muscle weakness, severe skin rashes, urticaria, swelling of the face, difficulty swallowing or breathing and blue discolouration of the lips or nails [16, 22, 29].

Tab. I. Dosage, administration, and usage recommendations.

Patient Type	Schedule	Notes
Infants < 8 months at first RSV season* and < 5 kg	50 mg	For infants born just before or during the RSV season (within the first week of life), it is advisable to administer the dose before discharge from the hospital or during their initial outpatient visit
Children < 8 months at first RSV season and ≥ 5 kg	100 mg	
Children between 8 and 19 months to second RSV season	1 dose** (50 or 100 mg)	Recommended for the second RSV season but may be given up to 24 months of age for children considered at high risk
Children who have received fewer than five doses of Palivizumab during the season	1 dose** (50 or 100 mg)	It is recommended to switch to Nirsevimab if not enough doses of Palivizumab have been received
Children entering the second season of RSV after receiving Palivizumab in the first season	1 dose** (50 or 100 mg)	It is recommended to switch to Nirsevimab in the second season; otherwise, continue with Palivizumab
Children who have received Palivizumab (less than five doses) and can receive Nirsevimab	1 dose** (50 or 100 mg)	Giving one dose of Nirsevimab instead of additional doses of Palivizumab is recommended
Children £ 24 months at high risk of severe RSV disease in their second RSV season or undergoing cardiac surgery/cardiopulmonary bypass	2 doses** (50 or 100 mg each)	Two doses were administered simultaneously. In children undergoing cardiac surgery/ cardiopulmonary bypass who have received a first dose within 90 days, the additional dose should be administered as soon as the child is stable after surgery [16]

* In temperate regions of the Northern Hemisphere, the RSV season typically spans from October to early May, experiencing its peak between December and February. ** 1 dose 50 mg/0.5 ml for children < 5 kg; 1 dose 100 mg/ml for children ≥ 5 kg.

Contraindications and co-administration with other drugs

Nirsevimab is contraindicated in children who have experienced severe hypersensitivity reactions to the active substance or its excipients. Caution should be exercised in children with bleeding disorders, thrombocytopenia, coagulation disorders, or on anticoagulant therapy [16, 20].

Since Nirsevimab is a mAb, that generates an RSV-specific passive immunisation, it is not expected to interfere with the active immune response generated by concomitantly administered vaccines. Clinical studies show that the safety and reactogenicity profile of concomitantly administered vaccines is similar to that of vaccines administered individually, although experience with co-administration is limited. Therefore, Nirsevimab can be administered concomitantly with childhood vaccines [30].

Efficacy Studies

Several clinical trials have studied the efficacy of Nirsevimab: NCT02878330 (2016-2018) [22]; NCT03979313 - MELODY (2019-2023) [29, 31]; NCT03959488 - MEDLEY (2019-2023) [32] and NCT04484935 - MUSIC (2023) [33].

The study NCT02878330 (randomised, double-blind, placebo-controlled phase 2b study), conducted in the USA, confirmed a 78.4% (95% CI: 51.9-90.3) reduction in the incidence of RSV-associated LRTIs and hospitalisations and a 70.1% (95% CI: 52.3-81.2) reduction in physician-assisted LRTIs in healthy preterm infants of Gestational Age (GA) between 29 and 35 weeks at their first RSV season [22].

The phase 3 of the MELODY (NCT03979313) study examined the efficacy of Nirsevimab in infants born at a gestational age of at least 35 weeks who were not eligible for RSV prophylaxis with Palivizumab. In the first cohort, the efficacy against physician-assisted RSV-associated LRTI was 74.5% (95% CI: 49.6-87.1) [29]. In the secondary exploratory cohort, the efficacy against hospitalisation for RSV-associated LRTI was 76.8% (95% CI: 49.4-89.4) and the efficacy against very severe RSV-associated LRTI attended by a physician was 78.6% (95% CI: 48.8-91.0) [31].

A comparison of safety, tolerability and pharmacokinetics of Nirsevimab and Palivizumab, was evaluated in preterm infants in their first RSV season, as well as in infants with CLD and CHD in their first and second RSV season, in the phases 2/3, randomised, double-blind study, NCT03959488-MEDLEY. The incidence of adverse events was similar between treatment groups and cohorts [32].

In the Simoes analysis, the efficacy of Nirsevimab was evaluated using a weight-based dosing regimen in infants born between 29 weeks gestational age and term. A total of 2,350 infants (1,564 in the Nirsevimab group and 786 in the placebo group) were included in the phase 2b and MELODY studies. Nirsevimab demonstrated significant efficacy compared to placebo in the primary endpoint of LRTI associated with physician-assisted RSV, with a relative risk reduction of 79.5%. In infants with risk conditions such as chronic pulmonary disease, CHD, or extreme preterm delivery (MEDLEY), serum exposures to Nirsevimab were like those of the general study population, with above-target exposures in more than 80% of cases [34].

The MUSIC study (NCT04484935) is a 12-month Phase 2 study in which a single dose of Nirsevimab was administered. This uncontrolled, open-label study was conducted to examine safety, pharmacokinetics, and the occurrence of anti-drug antibodies (ADA)

in immunocompromised children aged ≤ 24 months. It was observed that children who were ADA-positive at day 361 tended to have lower Nirsevimab levels than those who were ADA-negative, especially between day 151 and day 361, suggesting an influence of ADA on pharmacokinetics.
Nirsevimab serum concentrations at day 151 were like those shown to be effective in preventing RSV LRTI in healthy patients enrolled in the Phase 3 MELODY study. In addition, some children with underlying conditions involving protein loss showed a rapid decline in serum concentrations of Nirsevimab [33].

Real-world effectiveness data

The EMA approved the use of Nirsevimab shortly before the 2022-2023 RSV season (one year before the US FDA authorisation). Due to the short period between the EMA authorisation and the start of the RSV season, public health policies on universal immunisation of newborns have not been finalised. This delay has postponed the implementation in the relevant European countries until the 2023-2024 season [16].
However, during the 2022-2023 RSV season, a phase 3b efficacy study under real-world conditions on Nirsevimab - HARMONIE (NCT05437510) [35] - was initiated involving several European countries: the UK, France, and Germany. This pragmatic study evaluated Nirsevimab in the prevention of hospitalisation due to RSV-associated LRTI in neonates. Infants with gestational age ≥ 29 weeks were randomised openly in a 1:1 ratio to receive a single dose of Nirsevimab (< 5 kg 50 mg; ≥ 5 kg 100 mg) or no intervention (standard of care) before or during the RSV season. In the primary analysis of 8,058 healthy infants, an efficacy of 83% (95% CI: 67.8-92.0) was observed against hospitalisations for RSV-related LRTIs and 76% (95% CI: 32.8-92.9) against very severe LRTIs confirming consistency with the efficacy endpoints of randomised clinical trials. Furthermore, 58% (95% CI: 39.7-71.2) efficacy prevented real-world hospitalisation for all causes of LRTIs [35].
For the 2023-2024 RSV season, the global implementation of Nirsevimab was very successful in several countries. In Europe, France and Spain were the first countries to adopt a seasonal program. For logistical convenience, the UK opted for an annual immunisation programme with mAb or maternal vaccination. In the US, the CDC recommend the seasonal use of Nirsevimab or maternal vaccination against RSV, with no clear preference for one method over the other [36].
Early results on the effectiveness of Nirsevimab come from Luxembourg [37], Spain [38-43], the US [44], France [45], and Italy [46] (Tab. II).

Luxembourg

In July 2023, the Luxembourg Infectious Diseases Advisory Group recommended prophylaxis with one dose of Nirsevimab in all infants born between October 1, 2023, and March 30, 2024 (weeks 39/2023 - 13/2024); infants born between 1 January and 30 September 2023 for catch-up immunisation; and children under 2 years of age with risk factors for severe respiratory infections. A national immunisation campaign followed this recommendation in October 2023. Vaccination coverage was calculated weekly by dividing the doses of Nirsevimab administered in hospital maternity and neonatology wards by the number of births during the corresponding period. Between October and mid-December 2023, national coverage was estimated at 84% (1277 doses per 1524 births), varying from 66% to 94% between maternity wards, with no reports of adverse events associated with immunisation. However, in other contexts, coverage could not be monitored due to the absence of a vaccination register.
Results: by comparing weeks 39-52/2022 with the same weeks of the 2023/2024 RSV season, a reduction of 38% in cases of hospitalisation for RSV infection was observed in children under 5 years of age (389 cases in 2022 and 241 cases in 2023) and 69% in infants under 6 months of age compared to the previous season (232 (59.6%) in 2022 and 72 (29.9%) in 2023). In particular, during the study periods, the average age of children hospitalised in 2023 was significantly higher than in 2022 (14.4 months in 2023 compared to 7.8 months in 2022). Of the children admitted in 2023, 213 (88.4%) had not been immunised with Nirsevimab, and of these 47 (65.3%) were aged ≤ 6 months. The average length of hospital stay was significantly reduced in 2023 compared to 2022, especially in infants aged ≤ 6 months, as well as in the total number of RSV-related hospitalisation days. In 2023, most infants who required oxygen supplementation or high-flow nasal therapy had not been immunised. The proportion of hospitalised children under 5 years of age admitted to PICUs decreased from 9.3% (36/389) in 2022 to 6.2% (15/241) in 2023.
Strengths: this study provides the first solid evidence that immunisation with Nirsevimab protects infants against severe RSV disease in the context of relatively high immune coverage, as previous clinical studies have shown similar efficacy of Nirsevimab against LRTIs caused by RSV only in healthy patients.
Limitations: the comparison was only made between two seasons, hence it would be important to examine a broader period. Furthermore, the intensity of the 2022 epidemic could be influenced by the reduced circulation of RSV due to immunity depletion [37].

Spain

At the end of September 2023, Spain introduced universal prophylaxis against RSV in its national immunisation program for all infants born on or after 1 April 2023 [38]. Consequently, most of the effectiveness results stem from this country.
The initial results originate from a hospital-based multicentre active surveillance conducted in nine hospitals across three autonomous regions in Spain (five hospitals in Valencia, three in Murcia, and one in Valladolid) [38]. The study population included all infants born on or after 1 April 2023 eligible for immunisation

Tab. II. Real-world effectiveness data with a single dose of Nirsevimab.

Country	Study Details	Population	Main Results	Strengths
Luxembourg	Ernst et al. 2024 [36] Paediatric RSV-H in children ≤ 5 years	Infants born between Oct. 1, 2023, and Mar. 31, 2024: *N* = 1524 4 hospitals, the entire country	nIC coverage with Nirsevimab from Oct to mid-Dec.: 1277/1524 (84%) Reduction in RSV-H: children ≤ 5 years -38%, infants < 6 months -69% Reduction in the proportion of hospitalised children < 5 years in PICUs: 2022: 36/389 (9.3%), 2023: 15/241 (6.2%) Increase in the average age of children hospitalised in 2023: 7.8 months in 2022, 14.4 months in 2023	First real-world data on the effectiveness of Nirsevimab in protecting infants from severe RSV disease
Spain	Lopez-Lacort et al. 2024 [38] Paediatric RSV-LRTI-H in infants < 9 months	Infants during their first RSV season (born on or after Apr. 1, 2023) *N* = 15676 9 hospitals, 3 regions (Valencia, Murcia, Valladolid)	nIC with Nirsevimab ranges from 78.7% to 98.6% Effectiveness in preventing RSV-LRTI-H in infants < 9 months: 70.2% (95% CI: 38.3-88.5) Valencia: 69.3% (95% CI: 36.4-86.2), Murcia: 86.9% (95% CI: 77.1-92.9), Valladolid: 97.0% (95% CI: 87.7-99.6) Effectiveness in preventing LRTI-negative RSV admissions: 32.4% (95% CI: -27.5-63.4). Reduction in RSV-H in infants: 70.2% (95% CI: 38.3-88.5)	Uniform methodology to detect hospitalised RSV cases in three Spanish regions Simultaneous use of screening approach and test-negative design Active surveillance of respiratory infections in all nine hospitals
	Ezpeleta et al. 2024 [39] Paediatric RSV-H in children born in Navarra	Infants born between Oct. 2023 and Jan. 2024 *N* = 1771 All hospitals, 1 region (Navarra)	nIC with Nirsevimab from Oct 2023 to Jan.2024: 1083/1771 (92%) Effectiveness in preventing RSV-H in infants: 88.7% (95% CI: 69.6-95.8) Reduction in the risk of RSV-H: Immunised 8/1083 (0.7%), Non-immunised 8/94 (8.5%) Reduction in the risk of RSV-ICU admission: Immunised 3/1083 (0.3%), Non-immunised 2/94 (2.1%) Vaccination of infants born from Sep. 2023 to Jan. 2024 prevents one hospitalisation per 15.3 immunized infants and avoids 77.5% (95.4/121.5) of the hospitalisations	Effectiveness and impact of the prospective immunisation strategy against RSV-H Provides a benchmark to compare the effectiveness of different immunisation strategies against RSV
	Martinón-Torres et al. 2023 [37] Mallah et al. 2024 [40] Ares-Gómez et al. 2024 [41] Paediatric RSV-LRTI-H in children Very severe RSV-LRTI ICU admissions LRTI admission for all causes	Infants born between Sep. 25, 2023, and Mar. 31, 2024 *N* = 10259 14 hospitals, 1 region (Galicia)	nIC with Nirsevimab ranges from 81.4% to 97.5% Effectiveness in preventing RSV-LRTI-H in infants: 82.0% (95% CI 65.6-90.2%) Reduction in the risk of RSV-LRTI-H: Immunised 30/9408 (0.3%), Non-immunised 16/851 (1.9%) Effectiveness in preventing RSV-LRTI-H in ICU: 86.9% (95% CI 69.1-94.2%) Reduction in the risk of RSV-LRTI ICU admission: Immunised 15/9408 (0.16%), Non-immunised 10/851 (1.18%) Average RSV-LRTI-H prevented per 1000 infants: 407 (Effectiveness: 89.84%)	Rapid and effective implementation of Nirsevimab in the Galician neonatal population A robust information and education campaign and a flexible booking system facilitated high adherence Demonstration of Nirsevimab's effectiveness in preventing RSV-LRTI-H and hospitalisations for all causes, consistent with previous clinical and real-world studies [28, 34, 38]
	Coma et al. 2024 [42] Effectiveness against: RSV infection Primary care attended bronchiolitis Viral Pneumonia Hospital Emergency Visit Hospital admission ICU admission	Infants born between Apr. and Sep. 2023 *N* = 26525 All hospitals, 1 region (Catalonia)	nIC with Nirsevimab: 23127/26525 (87.2%) Reduction in the risk of RSV-related hospital and ICU admissions: Hospital admission: 87.6% (95% CI: 82.1-91.4%) ICU admission: 90.1% (95% CI: 76.3-95.9%) Reduction in the risk of: RSV Infection: 68.9% (95% CI: 51.7-80%) Primary care attended bronchiolitis: 48.1% (95% CI: 42.4-53.3%) Viral Pneumonia: 60.7% (95% CI: 24.2-79.7%) Hospital Emergency Visit: 55.4% (95% CI: 48.4-61.5%)	Use of an integrated database allowing comprehensive analysis of the impact of the Catalan immunisation program on the reduction of RSV-related outcomes The analysis included a wide range of outcomes, offering a comprehensive evaluation of the efficacy of Nirsevimab across different levels of healthcare

▶

Tab. II. Real-world effectiveness data with a single dose of Nirsevimab.

Country	Study Details	Population	Main Results	Strengths
United States	Moline et. Al 2024 [43] RSV-H among infants in their first RSV season	Infants born after Oct. 1, 2023, or aged less than 8 months on Oct. 1, 2023, *N* = 699 7 paediatric academic medical centres (Missouri, Ohio, New York, Washington, Texas, Pennsylvania, Tennessee)	nIC with Nirsevimab: High- Risk conditions 46% (18/39), No risk conditions 6% (41/660) Reduction in RSV-H: 90% (95% CI: 75-96%) Time elapsed between Nirsevimab administration and onset of ARI symptoms: 7-127 days; Median= 45 days (IQR = 19-76 days)	Inclusion of infants according to a standardised definition of ARI, ensuring uniformity of inclusion criteria Systematic testing for the presence of RSV reduces the risk of misdiagnosis or missed diagnosis
France	Paireau et al. 2024 [44] RSV bronchiolitis hospitalised in ICU from Sep. 15, 2023, to Jan. 31, 2024 (TND)	Infants (0-8 months) admitted to ICU in the period Sep. 15, 2023, to Jan. 31, 2024 *N* = 288 20 PICUs, metropolitan areas of the entire country	nIC with Nirsevimab: 58/288 (20.1%) Effectiveness in preventing severe RSV bronchiolitis in neonates admitted to the PICU: 75.9% (95%CI 48.5-88.7%)	Use TND to quickly estimate effectiveness based on surveillance data, reducing confounding bias and providing meaningful results
Italy	Consolati et. Al 2024 [45] RSV-H among infants in their first RSV season 2023-2024	Infants born between May 1, 2023, and Feb. 15, 2024, *N* = 537 1 hospital, 1 region (Valle d'Aosta)	nIC with Nirsevimab: in RSV season 77/89 (86%), out of RSV season 292/448 (65%) Reduction in hospitalisation cases for RSV bronchiolitis: -54% (47 cases in 2022-2023 season *vs* 18 cases in 2023-2024) Hospitalisations for bronchiolitis during the RSV season 2023-2024 after Nirsevimab introduction: Treated with Nirsevimab 0/369 (0%), No Prophylaxis 14/168 (8.3%)	Demonstration of the effectiveness and safety of universal prophylaxis with Nirsevimab in infants, with a marked reduction in the risk of RSV-H

RSV-H: RSV-related hospitalisation; RSV-LRTI-H: RSV-LRTI paediatric hospitalisation; nIC: neonatal immunisation coverage.

with Nirsevimab during their first RSV season, totalling 15,676 infants (6.4% of the Spanish child population eligible for immunisation). The surveillance period was from 1 October 2023 to 31 December 2023 or 10 January 2024, depending on the hospital.

Results: a total of 166 LRTI admissions were included, of which 95 were positive for RSV and 73 were between 0 and 3 months old. Among all 95 RSV cases, 56 (59%) had received immunisation. Population coverage with Nirsevimab was high, varying from 78.7% to 98.6% depending on the hospital. The effectiveness of immunoprophylaxis with Nirsevimab was assessed by region, resulting in 69.3% (95% CI: 36.4-86.2), 86.9% (95% CI: 77.1-92.9), and 97.0% (95% CI: 87.7-99.6) in Valencia, Murcia, and Valladolid, respectively. By using a test-negative design (TND), the immunisation odds of infants testing RSV-positive by PCR (*N* = 77) were compared to those of infants who tested negative (*N* = 71). The overall effectiveness of Nirsevimab in preventing RSV-LRTI hospitalisations was 70.2% (95% CI: 38.3-88.5). In a sensitivity analysis, the effectiveness in preventing LRTI-negative RSV admissions was 19.6% (95% CI: -180.8-82.3) in Valencia, 27.5% (95% CI: -47.3-66.2) in Murcia and, considering both regions, 32.4% (95% CI: -27.5-63.4). Data from Valladolid was not included due to the lack of RSV-negative cases.

Strengths*:* the study integrated data from three Spanish regions using a uniform methodology to detect hospitalised RSV cases. A screening approach and a TND were applied simultaneously, including cases with a negative outcome. Nirsevimab coverage in the eligible cohorts in the participating regions was high in the first three months, averaging around 90%, and effectiveness estimates in immunisation candidate infants (under 9 months of age) were above 70%. In addition to the clinical trial data, a significant reduction in RSV-related hospitalisations in infants under real-world conditions, was demonstrated. Active surveillance of respiratory infections in all nine hospitals provided reliable estimates of Nirsevimab's effectiveness.

Limitations: variations in RSV circulation, hospital admission policies, and case definitions between hospitals and regions influenced the reported effectiveness estimates. Due to the short period since the implementation of the immunisation program and the limited number of cases, it was not possible to assess regional effectiveness using the TND [39].

A second Spanish study aimed to examine the

effectiveness of Nirsevimab was conducted in the region of Navarra [40]. Also, in Navarra, immunoprophylaxis with Nirsevimab was publicly funded and it was offered prospectively to all infants born in maternity wards between October 2023 and January 2024 and to those born abroad but residing in Navarra during the period under review. The follow-up of infants ended after two consecutive weeks without hospitalisation for RSV or after eight weeks without further hospitalisation (28 January 2024). The study design included an analysis of epidemiological and immunisation data, a prospective cohort to assess the effectiveness of Nirsevimab, and an integration of the results to compare the immunisation's impact with other strategies. The proportion of hospitalisations for confirmed RSV infection in infants was calculated according to immunisation status with Nirsevimab.

Results: of the 1,177 infants examined, 1,083 (92.0%) received Nirsevimab and 21 went to the emergency room for RSV infection (11 immunised and 10 not). Only 16 babies were hospitalised (8 immunised and 8 not) and of these, 3 immunised and 2 non-immunised babies were transferred to intensive care. The estimated effectiveness of Nirsevimab was 88.7% (95% CI: 69.6-95.8), with a significantly lower risk of hospitalisation for RSV in immunised (8/1083) infants than in non-immunised (8/94) infants (0.7% and 8.5%, respectively). Vaccination of infants born between September 2023 and January 2024 prevents one hospitalisation per 15.3 vaccinated infants and avoids 77.5% (95.4/121.5) hospitalisations. In a prospective analysis combining the immunisation of babies born from September to January and the recovery of those born from April to August, the estimate was 81.8% (94.4/115.3). These results support immunisation with Nirsevimab at birth, to prevent severe RSV infections and alleviate paediatric hospital resource overload. The absence of reported adverse effects confirms the safety of this immunoprophylaxis.

Strengths: the study evaluates the efficacy of Nirsevimab and the impact of the use strategy against RSV-related hospitalisations, providing an important evaluation of the effectiveness of this immunoprophylaxis. The efficiency of the prospective immunisation strategy is evident, as only few doses of Nirsevimab were sufficient to prevent hospitalisation. Although the study's statistical power was limited by the low number of parents who refused vaccination, it allowed accurate estimates to be obtained. These results provide a good benchmark for comparing the effectiveness of passive immunisation of children and vaccination of pregnant women with new RSV vaccines.

Limitations: the absence of complete information on comorbidities and prematurity for all infants may influence the study to evaluate the efficacy of Nirsevimab and the impact of the use strategy against RSV-related hospitalisations, providing an important evaluation of the effectiveness of this immunoprophylaxis. Overlaps with other high-risk groups were not considered, limiting the understanding of efficacy in these populations. The potential impact of immunoprophylaxis was estimated considering immunisation coverage and the observed epidemiological pattern, which may vary in future years. There is the possibility of variability in the distribution of childhood hospitalisations for RSV according to the month of birth, but extending immunoprophylaxis to children born in different months could cover a significant proportion of infants at risk. Although the study was conducted in a specific region and season, the results could be valid for other similar scenarios. The analysis of emergency room patients may be biased due to intermittent routine testing for RSV, although the results are consistent with other findings of hospital admissions. Finally, while the effectiveness of immunoprophylaxis is high, the cost of Nirsevimab may require economic evaluation to determine the optimal use strategy in different national settings.

The NIRSE-GAL (NCT06180993) study is an impressive prospective longitudinal initiative in the Galicia region, Spain, with a follow-up period of three years [38, 41, 42]. Galicia offers a public health system with universal access, facilitating the involvement and monitoring of study participants. In 2022, 14,495 births occurred in Galicia, with a paediatric vaccination coverage rate of 90%. The Galician public health system (SERGAS), provides care through 14 public hospital complexes and a fully digital, centralised system.

For the 2023-2024 season, RSV cases were actively monitored from 25 September 2023 to 31 March 2024. The campaign end date was decided based on the expected conclusion of the RSV season, using data from the previous 12 seasons (excluding those during the 2020/2021 and 2021/2022 COVID-19 pandemic). Testing for RSV is routinely performed in hospital and emergency room settings, and a primary health surveillance program was developed for NIRSE-GAL that retrieves data on all eligible study participants from several registries in the SERGAS information system. Thanks to this continuous surveillance system, it will be possible to change the start and end dates of the campaigns in the coming years. RSV cases will be identified through hospital registers and laboratory tests, with a thorough evaluation by public health specialists. All the necessary electronic documents for NIRSE-GAL are updated weekly through the Galician Regional Surveillance Information System [47].

The NIRSE-GAL study involves approximately 14,000 children per RSV season, divided into three categories seasonal group (infants born during the RSV season), catch-up group (children aged less than six months at the start of the RSV season), and high-risk group (children aged between 6 and 24 months at the start of the RSV season who have CHD, BPD, severe immunosuppression, congenital metabolic disorders, neuromuscular diseases, severe pulmonary diseases, genetic syndromes causing significant respiratory problems, trisomy 21, cystic fibrosis, palliative care patients). If the immunisation recommendation changes in future seasons, the stratification strategy will be adjusted accordingly to the updated recommendation.

Nirsevimab is administered through the SERGAS network of public hospitals and primary health centres,

with an educational campaign for health workers and the general public. Infants will receive a dose of Nirsevimab depending on weight and risk conditions. Depending on the children's specific situation, the follow-up period varies from the immunisation date until the event of interest, death, or end of the observation period.

The primary objective of the NIRSE-GAL study is to evaluate the effectiveness of Nirsevimab on RSV-related LRTI admissions during the 2023-2024, 2024-2025, and 2025-2026 RSV seasons in the different patient groups. Secondary objectives, again subdivided according to enrolment group, includes: (I) to assess the effectiveness of Nirsevimab against 4 key secondary endpoints (a) very severe RSV-related LRTI (Padmissions), (b) very severe LRTI related to RSV is defined by the label of severity, (c) LRTI admission for all causes, (d) hospitalisation for any cause); (II) to assess the impact of Nirsevimab on primary care for any reason, primary care for respiratory disease, acute otitis media diagnosis, pneumonia diagnosis, acute respiratory diagnosis and antibiotic use in children; (III) to evaluate the impact of Nirsevimab on RSV-related visits in emergency departments and all-cause visits in emergency departments; (IV) longitudinal assessment of Nirsevimab's effect on wheezing and asthma; (V) safety evaluation of Nirsevimab and reporting of adverse events; (VI) assessment of absorption.

There are also composite endpoints including various respiratory conditions and infections along with exploratory objectives. These include evaluation of the RSV-related LRTI hospitalisation rate in infants and subsequently in children, exploring the impact of different primary and secondary endpoints, Nirsevimab's impact evaluation on bacterial respiratory infections, study of the reinfection/readmission rate and duration of hospitalisations for RSV and evaluation of trends in the duration of hospitalisations for RSV. Therefore, the results of this study will be significant for the conduct of appropriate cost-effectiveness studies [38, 41].

Results: preliminary results of the NIRSE-GAL study were published 3 weeks after the beginning of the immunisation campaign (31 October 2023). Immunisation adherence in infants born since the start of the campaign (seasonal group) reached 92.6% (1,104/1,192). In the recovery and high-risk infant groups, coverage was 81.4% (5,820/7,150) and 97.5% (317/325), respectively. No serious adverse effects were reported in this first analysis.

A second part of the results of the first season of the study, were published in May 2024 [42]. These were based on data collected done by 15 December 2023. 10,259 infants were eligible for Nirsevimab administration: 6,919 (67.4%) in the recovery group and 3,340 (32.6%) in the seasonal group; of these, 9,408 (91.7%) received Nirsevimab: 6,220 (89.9%) in the recovery group and 3,188 (95.4%) in the seasonal group. Immunisation was also offered to 360 high-risk infants achieving a coverage rate of 97.0% (348/360). 83.8% of infants in the recovery group, 96.4% in the high-risk group, and 92.6% in the seasonal group were vaccinated before the start of the RSV season (by 20 October 2023). Most of the missed vaccinations were due to missed appointments. Only 2.0% of households refused vaccination, with no significant differences between the seasonal and catch-up groups. The distribution by sex and age was even, with an average gestational age at birth of 4 months. 656 (6.6%) of the infants were premature, but 93.9% (616/656) still received Nirsevimab.

During the reporting period, 46 RSV-LRTI hospitalisations (30 in immunised and 16 in non-immunised children) and 25 ICU admissions (15 immunised and 10 non-immunised children) were observed. The effectiveness of Nirsevimab against RSV-related LRTI hospitalisations was 82.0% (95% CI: 65.6-90.2) and 86.9 (95% CI: 69.1-94.2). In addition, protection was found for both all-cause and LRTI hospitalisations. Sensitivity analysis confirmed these results. The 2023-24 RSV season showed significantly lower hospitalisation rates in infants treated with Nirsevimab compared to previous seasons. The immunisation campaign prevented an average of 407 RSV-related LRTI hospitalisations per 1,000 infants, with an effectiveness of 89.84% (IQR 87.58-90.30). Only five adverse events were reported, none of these related to Nirsevimab. The high-risk group was not included in the efficacy analysis because of the sample size (including only 12 in the non-Nirsevimab group) and the low number of events in this group: 22 all-cause hospitalisations, nine LRTI hospitalisations for all causes and three RSV-related LRTI hospitalisations.

Strengths: rapid and effective implementation of Nirsevimab occurred in the Galician neonatal population, with more than 90% of eligible infants immunised within 3 months of the campaign's start. The effectiveness of Nirsevimab in preventing RSV-related LRTI admissions and hospitalisations for all causes is comparable to the results of previous clinical and real-world studies [29, 31, 35, 39]. Finally, the use of historical RSV season data, which incorporates the variability of viral circulation over time, was essential to provide adequate context for the results.

Limitations: the report is based on data from the first 3 months of the immunisation campaign; therefore, the results may be unrepresentative of the entire 2023-24 RSV season. It was impossible to assess specific endpoints (*e.g.* ICU admissions or mechanical ventilation) to estimate the effectiveness of Nirsevimab in these conditions. Limitations related to sample size and missing data for some variables at birth, could influence the interpretation of the results (prematurity, birth weight, and gestational age at birth). Finally, while the data support the effectiveness of Nirsevimab, the analysis has not yet considered the cost-effectiveness, which will be evaluated in the future.

A final Spanish study is conducted in Catalonia by Coma et al. from 1 October 2023 to 31 January 2024 [43]. The study analysed the effectiveness of Nirsevimab against RSV infection and its potential severity using data collected from different Catalan healthcare databases from October 1, 2023, to January 31, 2024. In this retrospective cohort study, 26,525 infants born between April and September 2023 resident

in Catalonia and registered in the health databases were included. Several outcomes related to RSV infection and severity were examined including primary care-assisted bronchiolitis, RSV infection, viral pneumonia, hospital emergency room visits, and RSV-related hospital or ICU admissions. Other infectious diseases were also examined for unmeasured confounders. Covariates included sociodemographic data such as age, gender, residence, nationality, rurality, and socioeconomic status. The study included both infants immunised with Nirsevimab and non-immunised infants, following them until the event of interest, death, or the end of the study.
Results: 23,127 infants (87.2%) included in the study, were immunised with Nirsevimab. Vaccine coverage was rapid, with 76.3% immunised infants within the first month of the immunisation campaign. The control and Nirsevimab groups were adjusted by gender, rurality, and socio-economic status, but differed in age and nationality. In the control group, higher incidence rates for all outcomes were observed, especially severe cases, such as hospital and ICU admissions.
Nirsevimab demonstrated significant effectiveness in reducing the risk of hospitalisation and ICU admission, with an adjusted hazard ratio (HR) of 0.124 (0.086-0.179; immunised 52/control 76) and 0.099 (0.041-0.237; immunised 8/control 17), respectively. Higher incidence rates were also observed in the control group for all other outcomes: RSV infection HR 0.311 (0.2-0.483; immunised 71/control 31), primary care attended bronchiolitis HR 0. 519 (0.467-0.576; immunised 1560/control 617), viral pneumonia HR 0.393 (0.203-0.758; immunised 42/control 14), emergency room visits HR 0.446 (0.385-0.516; immunised 604/control 354).
The estimated effectiveness of Nirsevimab was 90.1% (95% CI: 76.3-95.9) versus ICU admission and 87.6% (95% CI: 82.1-91.4) versus hospital admission. Impetigo diagnoses were used as negative controls and were similar in the two groups. A sensitivity analysis confirmed the Nirsevimab's effectiveness in preventing hospitalisation for bronchiolitis caused by other pathogens.
Two deaths were reported in the study population, both in infants who were not immunised with Nirsevimab and unrelated to RSV infection. Therefore, these deaths were not considered significant study outcomes.
Strengths: the study utilises a linked database that integrates primary care and hospital data (including intensive care), allowing a comprehensive analysis of the impact of the Catalan immunisation program on the reduction of RSV-related outcomes. It offers a comprehensive view of Nirsevimab's impact across a wide range of outcomes of different severity and across all levels of care. The robustness of the results is confirmed by the comparability of the cohorts, which includes unobserved covariates. The conclusions are strengthened by the absence of an association between immunisation with Nirsevimab and impetigo, used as a negative control outcome.
Limitations: the analysis may be subject to confounding due to the observational nature of the data. A comprehensive analysis of less specific outcomes, such as bronchiolitis diagnosed in primary care or viral pneumonia, was not included due to the lack of complete testing for all patients in these settings. The analysis is based on the RSV epidemic period 2023-2024, potentially limiting the extensibility of the results to other periods.

United States

In the United States, the New Vaccine Surveillance Network (NVSN) evaluated the efficacy of Nirsevimab against RSV-associated hospitalisation among infants in their first RSV season during the period 1 October 2023-29 February 2024 at the seven US academic paediatric medical centres. Each site included in the analysis, had to have enrolled at least five infants who were treated with Nirsevimab at least 7 days before symptom onset [44].
The analysis involved infants who were born after 1 October 2023 or were less than 8 months of age on 1 October 2023, and who were admitted with an ARI and received the drug Nirsevimab. Infants who received Palivizumab maternal RSV vaccination or had inconclusive RSV test results were excluded.
The efficacy of Nirsevimab in avoiding RSV-related hospitalisation was evaluated in a TND case-control study. Cases included infants with positive RSV test results, while controls had test negative results. Effectiveness was calculated using multivariable logistic regression models, controlling age at recruitment, month of illness, enrolment site, and medical conditions at high risk for severe RSV disease. Prematurity status and insurance type were examined as potential confounding factors, but did not influence the estimates and therefore were not included in the final model.
Results*:* among the 1,036 eligible infants, 699 infants from four sites met the inclusion criteria: 146 preterm births (< 37 weeks), 551 term births 2 with unknown gestational age, and 39 with at least one risk factor. There were 407 (58%) patients with a positive RSV test result (cases) and 292 (42%) patients with a negative result (controls). Nirsevimab administration was more common among infants with high-risk medical conditions (18/39; 46%; $p < 0.001$) than among healthy infants 41/660 (6%). No significant differences were found in the frequency of Nirsevimab administration according to prematurity status or insurance type. The time elapsed between Nirsevimab administration, and the onset of ARI symptoms ranged from 7 to 127 days with a median of 45 days (IQR = 19-76 days). The effectiveness of Nirsevimab in preventing RSV-associated hospitalisation was 90% (95% CI: 75-96).
Strengths: infants were included according to a standardised definition of ARI, ensuring uniformity of the inclusion criteria. The presence of RSV was systematically tested, reducing the risk of misdiagnosis or missed diagnosis. The presence of Nirsevimab in the immunisation computer systems or medical records of all newborns was verified, ensuring adequate recording of treatments. Estimating the effectiveness of Nirsevimab under real-world conditions was crucial, especially for children at high risk of severe disease

(aged between 8 and 19 months) for whom Nirsevimab administration before the start of the second RSV season is recommended.
Limitations: only a small proportion of infants hospitalised with ARI received Nirsevimab, likely due to delayed and intermittent supply availability, as well as selection criteria favouring infants with baseline conditions. This prevented stratified estimates based on time since Nirsevimab administration. Some infants may have contracted RSV before receiving Nirsevimab, which could impact the estimated effectiveness of the drug. Since the dosage of Nirsevimab has not been established, it was impossible to assess dose-related effectiveness. Finally, effectiveness was only evaluated in preventing RSV-associated hospitalisation, without considering other outcomes such as outpatient and emergency room visits, which could be equally significant.

France

In France, in response to the increased intensity of recent RSV outbreaks, bronchiolitis surveillance has been reinforced for the 2023-2024 season through a multicentre network of volunteer PICUs coordinated by Santé Publique France [45].
Using surveillance data from this network, a case-control study based on the TND was conducted to evaluate the effectiveness of Nirsevimab in PICU hospitalisation for RSV bronchiolitis in metropolitan France between 15 September 2023 and 31 January 2024. Infants aged 0 to 8 months (including premature and comorbid) who had received Nirsevimab were included (319). Infants who tested positive for RSV were considered cases, while negative infants were considered controls. Exclusion criteria included lack of etiological research, unknown prior treatment against RSV other than Nirsevimab, unknown comorbidities/ prematurity, or missing data. In the main analysis, 31 infants who had received Nirsevimab <8 days before PICU admission or those with an unknown date of receipt were excluded. A second sensitivity analysis included 312 infants (aged > 1 month) in whom Nirsevimab administration had occurred more than 8 days before PICU admission. A final sensitivity analysis included all infants (319) who had received Nirsevimab, regardless of the time elapsed between administration and PICU admission. Two periods were defined based on RSV detection rates: low circulation from 15 September to 29 October 2023 and high circulation from 30 October 2023 to 07 January 2024. The effectiveness of Nirsevimab was estimated with a logistic regression model, adjusted for age group, gender, comorbidity, prematurity, and period.
Results: among the 542 reported cases of severe bronchiolitis, 288 infants admitted to 20 PICUs were included in the main analysis, of whom the majority (91%) were aged 0-3 months and 55% were male. RSV was identified in 83% of the infants, while rhinovirus was the most common pathogen in the controls. The cases were younger and had fewer males than the controls. During the study, 20% of the infants had received Nirsevimab at least 8 days before PICU admission, with an average delay of 35 days.
In the main analysis, the adjusted effectiveness of Nirsevimab against RSV bronchiolitis cases admitted to the PICU was estimated at 75.9% (95% CI: 48.5-88.7). In sensitivity analyses, the effectiveness of Nirsevimab was estimated at 80.6% (95% CI: 61.6-90.3%) for SA1 and 80.4% (95% CI: 61.7-89.9%) for SA2.
Strengths: the study found the high effectiveness of Nirsevimab in preventing severe RSV bronchiolitis in infants admitted to the PICU, with estimates ranging from 75.9% (95% CI: 48.5-88.7) to 80.6% (95% CI: 61.6-90.3) depending on the assumptions (≤ 8 days *vs* ≥ 8 days) in line with results from other clinical and surveillance studies. The TND allowed rapid estimation of effectiveness based on surveillance data, reducing confounding bias and providing meaningful results.
Limitations: The small sample size, especially for controls, limited the ability to perform subgroup analyses or to match cases and controls, thereby reducing the precision of the estimates. Although sensitivity analyses were conducted, there could be a bias if administration dates and prior treatment were reported less frequently when the pathogen was not RSV, leading to an underestimation of effectiveness. Furthermore, while the TND reduced confounding bias, bias may still exist if the use of healthcare differs between infants treated or not treated with Nirsevimab depending on the severity of the disease.

Italy

This is prospective observational cohort study examines the incidence of hospitalisation for RSV bronchiolitis or pneumonia in two groups of children, one receiving Nirsevimab prophylaxis and the other not [46]. The objectives include assessing Nirsevimab' safety and optimising its distribution. In Italy Nirsevimab became available from 20 December 2023, however, all children born in Valle d'Aosta between 1 May 2023 and 15 February 2024 (556) were included in the study, excluding those with risk factors already treated with Palivizumab and non-residents [20]. The subjects were categorised into in-season RSV births (95, for those born between 19/12/2023 and 15/02/2024) and out-of-season RSV births (461, for those born between 01/05/2023 and 18/12/2023). Eligibility for prophylaxis was determined via local information systems, and distribution was ensured by the Service of Hygiene and Public Health. Telephone interviews were conducted 7 and 14 days after Nirsevimab administration to monitor side effects, while data on hospitalisations for RSV bronchiolitis were obtained from local information systems. This approach allowed a comprehensive evaluation of the efficacy and safety of Nirsevimab, providing crucial information on its impact on hospitalisations and RSV-related adverse events.
Results: 69% of the 537 candidates for Nirsevimab's prophylaxis (89 born in the RSV season and 448 born out of RSV season) adhered with a coverage rate of 86% (77/89) in in-season births and 65% (292/448) in out-of-season births. During the RSV season 2023-2024, 29 RSV bronchiolitis hospitalisations occurred (18 recorded for children born after May 1, 2023), compared

to 61 (47 recorded for children born after May 1, 2022) in the previous season. Up to 20 December 2023, no infants treated with Nirsevimab were hospitalised for bronchiolitis, compared to 8.3% (14/168) of those not treated. Side effects of Nirsevimab were mild and short-lived, with no cases of serious complications. These results suggest effective prevention of RSV infections and good tolerability of Nirsevimab in the study population.

Strengths: the study demonstrates the effectiveness and safety of universal prophylaxis with Nirsevimab in infants, positioning Valle d'Aosta as pioneering Italian region in extending universal prophylaxis to infants without risk factors for RSV complications. Infants who received Nirsevimab showed a significant reduction in the risk of RSV-related hospitalization compared to those who did not, consistent with findings from other countries. No infants immunised with Nirsevimab required hospitalisation for RSV bronchiolitis, indicating robust effectiveness in preventing RSV infections in this vulnerable population. The universal prevention approach emerges as a compelling strategy, ensuring broad coverage and equitable access, and significantly improving health protection of infants and children. Evidence is the significant drop in hospitalisations for RSV infection in children not in their first epidemic season, suggesting that the program has had a real impact regardless of the reduction in epidemic frequency. The cost-effectiveness of universal prophylaxis with Nirsevimab is underlined by the direct savings resulting directly from the hospitalisation reduction and the discontinuation of selective prophylaxis with Palivizumab, as well as by the indirect savings resulting from decreased social care costs incurred by parents for RSV-infected children.

Limitations: the study was conducted in a small Italian region, so it may not fully reflect the complexities of larger and more diverse populations. Despite the promising results, further economic evaluations are needed to assess the cost-effectiveness of Nirsevimab compared to standard therapy. While the results are encouraging, it is important to continue surveillance to monitor any emergent patterns of resistance or changes in RSV epidemiology following the widespread adoption of Nirsevimab prophylaxis.

Trials in Progress

There are ongoing clinical trials evaluating efficacy and effectiveness: JUBILUS (NCT06042049) – Japan [48] CHIMES (NCT05110261) – China [49]; ENVIE (NCT06030505) – France [50]; EPINIR-BRON (NCT06185647) – France [51] and BEAR (NCT06325332) – US [52].

The JUBILUS (NCT06042049) clinical trial is a phase 3, single-arm, open-label study aimed at evaluating the safety, pharmacokinetics, and immune response to the administration of two doses of Nirsevimab to infants with immunodeficiency, CLD, CHD, Down syndrome or premature birth. The goal is to recruit 33 patients by April 2025, excluding those with a seizure disorder, on respiratory support, scheduled for cardiac surgery within six months [48].

The CHIMES study (NCT05110261) is a phase 3, double-blind, placebo-controlled trial evaluating the efficacy and safety of a single dose of Nirsevimab in healthy preterm and term infants in the first year of life. It is expected to enrol 800 children, with an estimated completion date of November 2025. Subjects meeting the criteria for treatment with Palivizumab are excluded from the study [49].

ENVIE (NCT06030505) is an observational case-control study to assess the effectiveness of Nirsevimab in children hospitalised with RSV bronchiolitis. The study plans to enrol 963 children < 12 months treated for RSV bronchiolitis (cases) and hospitalised for other causes (controls). Subjects who received Palivizumab or maternal RSV vaccination were excluded from the study. Enrolment started on October 17, 2023, with an estimated completion date of July 15, 2026. Secondary outcomes included the proportion of children hospitalised for RSV bronchiolitis requiring invasive or non-invasive ventilation, the duration of hospitalisation, the time between immunisation with Nirsevimab and hospitalisation for RSV bronchiolitis, the monthly frequency of hospitalisation for RSV bronchiolitis, and the proportion of children hospitalised for RSV bronchiolitis with concomitant viral detection or other than RSV on nasopharyngeal swab [50].

The retrospective observational study EPINIR-BRON (NCT06185647) started on October 14, 2023, and ended on February 29, 2024. The aim is to evaluate the Nirsevimab's ffectiveness in a real-life setting in the use of emergency rooms to treat bronchiolitis and to reduce hospitalisations in France. For the study, all infants aged < 12 months were enrolled, and two separate analyses were performed: a comparative analysis between infants who received Nirsevimab and those who did not receive it before their ER visit for bronchiolitis, and a comparison between infants diagnosed with bronchiolitis who received Nirsevimab and those who did not, to assess the drug's effectiveness on ER use and hospitalisation. The results have not yet been made public [51].

Lastly, the BEAR trial (NCT06325332) conducted in the United States (start 01/4/2024 and end 01/04/2025), involves the inclusion of 33000 infants born ≥ 37 weeks' gestation and aged 0-12 months facing their first season of RSV, with no significant medical history. The study is a retrospective observational cohort investigation designed to evaluate the effectiveness of Nirsevimab in preventing RSV-related medical visits and healthcare utilisation in infants facing their first season of RSV in the United States. Current primary outcome measures include the incidence of PCR-confirmed first RSV episodes with an ICD-identified diagnosis of LRTD, along with the number of physician visits associated with these episodes. Current secondary outcome measures assess the number of respiratory and LRTD-related physician visits, along with the effect of Nirsevimab on RSV confirmation by PCR, otitis media diagnoses, and antibiotic prescribing [52].

Conclusions

Studies examining the effectiveness of Nirsevimab in preventing hospitalisations due to RSV infections in infants provide a detailed overview of the benefits of this immunoprophylaxis.

Consistently high immunisation coverage rates with Nirsevimab have been reported, indicating successful implementation of immunisation programs with efficient and effective distribution among target populations in different countries.

Effectiveness estimates slightly varied from region to region, but demonstrated significant protection against RSV hospitalisations. Data on a meaningful reduction in hospitalisations for RSV infection among immunised infants were reported in all studies. In particular, the Spanish – Galician and Catalan – studies reported significant effectiveness of Nirsevimab in reducing the risk of hospitalisation and admission to PCIU for RSV-LRTIs, with variations from 86.9 % (95% CI: 69.1-94.2) to 90.1% (95% CI: 76.3-95.9) against PICU admissions and from 82.0% (95% CI: 65.6-90.2) to 87.6% (95% CI: 82.1-91.4) against hospital admissions [42, 43].

All the studies reviewed provide evidence of the effectiveness of immunisation with Nirsevimab in real-world settings, beyond the controlled conditions of clinical trials, and highlight its safety and feasibility. Once again, the Galician study -NIRSE-GAL- and the Catalan study stood out as they integrated primary care data with hospital data allowing a comprehensive analysis of the impact of the immunisation program on the reduction of RSV-related outcomes. Specifically, the NIRSE-GAL study established and utilised a primary care surveillance program that retrieves data on all participants eligible for Nirsevimab from several registries in the SERGAS information system [38, 41-43].

Although the studies provide valuable insights into the efficacy of Nirsevimab, there are limitations to consider. Delayed and intermittent availability of Nirsevimab supply, selection criteria favouring infants with underlying conditions, and small sample sizes limited the ability to conduct subgroup analyses or match cases and controls in some studies. Furthermore, despite efforts to standardise inclusion criteria and verify the presence of Nirsevimab in immunisation registries, hospital admission policies, and case definitions differed between countries. Potential confounding due to the observational nature of the data and the limited duration of the analysis should also be considered, resulting in a lack of long-term data that could limit the understanding of Nirsevimab's long-term effectiveness. Another consideration is the variation in RSV circulation across seasons. To achieve effective immunisation, it will be essential to accurately determine the beginning and end of the RSV season, which could be complicated, as evidenced by the disruptions caused by the COVID-19 pandemic [53]. As it is already the case in Galicia, ongoing surveillance will be necessary to comprehensively assess the circulation of RSV and monitor any emerging patterns of resistance or changes in RSV epidemiology following widespread vaccine uptake.

Our work has not included and examined cost-effectiveness studies: a thorough economic evaluation will be necessary to ensure the best use of Nirsevimab in different settings. Additional data that could complement and confirm the already proven effectiveness of the product are represented by long-term effects and epidemiological trends of RSV.

To comprehensively evaluate the effectiveness of Nirsevimab, it is essential to emphasise the importance of continuous research and surveillance in various settings. The results of ongoing clinical trials will be crucial, as they will examine the effectiveness of Nirsevimab in several different medical situations and conditions. Specifically, the JUBILUS trial in Japan will provide data on the safety, pharmacokinetics, and immune response of two doses of Nirsevimab administered to high-risk newborns. Similarly, the CHIMES trial in China will provide valuable information on effectiveness in preterm infants [48, 49].

Most of the results summarised in this work were instrumental in enabling international health authorities to promote the recommendation of Nirsevimab use in all infants and children in their first season of RSV. The first countries to recommend its use were the USA [21, 25, 26], France [54], Luxembourg [37], Spain [55], Chile [56] and Australia [57]. For the 2024/2025 season, seven other countries followed suit, recommending the universal implementation of Nirsevimab: Netherlands [58], England [59], Germany [60], Austria [61], Canada [62], Belgium [63] and Italy [64].

In particular, in Italy, the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI) and the Italian Society of Infectious and Tropical Diseases (SIMIT) suggest considering the availability of Nirsevimab as an important universal preventive tool against RSV diseases. They emphasise the need to consider Nirsevimab immunisation as a vaccine programme in regulatory and organisational documents, intended to cover the entire cohort of infants, recognising Nirsevimab as prevention and not treatment [65].

Overall, available data provide valuable insights into the efficacy, safety, and impact of immunisation with Nirsevimab in preventing severe RSV infections in infants, highlighting its potential to reduce the burden of RSV-related hospitalisations and improve paediatric health outcomes.

Fundings

This study did not receive any specific funding.

Conflict of interest statement

AO, V.B, MC, SG, EM, EP, CR, DP and GI: provided consultation and/or received speaker fees and/or received grants to conduct experimental and/or observational studies from CSL Seqirus, GSK, Moderna, Novavax, Pfizer, Sanofi, Viatris, MSD and AstraZeneca. MS and FB: declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Author's contributions

AO, MS, GI: conceptualization; AO, MS, DP: methodology; AO, MS: formal analysis; AO, MS: investigation; AO, DP, GI: resources; AO, MS: data analysis; AO, MS: writing-original draft preparation; VB, FB, MC, SG, EM, EP, CR: writing-review and editing; AO, DP, GI: visualization; DP, GI: supervision. All authors have read and agreed to the current version of the manuscript.

References

[1] Azzari C, Baraldi E, Bonanni P, Bozzola E, Coscia A, Lanari M, Manzoni P, Mazzone T, Sandri F, Checcucci Lisi G, Parisi S, Piacentini G, Mosca F. Epidemiology and prevention of respiratory syncytial virus infections in children in Italy. Ital J Pediatr 2021;47:198. https://doi.org/10.1186/s13052-021-01148-8.

[2] Dovizio M, Veronesi C, Bartolini F, Cavaliere A, Grego S, Pagliaro R, Procacci C, Ubertazzo L, Bertizzolo L, Muzii B, Parisi S, Perrone V, Baraldi E, Bozzola E, Mosca F, Esposti LD. Clinical and economic burden of respiratory syncytial virus in children aged 0-5 years in Italy. Ital J Pediatr 2024;50:57. https://doi.org/10.1186/s13052-024-01628-7.

[3] Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, Romagnoli C, Colonna P, Biondi A, Biban P, Chiamenti G, Bernardini R, Picca M, Cappa M, Magazzù G, Catassi C, Urbino AF, Memo L, Donzelli G, Minetti C, Paravati F, Di Mauro G, Festini F, Esposito S, Corsello G. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr 2014;40:65. https://doi.org/10.1186/1824-7288-40-65.

[4] Sommer C, Resch B, Simões EA Risk factors for severe respiratory syncytial virus lower respiratory tract infection. Open Microbiol J 2011;5:144-54. https://doi.org/10.2174/1874285801105010144.

[5] Barbieri E, Cavagnis S, Scamarcia A, Cantarutti L, Bertizzolo L, Bangert M, Parisi S, Cantarutti A, Baraldi E, Giaquinto C, Baldo V. Assessing the burden of bronchiolitis and lower respiratory tract infections in children ≤ 24 months of age in Italy, 2012-2019. Front Pediatr 2023;11:1143735. https://doi.org/10.3389/fped.2023.1143735.

[6] Rha B, Curns AT, Lively JY, Campbell AP, Englund JA, Boom JA, Azimi PH, Weinberg GA, Staat MA, Selvarangan R, Halasa NB, McNeal MM, Klein EJ, Harrison CJ, Williams JV, Szilagyi PG, Singer MN, Sahni LC, Figueroa-Downing D, McDaniel D, Prill MM, Whitaker BL, Stewart LS, Schuster JE, Pahud BA, Weddle G, Avadhanula V, Munoz FM, Piedra PA, Payne DC, Langley G, Gerber SI. Respiratory Syncytial Virus-Associated Hospitalizations Among Young Children: 2015-2016. Pediatrics 2020;146:e20193611. https://doi.org/10.1542/peds.2019-3611.

[7] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, Madhi SA, Omer SB, Simões EAF, Campbell H, Pariente AB, Bardach D, Bassat Q, Casalegno JS, Chakhunashvili G, Crawford N, Danilenko D, Do LAH, Echavarria M, Gentile A, Gordon A, Heikkinen T, Huang QS, Jullien S, Krishnan A, Lopez EL, Markić J, Mira-Iglesias A, Moore HC, Moyes J, Mwananyanda L, Nokes DJ, Noordeen F, Obodai E, Palani N, Romero C, Salimi V, Satav A, Seo E, Shchomak Z, Singleton R, Stolyarov K, Stoszek SK, von Gottberg A, Wurzel D, Yoshida LM, Yung CF, Zar HJ; Respiratory Virus Global Epidemiology Network; Nair H; RESCEU investigators. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet 2022;399:2047-64. https://doi.org/10.1016/S0140-6736(22)00478-0.

[8] Kuhdari P, Brosio F, Malaventura C, Stefanati A, Orsi A, Icardi G, Gabutti G. Human respiratory syncytial virus and hospitalization in young children in Italy. Ital J Pediatr 2018;44:50. https://doi.org/10.1186/s13052-018-0492-y.

[9] Barbati F, Moriondo M, Pisano L, Calistri E, Lodi L, Ricci S, Giovannini M, Canessa C, Indolfi G, Azzari C. Epidemiology of Respiratory Syncytial Virus-Related Hospitalization Over a 5-Year Period in Italy: Evaluation of Seasonality and Age Distribution Before Vaccine Introduction. Vaccines (Basel) 2020;8:15. https://doi.org/10.3390/vaccines8010015.

[10] Fortunato F, Campanozzi A, Maffei G, Arena F, Carri VD, Rollo T, Lopalco PL, Martinelli D. Respiratory syncytial virus-associated hospitalizations among children: an Italian retrospective observational study. Ital J Pediatr 2024;50:45. https://doi.org/10.1186/s13052-024-01617-w.

[11] Scarpaci M, Bracaloni S, Esposito E, De Angelis L, Baglivo F, Casini B, Panatto D, Ogliastro M, Loconsole D, Chironna M, Pariani E, Pellegrinelli L, Pandolfi E, Croci I, Rizzo C; RSVComNet Italia. RSV Disease Burden in Primary Care in Italy: A Multi-Region Pediatric Study, Winter Season 2022-2023. Influenza Other Respir Viruses 2024;18:e13282. https://doi.org/10.1111/irv.13282.

[12] Istituto Superiore di Sanità. Rapporto RespiVirNet Virologico 2024-17. Available at: https://respivirnet.iss.it/pagine/rapporto-Influnet.aspx (Accessed on: 14/05/2024).

[13] Sparrow E, Adetifa I, Chaiyakunapruk N, Cherian T, Fell DB, Graham BS, Innis B, Kaslow DC, Karron RA, Nair H, Neuzil KM, Saha S, Smith PG, Srikantiah P, Were F, Zar HJ, Feikin D. WHO preferred product characteristics for monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) disease in infants - Key considerations for global use. Vaccine 2022;40:3506-10. https://doi.org/10.1016/j.vaccine.2022.02.040.

[14] World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2016 - Conclusions and recommendations. Wkly Epidemiol Rec 2016;91:265-84.

[15] Esposito S, Abu Raya B, Baraldi E, Flanagan K, Martinon Torres F, Tsolia M, Zielen S. RSV Prevention in All Infants: Which Is the Most Preferable Strategy? Front Immunol. 2022;13:880368. https://doi.org/10.3389/fimmu.2022.880368.

[16] EMA. European Medicines Agency: Beyfortus. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/beyfortus (Accessed on: May 14, 2024).

[17] AIFA. Agenzia Italiana del Farmaco: Beyfortus. Available at: https://www.aifa.gov.it/documents/20142/1805944/DETERMINA_9-2023_BEYFORTUS.pdf (Accessed on: 14/05/2024).

[18] EMA. European Medicines Agency: Abrysvo. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo (Accessed on: 14/05/2024).

[19] AIFA. Agenzia Italiana del Farmaco: Abrysvo. Available at: https://www.aifa.gov.it/documents/20142/2128501/DETERMINA_127-2023_ABRYSVO.pdf (Accessed on: 14/05/2024).

[20] AstraZeneca, Sanofi Pasteur Beyfortus (nirsevimab - alip) [Prescribing information]. 2023. Available at: https://products.sanofi.us/beyfortus/beyfortus.pdf (Accessed on: 14/05/2024).

[21] US, Sanofi-Aventis. Available at: https://www.news.sanofi.us/2023-08-03-U-S-CDC-Advisory-Committee-unanimously-recommends-routine-use-of-Beyfortus-TM-nirsevimab-alip-to-protect-infants-against-RSV-disease [Online] 03-08-2023 (Accessed on: 14/05/2024).

[22] Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, Simões EAF, Esser MT, Khan AA, Dubovsky F, Villafana T, DeVincenzo JP; Nirsevimab Study Group. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med 2020;383:415-25. https://doi.org/10.1056/NEJMoa1913556.

[23] Zhu Q, McLellan JS, Kallewaard NL, Ulbrandt ND, Palaszynski S, Zhang J, Moldt B, Khan A, Svabek C, McAuliffe JM, Wrapp D, Patel NK, Cook KE, Richter BWM, Ryan PC, Yuan AQ, Suzich JA. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. Sci Transl Med 2017;9:eaaj1928. https://doi.org/10.1126/scitranslmed.aaj1928.

[24] Brady T, Cayatte C, Roe TL, Speer SD, Ji H, Machiesky L, Zhang T, Wilkins D, Tuffy KM, Kelly EJ. Fc-mediated functions of nirsevimab complement direct respiratory syncytial virus neutralization but are not required for optimal prophylactic protection. Front Immunol 2023;14:1283120. https://doi.org/10.3389/fimmu.2023.1283120.

[25] ACIP. Evidence to Recommendations for Use of Nirsevimab in Infants born during the RSV season or entering their first RSV season. Available at: https://www.cdc.gov/vaccines/acip/recs/grade/Nirsevimab-season1-rsv-infants-children-etr.html (Accessed on: 14/05/2024).

[26] AAP. Recommendations for the Prevention of RSV Disease in Infants and Children. Available at: https://publications.aap.org/redbook/resources/25379/AAP-Recommendations-for-the-Prevention-of-RSV?autologincheck=redirected (Accessed on: 14/05/2024).

[27] Jones JM, Fleming-Dutra KE, Prill MM, Roper LE, Brooks, Sánchez PJ, Kotton CN, Mahon BE, Meyer S, Long SS, McMorrow ML. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2023;72:920-5. https://doi.org/10.15585/mmwr.mm7234a4.

[28] Balbi H Nirsevimab: A Review. Pediatr Allergy Immunol Pulmonol 2024;37:3-6. https://doi.org/10.1089/ped.2024.0025.

[29] Hammitt LL, Dagan R, Yuan Y,Cots MB, Bosheva M, Madhi SA, Muller WJ, Zar HJ, Brooks D, Grenham A, Wählby Hamrén U, Mankad VS, Ren P, Takas T, Abram ME, Leach A, Griffin MP, Villafana T; MELODY Study Group. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. N Engl J Med 2022;386:837-46. https://doi.org/10.1056/NEJMoa2110275.

[30] Esposito S, Abu-Raya B, Bonanni P, Cahn-Sellem F, Flanagan KL, Martinon Torres F, Mejias A, Nadel S, Safadi MAP, Simon A. Coadministration of Anti-Viral Monoclonal Antibodies With Routine Pediatric Vaccines and Implications for Nirsevimab Use: A White Paper. Front Immunol 2021;12:708939. https://doi.org/10.3389/fimmu.2021.708939.

[31] Muller WJ, Madhi SA, Seoane Nuñez B, Baca Cots M, Bosheva M, Dagan R, Hammitt LL, Llapur CJ, Novoa JM, Saez Llorens X, Grenham A, Kelly EJ, Mankad VS, Shroff M, Takas T, Leach A, Villafana T; MELODY Study Group. Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants. N Engl J Med 2023;388:1533-34. https://doi.org/10.1056/NEJMc2214773.

[32] Domachowske J, Madhi SA, Simões EAF, Atanasova V, Cabañas F, Furuno K, Garcia-Garcia ML, Grantina I, Nguyen KA, Brooks D, Chang Y, Leach A, Takas T, Yuan Y, Griffin MP, Mankad VS, Villafana T; MEDLEY Study Group. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. N Engl J Med 2022;386:892-94. https://doi.org/10.1056/NEJMc2112186.

[33] Domachowske J, Wählby Hamren U, Basavaraju B, Koen A, Leach A, Mankad VS, Mori M, Ndibmun C, Soler-Palacin P, Pannaraj PS, Takas T, Villafanaet T. Safety, Tolerability, and Pharmacokinetics of Nirsevimab for the Prevention of RSV Disease in Immunocompromised Children Aged ≤ 24 Months: Music, an Open Label, Phase 2 Trial. Blood 2023;142(Suppl 1):1173. https://doi.org/10.1182/blood-2023-189096.

[34] Simões EAF, Madhi SA, Muller WJ, Atanasova V, Bosheva M, Cabañas F, Baca Cots M, Domachowske JB, Garcia-Garcia ML, Grantina I, Nguyen KA, Zar HJ, Berglind A, Cummings C, Griffin MP, Takas T, Yuan Y, Wählby Hamrén U, Leach A, Villafana T. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health 2023;7:180-9. https://doi.org/10.1016/S2352-4642(22)00321-2.

[35] Drysdale SB, Cathie K, Flamein F, Knuf M, Collins AM, Hill HC, Kaiser F, Cohen R, Pinquier D, Felter CT, Vassilouthis NC, Jin J, Bangert M, Mari K, Nteene R, Wague S, Roberts M, Tissières P, Royal S, Faust SN; HARMONIE Study Group. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. N Engl J Med 2023;389:2425-35. https://doi.org/10.1056/NEJMoa2309189.

[36] Hak SF, Venekamp RP, Wildenbeest JG, Bont LJ. Outpatient respiratory syncytial virus infections and novel preventive interventions. Curr Opin Pediatr 2024;36:171-81. https://doi.org/10.1097/MOP.0000000000001323.

[37] [37] Ernst C, Bejko D, Gaasch L, Hannelas E, Kahn I, Pierron C, Del Lero N, Schalbar C, Do Carmo E, Kohnen M, Andlauer E, Hublart P, Masi S, de la Fuente Garcia I, Vergison A, Mossong J. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. Euro Surveill 2024;29:2400033. https://doi.org/10.2807/1560-7917.ES.2024.29.4.2400033.

[38] Martinón-Torres F, Mirás-Carballal S, Durán-Parrondo C. Early lessons from the implementation of universal respiratory syncytial virus prophylaxis in infants with long-acting monoclonal antibodies, Galicia, Spain, September and October 2023. Euro Surveill 2023;28:2300606. https://doi.org/10.2807/1560-7917.ES.2023.28.49.2300606.

[39] López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, López-Labrador FX, Mengual-Chuliá B, Fernández-García C, Carballido-Fernández M, Pineda-Caplliure A, Mollar-Maseres J, Shalabi Benavent M, Sanz-Herrero F, Zornoza-Moreno M, Pérez-Martín JJ, Alfayate-Miguelez S, Pérez Crespo R, Bastida Sánchez E, Menasalvas-Ruiz AI, Téllez-González MC, Esquiva Soto S, Del Toro Saravia C, Sanz-Muñoz I, Eiros JM, Matías Del Pozo V, Toquero-Asensi M, Pastor-Villalba E, Lluch-Rodrigo JA, Díez-Domingo J, Orrico-Sánchez A. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. Euro Surveill 2024;29:2400046. https://doi.org/10.2807/1560-7917.ES.2024.29.6.2400046.

[40] Ezpeleta G, Navascués A, Viguria N, Herranz-Aguirre M, Juan Belloc SE, Gimeno Ballester J, Muruzábal JC, García-Cenoz M, Trobajo-Sanmartín C, Echeverria A, Martínez-Baz I, Vera-Punzano N, Casado I, López-Mendoza H, Ezpeleta C, Castilla J. Effectiveness of Nirsevimab Immunoprophylaxis Administered at Birth to Prevent Infant Hospitalisation for Respiratory Syncytial Virus Infection: A Population-Based Cohort Study. Vaccines (Basel) 2024;12:383. https://doi.org/10.3390/vaccines12040383.

[41] Mallah N, Ares-Gómez S, Pardo-Seco J, Malvar-Pintos A, Santiago-Pérez MI, Pérez-Martínez O, Otero-Barrós MT, Suárez-Gaiche N, Kramer R, Jin J, Platero-Alonso L, Alvárez-Gil RM, Ces-Ozores OM, Nartallo-Penas V, Mirás-Carballal S, Piñeiro-Sotelo M, González-Pérez JM, Rodríguez-Tenreiro C, Rivero-Calle I, Salas A, Durán-Parrondo C, Martinón-Torres F. Assessment of effectiveness and impact of universal prophylaxis with nirsevimab for prevention of hospitalizations due to respiratory syncytial virus in infants. The NIRSE-GAL study protocol. Hum Vaccin Immunother 2024;20:2348135. https://doi.org/10.1080/21645515.2024.2348135.

[42] Ares-Gómez S, Mallah N, Santiago-Pérez MI, Pardo-Seco J, Pérez-Martínez O, Otero-Barrós MT, Suárez-Gaiche N, Kramer R, Jin J, Platero-Alonso L, Alvárez-Gil RM, Ces-Ozores OM, Nartallo-Penas V, Mirás-Carballal S, Piñeiro-Sotelo M, Malvar-Pintos A, González-Pérez JM, Rodríguez-Tenreiro-Sánchez C, Rivero-Calle I, Salas A, Durán-Parrondo C, Martinón-Torres F; NIRSE-GAL study group. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. Lancet Infect Dis 2024;30:S1473-3099(24)00215-9. https://doi.org/10.1016/S1473-3099(24)00215-9. Erratum in: Lancet Infect Dis 2024;23:S1473-3099(24)00355-4. https://doi.org/10.1016/S1473-3099(24)00355-4.

[43] Coma E, Martinez-Marcos M, Hermosilla E, Mendioroz J, Reñé A, Fina F, Perramon-Malavez A, Prats C, Cereza G, Ciruela P, Pineda V, Antón A, Ricós-Furió G, Soriano-Arandes A, Cabezas C. Effectiveness of nirsevimab immunoprophylaxis against respiratory syncytial virus-related outcomes in hospital and primary care settings: a retrospective cohort study in infants in Catalo-

nia (Spain). Arch Dis Child 2024;10:archdischild-2024-327153. https://doi.org/10.1136/archdischild-2024-327153.

[44] [44] Moline HL, Tannis A, Toepfer AP, Williams JV, Boom JA, Englund JA, Halasa NB, Staat MA, Weinberg GA, Selvarangan R, Michaels MG, Sahni LC, Klein EJ, Stewart LS, Schlaudecker EP, Szilagyi PG, Schuster JE, Goldstein L, Musa S, Piedra PA, Zerr DM, Betters KA, Rohlfs C, Albertin C, Banerjee D, McKeever ER, Kalman C, Clopper BR; New Vaccine Surveillance Network Product Effectiveness Collaborators; McMorrow ML, Dawood FS. Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus-Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Virus Season - New Vaccine Surveillance Network, October 2023-February 2024. MMWR Morb Mortal Wkly Rep 2024;73:209-14. https://doi.org/10.15585/mmwr.mm7309a4.

[45] Paireau J, Durand C, Raimbault S, Cazaubon J, Mortamet G, Viriot D, Milesi C, Daudens-Vaysse E, Ploin D, Tessier S, Vanel N, Chappert JL, Levieux K, Ollivier R, Daoudi J, Coignard B, Leteurtre S, Parent-du-Châtelet I, Vaux S. Nirsevimab Effectiveness Against Cases of Respiratory Syncytial Virus Bronchiolitis Hospitalised in Paediatric Intensive Care Units in France, September 2023-January 2024. Influenza Other Respir Viruses 2024;18:e13311. https://doi.org/10.1111/irv.13311.

[46] Consolati A, Farinelli M, Serravalle P, Rollandin C, Apprato L, Esposito S, Bongiorno S. Safety and Efficacy of Nirsevimab in a Universal Prevention Program of Respiratory Syncytial Virus Bronchiolitis in Newborns and Infants in the First Year of Life in the Valle d'Aosta Region, Italy, in the 2023-2024 Epidemic Season. Vaccines (Basel) 2024;12:549. https://doi.org/10.3390/vaccines12050549.

[47] NIRSE-GAL Available at: https://www.nirsegal.es/en (Accessed on: 20/05/2024).

[48] NCT06042049, Clinical Trial. Available at: https://clinicaltrials.gov/study/NCT06042049?cond=NCT06042049.&rank=1 (Accessed on: 22/05/2024).

[49] NCT05110261, Clinical Trial. Available at: https://clinicaltrials.gov/study/NCT05110261?cond=NCT05110261&rank=1 (Accessed on: 22/05/2024).

[50] NCT06030505, Clinical Trial. Available at: https://clinicaltrials.gov/study/NCT06030505?cond=NCT06030505&rank=1 (Accessed on: 22/05/2024).

[51] NCT06185647, Clinical Trial. Available at: https://clinicaltrials.gov/study/NCT06185647?cond=NCT06185647&rank=1 (Accessed on: 22/05/2024).

[52] NCT06325332, Clinical Trial. Available at: https://clinicaltrials.gov/study/NCT06325332?cond=NCT06325332&rank=1 (Accessed on: 22/05/2024).

[53] Gebretekle GB, Yeung MW, Ximenes R, Cernat A, Simmons AE, et al. Cost-effectiveness of RSVpreF vaccine and nirsevimab for the prevention of respiratory syncytial virus disease in Canadian infants. MedRxiv 2024.03.21.24304675. https://doi.org/10.1101/2024.03.21.24304675.

[54] Position de la SP2A sur les stratégies de prévention de la Bronchiolite. Available at: https://afpa.org/recommandation/position-de-la-sp2a-sur-les-strategies-de-prevention-de-la-bronchiolite (Accessed on: 28/06/2024).

[55] Recomendaciones de utilización de nirsevimab para la temporada 2024-2025 en España. Available at: https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/comoTrabajamos/docs/Nirsevimab.pdf (Accessed on: 28/06/2024).

[56] Chile adquiere medicamento Nirsevimab para enfrentar virus respiratorio sincicial (VRS). Available at: https://www.gob.cl/noticias/chile-adquiere-medicamento-nirsevimab-para-enfrentar-virus-respiratorio-sincicial-vrs (Accessed on: 28/06/2024).

[57] Western Australian children first to access protection from RSV. Available at: https://www.wa.gov.au/government/media-statements/Cook-Labor-Government/Western-Australian-children-first-to-access-protection-from-RSV-20240305 (Accessed on: 28/06/2024).

[58] Immunisation against RSV in the first year of life. Available at: https://www.healthcouncil.nl/binaries/healthcouncil/documenten/advisory-reports/2024/02/14/immunisation-against-rsv-in-the-first-year-of-life/Immunisation-against-RSV-in-the-first-year-of-life-Summary.pdf (Accessed on: 28/06/2024).

[59] Joint Committee on Vaccination and Immunisation. Available at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation (Accessed on: 28/06/2024).

[60] RSV-Infektionen (Respiratorische Synzytial-Viren). Available at: https://www.rki.de/SharedDocs/FAQ/RSV/FAQ_Liste_RSV.html#FAQId16747596 (Accessed on: 28/06/2024).

[61] Respiratorisches Synzytial-Virus. Available at: https://www.sozialministerium.at/dam/jcr:eb64732e-1747-400a-beeb6d069f781182/Impfplan_%C3%96sterreich_2023_2024_Version1.0.pdf (Accessed on: 28/06/2024).

[62] Respiratory syncytial virus (RSV): Canadian Immunization Guide. Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/respiratory-syncytial-virus.html (Accessed on: 28/06/2024).

[63] Preventive strategies against RSV disease in children. Available at: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20231222_shc-9760_advice_rsv_children_vweb.pdf. Accessed on: 28/06/2024.

[64] Misure di prevenzione e immunizzazione contro il virus respiratorio sinciziale (VRS). Available at: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2024&codLeg=99716&parte=1%20&serie=null (Accessed on: 28/06/2024).

[65] Prevenzione delle infezioni da Virus Respiratorio Sinciziale nella popolazione italiana Available at: https://www.igienistionline.it/docs/2024/03rsv.pdf?_sm_nck=1 (Accessed on: 28/06/2024).

Received on July 1, 2024. Accepted on July 15, 2024.

Correspondence: Donatella Panatto, Department of Health Sciences, University of Genoa, Via Antonio Pastore, 16132 Genova, Italy. E-mail: panatto@unige.it

How to cite this article: Orsi A, Scarpaleggia M, Baldo V, Barbone F, Chironna M, Giuffrida S, Montomoli E, Pariani E, Rizzo C, Panatto D, Icardi G. First real-world data on universal respiratory syncytial virus prophylaxis with Nirsevimab in infants. J Prev Med Hyg 2024;65:E172-E187. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3329

Infectious disease

Trend of accesses to the Emergency Department of a Teaching Hospital of Tuscany due to bronchiolitis in 2018-2023: new challenges

ELENA CAPITANI[1], CLAUDIA BASAGNI[2], EMANUELA BARBINI[2], CARLOTTA LORENZINI[3], MARIA FRANCESCA DE MARCO[4], ILARIA MANINI[5], EMANUELE MONTOMOLI[5], NICOLA NANTE[1,5]
[1] Postgraduate School of Public Health, University of Siena, Siena, Italy; [2] UOC Hygiene and Epidemiology, Teaching Hospital "Le Scotte" of Siena, Siena, Italy; [3] Hospital Services Organisation Unit, Teaching Hospital "Le Scotte" of Siena, Siena, Italy; [4] Health Director, Teaching Hospital "Le Scotte" of Siena, Siena, Italy; [5] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy

Keywords

RSV • Bronchiolitis • Emergency Department • Infectious Disease

Summary

Introduction. *Acute bronchiolitis is one of leading causes of lower respiratory tract infection and hospitalisation in children less than one year old worldwide. The aim of our study is investigating the impact of bronchiolitis in children paediatric to the Emergency Department (ED) of Teaching Hospital (AOUS), Santa Maria alle Scotte of Siena, Tuscany (Italy).*
Methods. *A retrospective observational study was conducted on the accesses performed at the ED of the AOUS of Siena by children under 18 years of age suffering from bronchiolitis from September 2018 to April 2023.*
Results. *There were 36,031 patients between 0 and 18 years old in the Emergency Department, 383 of which presented bronchiolitis (age 4.8 months C.I.:3.5-6 months.; 54% male). Those who accessed the ED with a higher priority code were more likely to be subsequently admitted (O.R.:2.6; C.I.:1.3-5.1; $p < 0.01$). Those who accessed the ED with symptoms of bronchiolitis during the weekend were less likely to have been sent from community medicine services or professionals (O.R:0.1; C.I:0.0-0.5; $p < 0.001$). Children below 1 year old were more likely to access the ED with respiratory distress symptoms (O.R.:2.6; C.I.:1.5-4.3; $p < 0.001$). Finally, those who accessed the ED with bronchiolitis were more likely to be admitted than those who accessed for other conditions (O.R:24.5; C.I.:19.4-31; $p < 0.001$).*
Conclusions. *It is necessary to invest protocols integrating hospital services and community medicine in order to achieve a timely diagnosis and to reduce the accesses to the ED of children presenting mild, non-severe form of bronchiolitis in order to avoid the overload of hospital services.*

Background

In the last 2 years in Italy and worldwide, several epidemics of bronchiolitis that significantly stressed health care facilities and services, due to bed saturation in wards and intensive care units were observed. Most of these kinds of hospitalisations concern infants in their first year of life [1].
Bronchiolitis is a viral lower respiratory tract infection characterized by obstruction of small airways and terminal bronchioles caused by acute inflammation, oedema, increased mucus production and necrosis of the epithelium composing the small airways [2].
The main cause of Bronchiolitis is Respiratory Syncytial Virus (RSV); it has been estimated that this pathogen infects more than 60% of all children during their first year of life, reaching almost 100% of them by the time they turn 2 [3]. Human Rhinovirus (HRV), human Parainfluenza virus (HPIV), human Metapneumovirus (HMPV), Influenza virus (IAV, IBV), and human Adenovirus (HAdV), alone or in the form of co-infection, have also been reported [4].
The estimated global impact of RSV-caused infections in infants younger than 5 years of age was reported being approximately 33 million children (range: 21.6-50.3 million), with 3.2 million hospitalizations (range: 2.7-3.8 million), and 120,000 deaths (range: 94,000-149,000) per year [5].
During the pre-pandemic years, analysing the medical databases of national RSV surveillance of 27 countries worldwide reports, the RSV wave started cyclically every year roughly between March and June in the Southern Hemisphere. In the Northen Hemisphere, waves began sometime between September and December. Decrease in RSV activity was observed from August to October in Southern Hemisphere and from February to May in Northen Hemisphere each year, estimating an average of5-6 months for every RSV wave [6].
In March 2020, global SARS-CoV-2 pandemic was declared [7]. In Italy, following this declaration, a lockdown was carried out: all non-essential facilities and activities were shut down [8]. During most 2020 and 2021, in Italy, social interactions were limited, and schools were occasionally closed, replaced by distance learning activities [9].
During the 2020/2021 cold season a significant reduction in the incidence of bronchiolitis patient accessing the Emergency Ward was observed, alongside a general

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3204

decrease in the incidence of acute respiratory tract infection among the population, leading to a decrease in hospitalized patients in Italy [10]. It is also worth noting that no cases of Influenza were recorded during winter 2020-2021, not even during the "flu season", identified as the timeframe between the 42nd week and the 17th week of the following year [11].
An increase in cases of bronchiolitis has been detected in Italy from September 2021, anticipating the seasonal peak compared to previous years [12,10]. For that reason, a surveillance has been introduced for RSV through the InfluNet & RespiVirNet operating protocol [13].
In Italy, currently, in the age group 0-4 years the incidence of influenza syndromes is 13.17 cases per thousand patients. In 2022/2023 season, in subjects under two years of age, 54.9% of the samples positive for a respiratory virus detected RSV, 30.4% influenza and 2.6% SARS-CoV-2 [11].
Bronchiolitis' diagnosis is based on directed history and physical examination. Neither laboratory tests nor radiological exams are usually indicated for the routine work-up of infants with bronchiolitis [1, 14, 15].
Laboratory and instrumental investigations are not routinely recommended [14]. Bronchiolitis may present with a wide range of symptoms and severity, from a mild upper respiratory tract infection (URTI) to impending respiratory failure [5].
Diagnostic criteria for the disease include, but are not limited to, the following [1, 5]: onset with rhinorrhoea and/or upper respiratory tract infections; first episode of respiratory distress associated with: crackles and/or wheezing, use of accessory muscles or lower chest wall retractions, low O2 saturation levels, high respiratory rate, skin colour alterations, nasal flaring, fever.
Risk factors for severe bronchiolitis are [14] also known premature birth (< 35 weeks' gestation); being less than 3 months old; decreased hydration and feeding (< 50% of usual fluid intake in preceding 24 h); hemodynamically significant cardiac disease; chronic lung disease; neurological disorders; immunodeficiency and environmental factors, such as exposure to tobacco smoke and or air pollution.
Moderate-to-severe cases and risk factors associated with severe bronchiolitis must be considered for hospital admission [14].
Severity classification is based on: respiratory rate, respiratory effort, oxygen saturation, feeding, apnoea, wheezing, crackles, effort, inspiration to expiration ratio [14].
Most children with acute bronchiolitis may be adequately managed in the outpatient setting by primary care paediatricians, parents or caregivers able to provide assistance and monitoring [14-16].
Bronchiolitis lasts 12 days (average) in children under 24 months; after 21 days about 18% still have the disease and after 28 days 9% [16]. Most infants who contract bronchiolitis recover without sequelae; however, up to 40% may have subsequent wheezing episodes up to their fifth year of age and approximately ten percent will have wheezing episodes after that timeframe [16-19].
In addition to its impact on children, bronchiolitis also has a major impact in terms of hospitalisation costs even for mild and moderate forms [20]. Moreover, the need for intensive care almost doubles the necessary costs [20].
The aim of our study is to assess the impact of this condition in the emergency services and the severity of the cases that lead to hospitalisation.

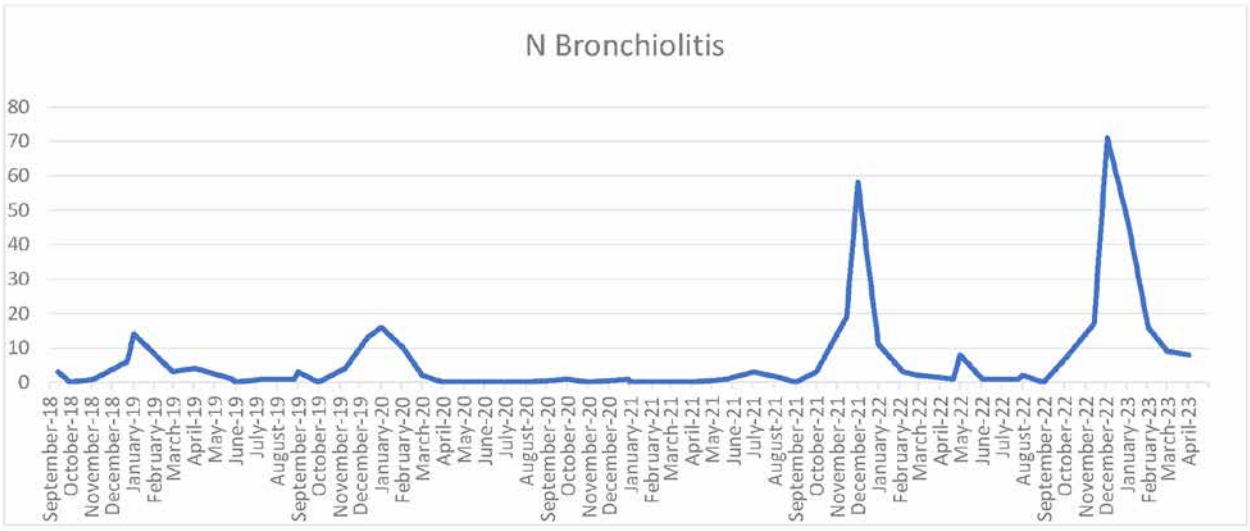
Materials and methods

An observational retrospective pilot study was conducted in the Emergency Department (ED) of Teaching Hospital of Siena, Tuscany, inall children under 18 years of age who had a diagnosis of bronchiolitis at the time of discharge from the ED of the Teaching Hospital of Siena by from September 2018 to April 2023 were included in the study.
All children under 18 years of age who had a diagnosis of bronchiolitis at the time of discharge from the ED were included in the study.
Clinical examination and anamnesis were performed to confirm the diagnosis of bronchiolitis.
Data were taken from the ED software management 'Aurora'.
The "Aurora" management software is the management software that is used in the ED to register entering patients Master data, triage, medical and nursing diary and discharge diagnosis are entered in the management software.
Of all patients, gathered variables included gender, residence, age, during which day of the week they accessed the ED, how were patients sent to ED or how they reached it, whether they had previously been seen by community medicine services, admission code, access symptoms, admission and ward in which they were admitted.
Statistical analysis was performed with STATA 17. The tests performed were X2 test to see if there was a statistically significant correlation between two variables and the Odds Ratio to see how likely one variable influenced the other.
No ethics committee approval was required as for epidemiological studies using health care administrative databases and anonymized data for researcher purpose.

Results

A total of 382 patients visited the emergency department for bronchiolitis.
54.7% were male and the average age was 4.8 months (C.I: 3.5-6.0 months).
The highest number of accesses, 175, occurred in the 2022/2023 season as shown in Figure 1. Only 1 case was recorded in the 2020/2021 season.
The annual distribution of accesses for bronchiolitis shows a progressive increase in cases, in particular 10 cases was recorded in 2018, 80 in 2023, with a peak of

Fig. 1. Number of accesses for bronchiolitis in Emergency Department (ED), (September 2018- April 2023).



124 cases in 2022, only in 2020, where the accesses wee only 31.

Most of our samples (89.8%) came from the province of Siena and 26.7% of them were admitted to the ED during the weekend.

Only 14.1% accessed the emergency room referred by the paediatrician or the doctor on duty.

The most commonly reported symptoms were fever (33.5%), cough (41.1%), but mainly respiratory difficulties in 74.3%.

Most of our sample accessed the ED with code 3, while 21.8% accessed with a higher severity code (1 and 2).

72.8% of our sample were subsequently hospitalised, 17.6% of them in an intensive care unit.

A statistically significant correlation was found between the presence of bronchiolitis and the season being either autumn or winter ($p < 0.001$).

A statistically significant correlation was found between the year of admission and hospitalisation ($p < 0.05$), with an increase in admissions in the post-COVID-19 lockdown. Those who accessed the ED with symptoms of bronchiolitis during the weekend were less likely to have been referred from community medicine services or professionals (O.R: 0.1; C.I: 0.0-0.5; $p < 0.001$).

Children below 1 year of age were more likely to access the ED with respiratory distress (O.R.: 2.6; C.I.: 1.5-4.3; $p < 0.001$).

Those who accessed the ED with bronchiolitis were more likely to be hospitalizedthan those who accessed for other conditions (O.R: 24.5; C.I.: 19.4-31; $p < 0.001$).

Discussion

In our sample, the average age of children which were most affected by bronchiolitis and accessed the Emergency Department was less than 1 year, in line with national and international data in literature [1, 16].

Like most parainfluenza viruses, the trend of bronchiolitis waves is seasonal [5, 15]. The results of our study highlight seasonal incidence peaks from November to February. Our results are in fact in line with previous Italian studies, which peaked between November and February [21, 22].

It's worth highlighting that from November 2020 to February 2021 there was only 1 case of bronchiolitis in Siena Hospital and 3 cases occurred in July 2021. In addition to that, it's important to point out that from March 2020 the SARS-CoV-2 pandemic began [23], which brought Health Authorities to recommend social distancing measures and regulated the mandatory use of masks [24], providing protection not only from SARS-CoV-2, but also from several airborne diseases such as influenza and parainfluenza, causing a decrease in their diffusion [25-27]. An increase in cases during the summer season was also reported in a British study, possibly due to the relaxation of restrictive measures [28]. Many countries have reported a lack of RSV cases during the expected peak season, followed by an out-of-season surge upon relaxation of NPI use. These dynamics have disrupted traditional RSV disease patterns and assumptions, while also provide a unique opportunity to learn more about the transmission of RSV and other respiratory viruses in order to tackle future RSV preventive strategies [29].

The InfluNet report also shows an incidence of 0.8 cases per thousand of influenza syndromes (ILI) by sentinel physicians and out of a total of 6818 samples analysed, none were found positive for influenza in the 2020/2021 season [30].

The 2022/2023 season has registered the most severe increase in incidence of the timeframe of our study, reporting 175 bronchiolitis incidents. This increase has not only occurred in our study, but has been reported throughout Europe, so much so that the ECDC issued a note highlighting this scenario, leading to increased pressure on hospitals and thus recommending enhanced surveillance measures [31].

As previously stated, bronchiolitis is the first cause of hospitalisation in children aged 1 year or lower: most of the children in our study were hospitalised and children aged < 1 year presented respiratory distress symptoms on admission to the emergency department.
Those who accessed the emergency department during the weekend were less likely to have been visited by the family paediatrician or out-of-hours service doctors. We hypothesized this might occur due to the lack of available paediatricians in community services on Saturdays and Sundays, which can manage and treat mild cases before they get worse, thus gatekeeping the emergency department when possible [32].
This public health scenario is important to address because, as already mentioned, bronchiolitis has a big impact on the cost of emergency room services and admissions [20].
Italy is currently developing a reform of territorial and community medicine with the goal to allow patients to be treated mainly at home, with the vision of "home as the first and main healthcare location" [33]. Among the various actions identified to achieve this goal, a huge part of it is the implementation of telemedicine and telemonitoring services. During the COVID-19 emergency, positive patients with mild to moderate symptoms were monitored at home by devices capable of detecting vital parameters in real time and transmitting them to the territorial emergency services [34]. This type of telemonitoring could also be impractical in paediatric patients with parental/caregiver support. However, one possible prevention strategy currently available is a monoclonal antibody (mAb) indicated in a subset of preterm infants or those with comorbidities, hence leaving the majority of the infant population unprotected against this virus. Therefore, development of prevention strategies against RSV for all infants entering their first RSV season constitutes a large unmet medical need [35].
In the next future, it is likely that new possibilities of prevention will add, including use of more potent and longer-acting monoclonal antibodies, implementation of maternal vaccination in pregnancy, and active immunization in children [36, 37].
In 2023, the European Union approved the first RSV vaccine suitable for protecting infants up to six months of age as well as two vaccines for older adults. When given to a mother during pregnancy, the antibodies generated in response to the vaccine can cross the placenta to the foetus, protecting the child for up to six months following birth [38].
Despite all the efforts, prevention remains, to date, the most effective strategy to reduce RSV-related morbidity. Among the current prevention strategies, strict hygiene, breastfeeding and passive immunization with the monoclonal antibody and maternal vaccination are the cornerstone.
The limitations of our study are that the children enrolled were taken from the ED computerised system, so they were not followed up during their admission and the diagnosis is based on the clinic and the objective examination. Yet, we were still able to observe the trends of admission in the ER departments and future studies tackling samples of children followed after the ER discharge can be a relevant research issue to tackle. Moreover, the limitations of this study are given above all by the very small sample. In the Region of Tuscany, the paediatric hub hospital is the Meyer Hospital in Florence. About the University Hospital of Siena, the specific catchment area is structured, for basic activities, on 17 Municipalities of the Sienese Area with approximately 120,000 inhabitants, and for specialist services on 36 Municipalities of the Province of Siena with approximately 254,000 inhabitants. The study is a preliminary study to evaluate the trend of paediatric patients' accesses for RSV, subsequently the study will be extended.

Conclusions

In conclusion, our study also supports evidence confirming the increasing trend of bronchiolitis cases in the 2022/2023 season. Our study also highlights the importance of taking preventive action to avoid the spread of viruses that cause bronchiolitis, such as RSV, through surveillance and vaccine development. Furthermore, it is necessary to invest in hospital-territory integration pathways for timely diagnosis and to reduce the number of children with bronchiolitis with minor codes entering the ED, thus overburdening hospital services. RSV has been identified as a major global priority but a solution to tackle this unmet need for all children has yet to be implemented.

Acknowledgements

All the authors declare no funding source.

Conflicts of interest statement

The authors declare that they have no conflict of interest.

Ethics approval

No ethics commitee approval is required in Italy for epidemiological studies using health care administrative databases for research purposes and with individuals identified by an anonymous patient code. All methods were carried out in accordance with the Declaration of Helsinki.

Authors' contribution

All Authors made substantial contributions to the concept and design, analysis and interpretation of data, and drafting and revisions.

References

[1] Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, Romagnoli C, Colonna P, Biondi A, Biban P, Chiamenti G, Bernardini R, Picca M, Cappa M, Magazzù G, Catassi C, Urbino AF, Memo L, Donzelli G, Minetti C, Paravati F, Di Mauro G, Festini F, Esposito S, Corsello G. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr 2014;40:65. https://doi.org/10.1186/1824-7288-40-65.

[2] Friedman JN, Rieder MJ, Walton JM; Canadian Paediatric Society, Acute Care Committee, Drug Therapy and Hazardous Substances Committee. Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age. Paediatr Child Health 2014;19:485-98. https://doi.org/10.1093/pch/19.9.485.

[3] Centers for Disease Control and Prevention. RSV in infants and young children. 2020. Available at: https://www.cdc.gov/rsv/high-risk/infants-young-children.html (Accessed on: 01/07/2023).

[4] Meissner HC. Viral Bronchiolitis in Children. N Engl J Med 2016;374:1793-4. https://doi.org/10.1056/NEJMc1601509.

[5] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, Polack FP, Balsells E, Acacio S, Aguayo C, Alassani I, Ali A, Antonio M, Awasthi S, Awori JO, Azziz-Baumgartner E, Baggett HC, Baillie VL, Balmaseda A, Barahona A, Basnet S, Bassat Q, Basualdo W, Bigogo G, Bont L, Breiman RF, Brooks WA, Broor S, Bruce N, Bruden D, Buchy P, Campbell S, Carosone-Link P, Chadha M, Chipeta J, Chou M, Clara W, Cohen C, de Cuellar E, Dang DA, Dash-Yandag B, Deloria-Knoll M, Dherani M, Eap T, Ebruke BE, Echavarria M, de Freitas Lázaro Emediato CC, Fasce RA, Feikin DR, Feng L, Gentile A, Gordon A, Goswami D, Goyet S, Groome M, Halasa N, Hirve S, Homaira N, Howie SRC, Jara J, Jroundi I, Kartasasmita CB, Khuri-Bulos N, Kotloff KL, Krishnan A, Libster R, Lopez O, Lucero MG, Lucion F, Lupisan SP, Marcone DN, McCracken JP, Mejia M, Moisi JC, Montgomery JM, Moore DP, Moraleda C, Moyes J, Munywoki P, Mutyara K, Nicol MP, Nokes DJ, Nymadawa P, da Costa Oliveira MT, Oshitani H, Pandey N, Paranhos-Baccalà G, Phillips LN, Picot VS, Rahman M, Rakoto-Andrianarivelo M, Rasmussen ZA, Rath BA, Robinson A, Romero C, Russomando G, Salimi V, Sawatwong P, Scheltema N, Schweiger B, Scott JAG, Seidenberg P, Shen K, Singleton R, Sotomayor V, Strand TA, Sutanto A, Sylla M, Tapia MD, Thamthitiwat S, Thomas ED, Tokarz R, Turner C, Venter M, Waicharoen S, Wang J, Watthanaworawit W, Yoshida LM, Yu H, Zar HJ, Campbell H, Nair H; RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946-58. https://doi.org/10.1016/S0140-6736(17)30938-8.

[6] Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, Rodríguez-Tenreiro C, Sly P, Ramilo O, Mejías A, Baraldi E, Papadopoulos NG, Nair H, Nunes MC, Kragten-Tabatabaie L, Heikkinen T, Greenough A, Stein RT, Manzoni P, Bont L, Martinón-Torres F. Respiratory syncytial virus seasonality: a global overview. J Infect Dis 2018;217:1356-64. https://doi.org/10.1093/infdis/jiy056.

[7] Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91:157-60. https://doi.org/10.23750/abm.v91i1.9397.

[8] DPCME Decreto del Presidente del Consiglio dei Ministri 09 marzo 2020. Available at https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=73629 (Accessed on: 01/07/2023).

[9] DPCM Decreto del Presidente del Consiglio dei Ministri 3 novembre 2020. Available at https://www.miur.gov.it/documents/20182/0/m_pi.AOODPIT.REGISTRO+UFFICIALE%28U%29.0001990.05-11-2020.pdf/f37c907d-f834-d277-f439-ea40ae408093?t=1604594338648 (Accessed on: 11/07/2023).

[10] Faraguna MC, Lepri I, Clavenna A, Bonati M, Vimercati C, Sala D, Cattoni A, Melzi ML, Biondi A. The bronchiolitis epidemic in 2021-2022 during the SARS-CoV-2 pandemic: experience of a third level centre in Northern Italy. Ital J Pediatr 2023;49:26. https://doi.org/10.1186/s13052-023-01425-8.

[11] EpiCentro. L'epidemiologia per la sanità pubblica. Available at https://www.epicentro.iss.it/influenza/aggiornamenti (Accessed on: 20/07/2023).

[12] Indolfi G, Resti M, Zanobini A; Associazione Ospedali Pediatrici Italiani Research Group on Bronchiolitis. Outbreak of respiratory syncytial virus bronchiolitis in Italy. Clin Infect Dis 2022;75:549-50. https://doi.org/10.1093/cid/ciac120. Erratum in: Clin Infect Dis 2023;76:777-9. https://doi.org/10.1093/cid/ciac908.

[13] Sistema di Sorveglianza Sentinella delle sindromi simil-influenzali, dei virus influenzali, del virus SARS-CoV-2 e di altri virus respiratori. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_3267_allegato.pdf (Accessed on: 20/07/2023).

[14] Manti S, Staiano A, Orfeo L, Midulla F, Marseglia GL, Ghizzi C, Zampogna S, Carnielli VP, Favilli S, Ruggieri M, Perri D, Di Mauro G, Gattinara GC, D'Avino A, Becherucci P, Prete A, Zampino G, Lanari M, Biban P, Manzoni P, Esposito S, Corsello G, Baraldi E. UPDATE - 2022 Italian guidelines on the management of bronchiolitis in infants. Ital J Pediatr 2023;49:19. https://doi.org/10.1186/s13052-022-01392-6.

[15] Dalziel SR, Haskell L, O'Brien S, Borland ML, Plint AC, Babl FE, Oakley E. Bronchiolitis. Lancet 2022;400:392-406. https://doi.org/10.1016/S0140-6736(22)01016-9.

[16] Bronchiolitis Guideline Team, Cincinnati Children's Hospital Medical Center: Evidence-based care guideline for management of bronchiolitis in infants one year of age or less with a first time episode. Cincinnati Child Hosp Med Cent 2010;1:1-13.

[17] van Woensel JB, Kimpen JL, Sprikkelman AB, Ouwehand A, van Aalderen WM. Long-term effects of prednisolone in the acute phase of bronchiolitis caused by respiratory syncytial virus. Pediatr Pulmonol 2000;30:92-6. https://doi.org/10.1002/1099-0496(200008)30:2<92::aid-ppul3>3.0.co;2-x.

[18] Rinawi F, Kassis I, Tamir R, Kugelman A, Srugo I, Miron D. Bronchiolitis in young infants: is it a risk factor for recurrent wheezing in childhood? World J Pediatr 2017;13:41-8. https://doi.org/10.1007/s12519-016-0056-4.

[19] Driscoll AJ, Arshad SH, Bont L, Brunwasser SM, Cherian T, Englund JA, Fell DB, Hammitt LL, Hartert TV, Innis BL, Karron RA, Langley GE, Mulholland EK, Munywoki PK, Nair H, Ortiz JR, Savitz DA, Scheltema NM, Simões EAF, Smith PG, Were F, Zar HJ, Feikin DR. Does respiratory syncytial virus lower respiratory illness in early life cause recurrent wheeze of early childhood and asthma? Critical review of the evidence and guidance for future studies from a World Health Organization-sponsored meeting. Vaccine 2020;38:2435-48. https://doi.org/10.1016/j.vaccine.2020.01.020.

[20] Bozzola E, Ciarlitto C, Guolo S, Brusco C, Cerone G, Antilici L, Schettini L, Piscitelli AL, Chiara Vittucci A, Cutrera R, Raponi M, Villani A. Respiratory syncytial virus bronchiolitis in infancy: the acute hospitalization cost. Front Pediatr 2021;8:594898. https://doi.org/10.3389/fped.2020.594898.

[21] Azzari C, Baraldi E, Bonanni P, Bozzola E, Coscia A, Lanari M, Manzoni P, Mazzone T, Sandri F, Checcucci Lisi G, Parisi S, Piacentini G, Mosca F. Epidemiology and prevention of respiratory syncytial virus infections in children in Italy. Ital J Pediatr 2021;47:198. https://doi.org/10.1186/s13052-021-01148-8.

[22] Barbati F, Moriondo M, Pisano L, Calistri E, Lodi L, Ricci S, Giovannini M, Canessa C, Indolfi G, Azzari C. Epidemiology of respiratory syncytial virus-related hospitalization over a 5-year period in italy: evaluation of seasonality and age distribution before vaccine introduction. Vaccines 2020;8:15. https://doi.org/10.3390/vaccines8010015.

[23] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433. https://doi.org/10.1016/j.jaut.2020.102433.

[24] DPCM Decreto Presidente Consiglio dei Ministri 1 marzo 2020. Available at https://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?menu=notizie&id=4137 (Accessed on: 27/07/2023).

[25] InfluNet. Available at: https://www.salute.gov.it/portale/temi/documenti/epidemiologica/Influnet_2021_2.pdf (Accessed on: 27/07/2023).

[26] Pellegrinelli L, Galli C, Bubba L, Seiti A, Anselmi G, Primache V, Signorini L, Delbue S, Binda S, Pariani E. Respiratory syncytial virus in pediatric influenza-like illness cases in Lombardy, Northern Italy, during seven consecutive winter seasons (from 2014-2015 to 2020-2021). Influenza Other Respir Viruses 2022;16:481-91. https://doi.org/10.1111/irv.12940.

[27] Capitani E, Montomoli E, Camarri A, Bova G, Capecchi PL, Mercone A, Nante N, Manini I. Epidemiological and virological surveillance of severe acute respiratory infections in the 2019/2020 season in Siena, Tuscany, Italy. J Prev Med Hyg 2021;62:E782-8. https://doi.org/10.15167/2421-4248/jpmh2021.62.3.2297.

[28] Bardsley M, Morbey RA, Hughes HE, Beck CR, Watson CH, Zhao H, Ellis J, Smith GE, Elliot AJ. Epidemiology of respiratory syncytial virus in children younger than 5 years in England during the COVID-19 pandemic, measured by laboratory, clinical, and syndromic surveillance: a retrospective observational study. Lancet Infect Dis 2023;23:56-66. https://doi.org/10.1016/S1473-3099(22)00525-4.

[29] Stein RT, Zar HJ. RSV through the COVID-19 pandemic: Burden, shifting epidemiology, and implications for the future. Pediatr Pulmonol 2023;58:1631-9. https://doi.org/10.1002/ppul.26370.

[30] Rapporto InfluNet Epi-Vir 2020/2021. Available at: https://www.epicentro.iss.it/influenza/flunews20-21#vir (Accessed on: 03/02/ 2024).

[31] Intensified circulation of respiratory syncytial virus (RSV) and associated hospital burden in the EU/EEA. Available at: https://www.ecdc.europa.eu/en/publications-data/intensified-circulation-respiratory-syncytial-virus-rsv-and-associated-hospital (Accessed on: 22/07/2023).

[32] Vitello AS, Clavenna A, Cartabia M, et al. Evaluation of the Pattern of Use of a Pediatric Emergency Department in Italy. Pediatr Emerg Care 2021;37:e1494-8. https://doi.org/10.1097/PEC.0000000000002091.

[33] DPCM Decreto Presidente Consiglio dei Ministri 23 maggio 2022, n. 77. Available at: https://www.gazzettaufficiale.it/eli/id/2022/06/22/22G00085/sg (Accessed on: 07/07/2023).

[34] Limaj S, D'Amato MG, Turillazzi R, Dei S. Management of chronicity and emergencies with telemedicine: the USL Toscana Sud-Est experience. Sistema Salute 2022;66:447-60. https://doi.org/10.48291/SISA.66.4.5.

[35] Esposito S, Abu Raya B, Baraldi E, Flanagan K, Martinon Torres F, Tsolia M, Zielen S. RSV Prevention in All Infants: Which Is the Most Preferable Strategy? Front Immunol 2022;13:880368. https://doi.org/10.3389/fimmu.2022.880368.

[36] Messina A, Germano C, Avellis V, Tavella E, Dodaro V, Massaro A, Vitale R, Masturzo B, Manzoni P. New strategies for the prevention of respiratory syncytial virus (RSV). Early Hum Dev 2022;174:105666. https://doi.org/10.1016/j.earlhumdev.2022.105666.

[37] Kampmann B, Madhi SA, Munjal I, Simões EAF, Pahud BA, Llapur C, Baker J, Pérez Marc G, Radley D, Shittu E, Glanternik J, Snaggs H, Baber J, Zachariah P, Barnabas SL, Fausett M, Adam T, Perreras N, Van Houten MA, Kantele A, Huang LM, Bont LJ, Otsuki T, Vargas SL, Gullam J, Tapiero B, Stein RT, Polack FP, Zar HJ, Staerke NB, Duron Padilla M, Richmond PC, Koury K, Schneider K, Kalinina EV, Cooper D, Jansen KU, Anderson AS, Swanson KA, Gruber WC, Gurtman A; MATISSE Study Group. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023;388:1451-64. https://doi.org/10.1056/NEJMoa2216480.

[38] European Medicines Agency. First RSV vaccine to protect infants up to 6 months of age and older adults. Available at: https://www.ema.europa.eu/en/news/first-rsv-vaccine-protect-infants-6-months-age-and-older-adults (Accessed on: 05/03/2024).

Received on February 15, 2024. Accepted on April 4, 2024.

Correspondence: Elena Capitani, Department of Molecular and Development Medicine University of Siena, Via Aldo Moro 2, 53100 Siena, Italy. E-mail: capitani4@student.unisi.it

How to cite this article: Capitani E, Basagni C, Barbini E, Lorenzini C, De Marco MF, Manini I, Montomoli E, Nante N. Trend of accesses to the Emergency Department of a Teaching Hospital of Tuscany due to bronchiolitis in 2018-2023: new challenges. J Prev Med Hyg 2024;65:E188-E193. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3204

Non-comunicable disease

Interaction of protein intake and number of family members as a risk factor for chronic energy deficiency in women of childbearing age

DEMSA SUMBOLON[1], LIA LORENA[1], OKDI NATHAN[1]
[1] Department of Nutrition, Poltekkes Kemenkes Bengkulu

Keywords

Dietary energy intake • Education •Work

Summary

Background. *Chronic Energy Deficiency (CED) is a condition in which the body is underweight or thin and the body has insufficient reserves of energy intake, this condition occurs due to a lack of nutrients. A person's condition can be said to be CED if the Mid-Upper Arm Circumference (MUAC) is low or < 23,5 cm. Women of Reproductive Age (WRA) who experience CED will have an impact on pregnancy. Based on the 2017 World Health Organization (WHO) the percentage of CED in pregnancy globally is 35-75% and deaths in developing countries related to CED are 40%.*
Methods. *Research design Descriptive analytic cross-sectional approach. The population WRA with a population of 7,183 the sample being 143 WRA. The analysis is univariate, bivariate (Chi-square), and multivariate (Regression Logistic)*
Results. *Found that the determinants of CED were factors affecting CED for WRA in the Kandang Health Center in Bengkulu City in 2023 are age (p-value = 0.018; ORa95% CI=2,495: 1.171-5.317), energy intake (p-value = 0.013; ORa95% CI = 2.990: 1.256-7.117), and the interaction of protein intake by several family members (p-value = 0.03; ORa 95%CI = 21.327: 1.343-338.671). The dominant factor is the interaction between protein intake and the number of family members. WRA with large families when protein intake is not enough risk 21 times to experience chronic lack of energy compared to adequate protein intake.*
Conclusions. *Health workers need to make promotive and preventive efforts that can be done through community empowerment through health education about nutritional intake and family planning, so WRA understands about prevention of Chronic Energy Deficiency.*

Introduction

Chronic Energy Deficiency (CED) occurs due to a long-term lack of nutrients which causes underweight or thinness [1]. Women of Childbearing Age (WRA) are said to be CED if the Upper Arm Circumference (MUAC) is < 23.5 cm. CED in WRA will have an impact during pregnancy, risking a decrease in muscle strength during delivery [34]. Pregnant women with CED are at risk of giving birth to Low Birth Weight (LBW) and have a risk of death for both mother and child [5].
World Health Organization (WHO) data for 2017 the percentage of CED in pregnancy globally is 35-75% and deaths in developing countries related to CED are 40%. National Health Research Data for 2018, the percentage of CED in WRA who are not pregnant nationally reaches 14,5% [6]. The prevalence of CED in Bengkulu province is 11,10% (4533 people), with the prevalence for Bengkulu City itself being 14,59% (661 people). Data Bengkulu City Health Office for 2021 number WRA in Bengkulu City is 84.506 WRA. The highest CED problem was found in the Kandang Health Center in Bengkulu City, which was 46,8% (277 WRA) [7]. This study aims to determine the interaction risk between protein intake and the number of family members with Chronic Lack of Energy in Women of Childbearing Age.

Method

This study used a cross-sectional approach by examining the dynamics and risk factors and their impacts through direct observation and data collection. This research was conducted for 3 months (January-March 2023). The population used in this study were all Women of Reproductive Age (WRA) between 20-45 years at Kandang Health Center, Bengkulu City, with a population of 7,183 WRA. The minimum sample size required in this study was calculated by the application of the Sample Size in Health Study (Lwanga and Lemeshow) to test the proportion difference hypothesis to test the hypothesis *that the proportion of children not vaccinated is 50% or more, at the 5% level of significance*. The number of samples, namely 143 WRA in the Kandang Health Center, Bengkulu City. The inclusion criteria consisted of WRA Kandang Health Center, WRA aged 20-49 years, the sample lived permanently and was registered as residents in the Kandang Health Center, WRA was willing to be interviewed and used as research samples, WRA was in good health during the research, and exclusion criteria during the research process WRA moved house in the Kandang Health Center, WRA was sick, WRA was not willingly interviewed and not willing to be sampled. The sampling technique uses convenience sampling as a *non-probability sampling method where*

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3065

units are selected for inclusion in the sample due to convenience.

Data collection of Chronic Energy Deficiency (CED) by measuring Mid-Upper Arm Circumference (MUAC) with MUAC tape, WRA is declared CED if the size of MUAC < 23.5 cm. Collection of WRA characteristic data by conducting interviews using structured questionnaires. The age of WRA is categorized into risky (> 35 years) and not at risk (20-35 years) [41], WRA education is categorized as low (elementary and secondary) and high (diploma and bachelor education), employment status is categorized as working (getting treatment) and not working, the number of family members is categorized as a large family (> 4 people) and small family (≤ people) [14], history of infectious diseases (diarrhea, upper respiratory tract infection, malaria, tuberculosis) in one month is categorized as ever and never [42]. Nutritional intake was collected using Semi Food Frequency Questionnaire (S-FFQ) forms, food photo books, and measuring tape. The research procedure began by asking questions on a questionnaire and the S-FFQ form using a food photo book to clarify household size followed by measuring arm circumference. Categorization of nutritional intake based on Daily Value (DV) for Indonesians. Energy intake (Kcal), carbohydrate intake (gr), protein intake (gr), and fat intake (gr) are categorized as insufficient (< 80% DV) and sufficient (≥ 80% DV) [32]. Eating frequency data is the main eating frequency collected by interviews using questionnaires then categorized into good (≥ 3 times a day) and less good (< 3 times a day) [42].

Data analysis used univariate analysis to describe the characteristics of each research variable (age, occupation, education, number of family members, history of infectious disease in the last 1 month, energy intake, protein intake, fat intake, carbohydrate intake, and frequency of main meals in a day). Bivariate analysis used the Chi-Square test to determine the relationship between independent variable (age, occupation, education, number of family members, history of infectious disease in the last 1 month, energy intake, protein intake, fat intake, carbohydrate intake, and frequency of main meals per day) with CED. If the bivariate analysis results show a p-value < 0.25, it will be included in the multivariate analysis. Multivariate analysis uses multivariate logistic regression to determine the most influential variable the determinants of CED.

Before the research was carried out, there was an ethics research permit. The permit was first submitted to the Health Research Ethics Commission of the Ministry of Bengkulu Health Polytechnic with the Ethical Clearance Number No. KEPK.BKL/054/02/2023. Respondents who had been involved in this study had previously given written informed consent after explanation. The explanation given is in the form of the researcher's name, institution of origin, aims, and objectives as well as asking for approval regarding the availability of being a respondent.

Results

Table I shows that the individual characteristics show that most of the WRA age group are not at risk (51.7%), do not have work outside the home (83.9%), have low education (83.2%), lived with a small number of family members (65.7%), multipara parity (74.1%), and had no history of infection in the last 1 month (65%).

Table II shows that the description of intake and frequency of main meals in the day shows the most intake of good energy (67.8 %) with an average energy intake of 1840.4 kcal with a range between 1332.2-2606.5 kcal. Protein intake was mostly adequate (87.4%) with an average of 57.6 g with a range between 57.6±9.6 gr. Fat intake was mostly Not enough (66,4%) with an average of 77.2 g, ranging between 47-129.9 gr. Carbohydrate intake was mostly Not enough (88,8%) with an average of 231.8 g with a range between 153.4-370.1 gr, and most of the frequency of main meals in a day is good (62.2%).

Table III shows that 37.8% of WRA in the Kandang Health Center in Bengkulu City have experienced CED. The average size of MUAC WRA is 26.4 cm, with a range between 18.6 cm to 33 cm.

Table IV shows the results of the analysis with Chi-Square to determine the relationship of each independent variable with the incidence of CED and as a selection stage of independent variables that will be candidates for multivariate analysis (p-value = 0.25). The results showed there was a significant relationship between age (p-value = 0.037; ORc = 2.082) and number of family members (p-value = 0.046; ORc = 2.048) with the incidence of CED, but WRA characteristics based on maternal occupation (p-value = 0.748; ORc = 0.858), education (p-value = 0.069; ORc = 2.248), and a history of infection in the last 1 month (p-value = 0.259; ORc = 0.668) was not significantly associated with the incidence of CED. The prevalence of Chronic Energy Deficiency was higher in WRA aged ≤ 35 years (29%) compared to WRA aged > 35 years (45.9%), WRA not working (38.3%) compared to WRA working (34.8%), WRA higher education (54.2%) compared to WRA lower education (34.5%), extended family (49%) compared to small families (31.9%), and WRA who have experienced infectious diseases (44%) compared to those who have not experienced infectious diseases in the last 1 month (34.4%). Table IV also shows that the independent variables that are candidates for multivariate logistic regression analysis are WRA age, number of family members, and WRA education.

Table V shows a significant relationship between energy intake (p-value = 0.014; ORc = 2.436) and carbohydrate intake (p-value = 0.027; ORc = 4.853) with the incidence of CED, but no significant relationship between protein intake (p-value = 0.252; ORc = 0.562) and fat intake (p-value = 0.016; ORc = 2.781) with the incidence of CED. The prevalence of CED was higher. WRA with less energy intake (52.2%) than adequate energy intake (30.9%), insufficient protein intake (50%) compared to adequate protein intake (36%), fat intake less (100%),

Tab. I. Women of reproductive age characteristics.

Characteristics	Frequency		Statistics	
	n	%	Min-Max	$\bar{X}$ ± SD
Age (year)				
Risk (> 35 years)	69	48.3	21-48	34 ± 6.69
No risk (≤ 35 years)	74	51.7		
Work				
Not Working	120	83.9	-	-
Work	23	16.1		
Education				
Low (Primary and Secondary)	119	83.2	-	-
Hight (Diploma and Bachelor)	24	16.8		
Number of family members				
Small (≤ 4 person)	94	65.7	2-8	4 ± 1.22
Big (> 4 person)	49	34.3		
Parity				
Primipara (1 child)	35	24.5		
Multipara (1-3 children)	106	74.1	0-5	2 ± 0.96
Grandemultipara (> 3 children)	2	1.4		
History of infectious disease				
Ever	50	35.0	-	-
Never	93	65.0		

less carbohydrate intake (40.9%) compared to adequate carbohydrate intake (12.5%), fat intake was less (35.9%) than adequate fat intake (18.1%), and the frequency of

Tab. II. Overview of intake and frequency of eating women of child-bearing age.

Intake and Frequency of Eating	Frequency		Statistics	
	n	%	Min-Max	$\bar{X}$ ± SD
Energy Intake (Kcal)				
Not enough (< 80% DV)	46	32.2	1332.2-2606.5	1840.4 ± 230
Good (≥ 80 DV)	97	67.8		
Protein Intake (gr)				
Not enough (< 80% DV)	18	12.6	47-129.9	57.6 ± 9.6
Good (≥ 80 DV)	125	87.4		
Fat Intake (gr)				
Not enough (< 80% DV)	95	66,4	47-129.9	77.2 ± 14
Good (≥ 80 DV)	48	33,6		
Carbohydrate Intake (gr)				
Not enough (< 80% DV)	127	88.8	153.4-370.1	231.8 ± 37.5
Good (≥ 80 DV)	16	11.2		
Main Meal Frequency (times/day)				
Not enough (< 3 times/day)	54	37.8	2-4	2.7 ± 0.6
Good (≥ 3 times/ day)	89	62.2		

DV: Daily Value

Tab. III. Overview of chronic energy deficiency.

Size of Mid-Upper Arm Circumference (MUAC)	Frequency		Statistics	
	n	%	Min-Max	$\bar{X}$ ±SD
CED (MUAC < 23.5 cm)	54	37,8	18,6-33.0	26,4 ± 3,57
No CED (MUAC ≥ 23.5 cm)	89	62,2		

CED: Chronic Energy Deficiency; MUAC: Mid-Upper Arm Circumference

eating was good (24.5%) compared to the frequency of eating was not good (13.3%). Table V also shows that the independent variables that are candidates for multivariate logistic regression analysis are WRA age, number of family members, and WRA education.

Table VI shows that the factors affecting CED for WRA in the Kandang Health Center in Bengkulu City in 2023 are age (p-value = 0.018; ORa95% CI = 2,495: 1.171-5.317), energy intake (p-value = 0.013; ORa95% CI = 2.990: 1.256-7.117), and the interaction of protein intake by several family members (p-value = 0.03; ORa95%CI = 21.327: 1.343-338.671). The dominant factor for CED is the interaction between protein intake and several family members, meaning the interaction between protein intake with family members this means that the number of family members influences the amount of WRA protein intake. WRA who have less protein intake, the risk of the number of small family members experiencing CED is 3,643 times (OR = $e^{-1,767 + 3,060}$ = 3,643) compared to the number of extended family members. For those at WRA who have good protein intake, the risk of the number of large family members for CED occurring is only 0.17 times (OR = $e^{-1,767}$ = 0.17) compared to the number of extended family members. This shows that protein deficiency is a precondition for the effect of the number of family members on the incidence of CED.

The results of the multivariate analysis obtained the last model as shown in Table VI the regression equation is as follows:

Logit P (CED Occurrence) = -1.024 + (0.914*at risk age) + (1.095*deficient energy) + (-0.849*deficient proteins) + (-1.767*small number of family members) + (3.060*protein intake*number of family members)

$$\mathbf{P} = \frac{1}{1+e^{-(\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\cdots .kXk)}}$$

$$\mathbf{P} = \frac{1}{1+e^{-[-1.024+0.914-1.767+1.095-0.849+3.060]}} = 0.813 = 81.3\%$$

Based on the P = 81.3%, it means that 81.3% of the variation in the incidence of Chronic Energy Deficiency in. WRA is explained by risk age factors (> 35 years), less energy intake, less protein intake, large families, and interactions between less protein intake with large families. The remaining 18.7% variation in CED events in WRA is explained by other factors.

Tab. IV. Relationship between women of childbearing age characteristics and chronic energy deficiency.

Variable	Chronic Energy Deficiency Events						P-values[a]	ORc (95% CI)
	CED		No CED		Total			
	n	%	n	%	n	%		
Age (year)								
Risk (> 35 years)	20	29.0	49	71.0	69	100	0.037*	2.082 (1.042-4.162)
No risk (≤ 35 years)	34	45.9	40	54.1	74	100		
Work								
Not Working	46	38.3	74	61.7	120	100	0.748	0.858 (0.337-2.182)
Work	8	34.8	15	65.2	23	100		
Education								
Low (Primary and Secondary)	41	34.5	78	65.5	119	100	0.069*	2.248 (0.926-5.461)
Hight (Diploma and Bachelor)	13	54.2	11	45.8	24	100		
Number of Family Members								
Small (≤ 4 person)	30	31.9	64	68.1	94	100	0.046*	2.048 (1.009-4.159)
Big (> 4 person)	24	49.0	25	51.0	49	100		
History of infection in the Last 1 Month								
Ever	22	44.0	28	56.0	50	100	0.259	0.668 (0.330-1.349)
Never	32	34.4	61	65.6	93	100		

ORc: Odd Ratio Crude. *Candidate for multivariate analysis. [a] Chi-Square Test.

Discussion

Age and Chronic Energy Deficiency

This study found a significant relationship between age and incidence of CED. This happened because at the time the study was carried out on WRA who were in the Puskesmas, out of 143 WRA who were classified as at risk. This study is in line with research in Pati Regency, which obtained p = 0.003 which indicates an effect of age on the incidence of CED [8]. In addition, research in Betung Bay, Bandar Lampung Sari City, obtained a p-value = 0.000 which indicates the relationship between age and incidence of CED [9]. However, it is different from research in Central Kluet District, South Aceh Regency, which obtained p-value = 0.399 and shows no relationship between age and incidence of CED [10]. Age (35-49 years) is said to be vulnerable to CED events because besides this age there is aging and decreased body functions where at that age WRA still have young children which adds to the workload. In the old category (35-49 years) the metabolic process gradually decreases regularly so that the need for nutrients cannot be fully met [11, 12]. Apart from that, at this age, it is also susceptible to disease because the organs of the body are getting older and weaker, as well as the aging process that is starting to appear [8]. Affects during pregnancy, it requires a lot of energy. Then it takes additional energy sufficient to support the ongoing pregnancy [13].

Tab. V. Relationship between intake and frequency of main meals with chronic energy deficiency.

Variable	CED events						P-values[a]	ORc (95% CI)
	CED		No CED		Total			
	n	%	n	%	n	%		
Energy Intake (kcal)								
Not enough (< 80% DV)	24	52.2	22	47.8	46	100	0.014*	2.436 (1.185-5.011)
Good (≥ 80 DV)	30	30.9	67	69.1	97	100		
Protein Intake (grams)								
Not enough (< 80% DV)	9	50.0	9	50.0	18	100	0.252*	0.562 (0.208-1.519)
Good (≥ 80 DV)	45	36.0	80	64.0	125	100		
Fat Intake (grams)								
Not enough (<80% DV)	43	35.9	52	59.129.9	95	100	0.016*	2.781 (1.269-6.098)
Good (≥ 80 DV)	11	18,1	37		48	100		
Carbohydrate Intake (grams)								
Not enough (< 80% DV)	52	40.9	75	59.1	127	100	0.027*	4.853 (1.058-22.262)
Good (≥ 80 DV)	2	12.5	14	87.5	16	100		
Main Meal Frequency Per Day								
Not enough (< 3 times/day)	19	13.3	35	24.5	54	100	0.620	1.194 (0.592-2.409)
Good (≥ 3 times/day)	35	24.5	54	37.8	89	100		

DV: Daily Value; ORc: Odd Ratio Crude; * Candidate for multivariate analysis; [a] Chi-Square Test.

Tab. VI. Determinants of chronic energy deficiency.

Variable	B	P-values[a]	ORa (95% CI)
Age*	0.914	0.018	2.495 (1.171-5.317)
Energy intake*	1.095	0.013	2.990 (1.256-7.117)
Protein intake*	-0.849	0.192	0.428 (0.119-1.533)
Number of family members*	-1.767	0.185	0.171 (0.013-2.327)
Protein intake*number of family members*	3.060	0.030	21.327 (1.343-338.671)
Constant	-1.024		

[multivariate]Logistic Regression Test with categorical data scales; ORa: Odd Ratio Adjusted.

Interaction Number of Family Members and Protein Intake

This study found a significant relationship between the interaction number of family members and protein intake with the incidence of CED (p-value = 0.03; ORa95% CI = 21.327: 1.343-338.671). The interaction between protein intake with family members means that the number of family members influences the amount of WRA protein intake. WRA with large families when protein intake is not enough risk 21 times to experience chronic lack of energy compared to adequate protein intake. Based on the results of research in the field where WRA who live with a small number of family members experience as much as 31.9%. This is because a small family has just married and the family economy is not yet stable. The results of this study are in line with research in Tuban Regency, which obtained p-value = 0.000 which shows that the number of family members is related to the incidence of CED [17]. This is different from research in a large-scale unbalanced district with p-value = 0.4 which shows that the total number of household members is not related to the occurrence of CED [18]. It is also different from studies in the City of Kupang and the City of Bengkulu, which obtained p-value = 0.302, which has no relationship between the number of family members and incidence [19].

Dependents are WRAs who are still related to the family or are considered family and their lives are borne. The number of dependents is determined by the number of family members living in a household [20]. Even though in this study the majority of family members from WRA were ≤4 person, which means that the number of children they had was only 1 or 2 person, nutrition fulfillment was still on WRA is still neglected. Even though the number of family members at WRA averages ≤ 4 people, which is not balanced with sufficient income will determine the nutritional status of WRA [21]. A heavy workload will increase the body's energy needs which can cause fatigue [22].

The results of this study found that protein intake was not directly related to the incidence of CED, but depended on the number of family members. WUS in this study have good protein consumption, this can be seen in habits of protein consumption and the portions consumed. Almost every WRA consumes 2-3x protein every week, especially animal protein. In addition, the availability of these foodstuffs is not difficult to obtain. This study is in line with research in the Terbanggi Besar District, Central Ampang Regency, which obtained p-value = 0.230 which indicated that there was no relationship between protein intake and incidence of CED. did not have a significant relationship with the incidence of CED [32]. In contrast to the study in Palembang, p-value = 0.004 was obtained which indicated that there was a relationship between protein intake and the risk of CED [29].

Foods that contain a lot of protein are tofu, tempeh, chicken, fish, eggs and milk. Protein has an important function for the body, protein is a source of energy after glycogen, besides that protein is also used as a constituent of tissue cell structures. There a person must have sufficient protein intake because this can have an impact on the health of WRA if it lasts for a long time. Protein intake that is less or more does not affect changes in body weight because excess protein intake is not stored by the body as occurs due to excess energy [32].

Energy Intake and Chronic Energy Deficiency

This study found a significant relationship between energy intake and incidence in WRA Kandang Health Center, Bengkulu City in 2023. This research is in line with research in Hibun village, Sanggau Regency, which obtained a p-value = 0.009 which indicates the relationship between energy intake and risk [28]. In addition, the study in Palembang obtained p-value = 0.004 which showed that there was a relationship between energy intake and the risk [29]. Just like the study in Makassar, it obtained a p-value = 0.011 which showed that there was a relationship between energy intake and the risk of Chronic Energy Deficiency [30].

The energy in the human body is the result of burning proteins, fats, and carbohydrates. Energy results can be stored by the body in adipose tissue. This energy reserve will be used if the intake of protein, fat, and carbohydrates is insufficient. Therefore, muscle mass is influenced by the intake of macronutrients, especially energy and protein. If energy reserves are continuously used for a long time, it will result in changes in nutritional status [31].

Carbohydrates and Chronic Energy Deficiency

This study found a significant relationship between carbohydrate intake and the incidence of CED. This is because most WRA have less carbohydrate intake, whereas a high-carbohydrate food ingredient that is often consumed is rice. In addition, the consumption of high-carb foodstuffs did not vary, they were rarely consumed even if only a small amount was consumed. This study is in line with research in Tapung District, Kampar Regency, Riau, which obtained p-value = 0.027 which indicated that there was a relationship between carbohydrate intake and incidence of CED [33]. In contrast to the

study in Palembang, p-value = 0.094 was found which showed no relationship between carbohydrate intake and the risk of CED [29]. The results of this study were also different from studies in Central Lampung Regency, which obtained p-value = 0.455 indicating that there was no relationship between carbohydrate intake and incidence [32].

In the human body, there are specific cells such as neurons that require high glucose [37].Glucose is found in food sources of carbohydrates. The most consumed foods contain high carbohydrates such as rice, bread, noodles, corn, wheat flour, tubers, and others. Carbohydrate consumption generally comes from staple foods. Energy consumption that does not vary will affect energy intake. Where carbohydrates function as the main source of energy, carry out and carry out fat metabolism, and others. Carbohydrate intake was as much as 88.8% with an average of 231,8 g and was not sufficient for the daily RDA according to the standard [32].

Occupational and Chronic Energy Deficiency

This study found no significant relationship between work and incidence of CED. This can be a factor in the occurrence of CED. Even though the results of this study stated that there was no relationship, CED was often found in WRA who did not have jobs outside the home. This study is in line with research in Kediri Regency, which obtained p = 0.269 which indicated that the mother's occupation was not related to the incidence of CED [14]. In addition, research in the District of Central Kluet, South Aceh District with p=0.686 showed that there was no relationship between work and. the incidence of CED [10]. In contrast to research in Tuban Regency, p-value = 0.008 was obtained which indicated that there was a relationship between work and incidence of CED [2].

Stress is a condition that occurs due to a gap between physiology and psychology in a situation that originates from a person's biological, psychological, or social origins [15]. A person is inevitably very vulnerable to stress caused by various problems. Stress triggers themselves can be from within or outside the body which can influence a person's behavior towards food. WRA who work outside the home or do not have different stress factors. For example, for WRA who work stress factors can be caused by work outside the home not to mention work at home, while WRA who do not work outside the home have to think about housework, caring for children, and others [16].

Education and Chronic Energy Deficiency

This study found no significant relationship between education and incidence of CED. The results of this study also indicate that there are samples with low education that have normal MUAC sizes. Even though the results of the study stated that education had no relationship with the incidence of CED in WRA, CED was often found in WRA with low education.

This research is in line with research in Kediri Regency, which obtained p = 0.689 which indicated that education was not related to the incidence of CED [14]. In addition, research in Indramayu District obtained p-value = 1,000 indicating that education was not related to the nutritional status of pregnant women [16]. Tuban obtained p-value = 0.013 which shows the relationship between education and incidence [2].

Education affects nutritional status because a high level of education will participate in determining or influencing a person to receive nutrition information. Nutrition and health problems often occur due to ignorance and lack of information about fulfilling nutrition for health. This will have an impact on awareness and willingness to behave regarding health in everyday life [13].

However, the facts on the ground found that WRA with a high level of education experienced CED. What causes this to happen is that WRA who have a low level of education are not necessarily less able to meet their needs for nutrients and food compared to WRA who have a high level of education. Even though WRA have low education, they do not necessarily have low knowledge about nutrition and health, this is because health information is not only obtained by taking education. Apart from that, it could be because higher education provides opportunities for WRA to work with strenuous activities outside the home which can have an impact on workload which can become a burden on the mind (stress), and irregular eating patterns which can put WRA at risk of experiencing [13].

History of Infection and Chronic Energy Deficiency

This study found no significant relationship between a history of infection and the incidence of CED. Results of interviews WRA who experienced. on average did not have a history of infection in the last 1 month. Even though infectious diseases can affect nutritional status, the history of illness experienced by WRA in the field is susceptible to a long period with the MUAC measurements carried out, besides that the history of illness experienced does not last for a long time. The most common infectious disease is upper respiratory tract infection, where if you are sick, you will go to the Puskesmas for treatment at the WRA so that the illness does not last long.

This research is in line with the study in Purwokerto, which obtained p = 0.121 which indicated that there was no relationship between. and infectious diseases [23]. In addition, the research conducted in Purwokertal has p-value = 0.156 which shows that contagious diseases are not related to Chronic Energy Deficiency Among Non-pregnant and Non-lactating Women of Reproductive Age [24]. The city of Bogor obtained p = 0.000 which indicated a relationship between infectious diseases and incidence [25].

Infectious disease is one of the factors that can affect the nutritional status of WRA. There is a relationship between infectious diseases and nutritional status [26]. Infectious diseases are closely related to malnutrition or undernutrition where there is a reciprocal relationship, namely infectious diseases can worsen the nutritional condition of WRA, and vice versa WRA who are in

poor nutritional conditions will make it easier for them to get infected [27]. WRA who suffer from infectious diseases will have an impact on the nutritional status of the WRA, this is because infectious diseases affect food intake which often decreases [26].

Fat Intake and Chronic Energy Deficiency

This study found no significant relationship between fat intake and the incidence of CED. Results of interviews with WRA, the average WRA often consume foods that contain lots of fat, such as coconut milk and fried dishes that are cooked by themselves or bought outside the home. The habit of consuming foods that are high in fat will make fat intake sufficient.

This study is in line with the study in Makassar, which obtained p-value = 0.595 which indicated that there was no relationship between fat intake and CED [30]. In addition, this study is also in line with research in Bandar Lampung, which obtained p-value = 0.204 which indicated that there was no relationship between fat intake and incidence of CED [34]. In contrast to the study in Palembang, p-value = 0.031 was obtained which showed that there was a relationship between fat intake and the risk [29].

Frequency of main meals in a day and Chronic Energy Deficiency

This study found no significant relationship between the frequency of main meals in a day and the incidence of CED. In this study, there were WRA whose eating frequency was in the good category but experienced, which was 24,5%. This can happen because the main eating frequency is not a factor causing it.

This can be caused by intake or food consumed does not meet the nutritional adequacy rate (RDA). In addition, imbalanced intake, type and variety of food consumed, nutrient content, meal portions, and frequency can affect whether intake is fulfilled or not. So even though the main meal frequency is good, in terms of intake it cannot be fulfilled or is not adequate for a long period, it does not rule out the possibility that the WRA will not experience [35].

This study is in line with research in Makassar City, which obtained p-value=0.667 which indicated no relationship between the frequency of the main meals in a day and the incidence of CED [20]. In addition, research in Kediri Regency obtained p-value=0.383 which showed that there was no relationship between eating frequency and incidence of CED [14]. In contrast to research in the city of Lampung, p-value=0.015 was obtained which showed that there was an effect of eating frequency on the incidence of Chronic Energy Deficiency (CED) in Pregnant Women [36].

Based on the researcher's direct experience in this research process, there are several limitations experienced and there can be several factors that future researchers can pay more attention to in further perfecting their research because this research itself certainly has shortcomings that need to be continuously improved. Further research, for example, needs to increase the number of samples, use the cohort method, and collect consumption data using more valid instruments. Several limitations in this research include: the number of respondents was only 143 people, which is certainly not enough to describe the actual situation; the research object only focuses on WRA who are only aged 20-49 years; in the process of collecting data, the information provided by respondents via S-FFQ sometimes does not show the actual condition of the respondents, this happens because sometimes respondents do not remember what food they consumed in the last month as well as other factors such as the honesty factor in filling out the questionnaire.

Conclusions

Factors associated with the incidence of Chronic Energy Deficiency (CED) in Women of Reproductive Age (WRA) 20-45 years are age, energy intake, protein intake, number of family members, and the interaction between protein intake and the number of family members. The dominant factor is the interaction between protein intake and the number of family members. The effect of protein intake on the incidence of CED depends on the number of family members. In large families, WRA with less protein intake are at higher risk of developing CED compared to WRA from small families. Relevant health workers need to make promotive and preventive efforts that can be done through community empowerment through health education about nutritional intake and family planning, so WRA understands about prevention of chronic lack of energy through family planning, meeting nutritional needs, especially energy and protein intake. For future researchers, they can conduct further research on other factors in WRA such as culture, family income, socioeconomic status, age at marriage, and others.

Acknowledgments

Acknowledgments were conveyed to the Head of the Kandang Community Health Center in Bengkulu City who had facilitated and provided support in the implementation of this research in the working area of the Kandang Health Center. Thanks to the nutritionist who has assisted in the screening of the research sample.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DS and LL: conceived of the presented idea, collected the data, performed the analysis, conceived and designed the analysis, and contributed data or analysis tools. DS and LL: verified the analytical methods, contributed to

the interpretation of the results, and designed the model and the computational framework. All Authors discussed the results and contributed to the final manuscript.

References

[1] Sintia S, Septiani W, Rany N, Kursani E. Determinant Of Chronic Energy Deficiency (Kek) In Pregnant Women In The Working Area Of Siak Hulu Iii Health Center Of Kampar Regency. J Keskom 2021;7:64-9. https://doi.org/10.25311/keskom.vol7.iss1.775.

[2] Ananda MD, Jumiyati, Yuliantini E. The Effect of Nutrition Counseling on Knowledge and Intake of Macronutrients for WRA CED in the Work Area of the Sawah Lebar Health Center, Bengkulu City. Journal Health Technology and Arts 2019;10:35-45. https://doi.org/10.36525/sanitasi.2019.4.

[3] Paramata Y, Sandalayuk M. Chronic Energy Deficiency in Women of Reproductive Age in the Limboto District, Gorontalo Regency. Gorontalo Journal of Public Health 2019;2:120-5. https://doi.org/10.32662/gjph.v2i1.390.

[4] Widyawati W, Sulistyoningtyas S. Characteristics of Pregnant Women with Chronic Energy Deficiency (CED) at the Pajangan Bantul Health Center. Jurnal JKFT 2020;5:68-74. https://doi.org/10.31000/jkft.v5i2.3925.

[5] Moradi G, Zokaeii M, Goodarzi E, Khazaei Z. Maternal Risk Factors for Low Birth Weight Infants: A Nested Case-control Study of Rural Areas in Kurdistan (western Iran). J Prev Med Hyg 2021;62:E399-406. https://doi.org/10.15167/2421-4248/jpmh2021.62.2.1635.

[6] Kemenkes RI. Laporan Nasional Riskesdas 2018. Jakarta: Badan Penelitian dan Pengembangan Kesehatan 2018. Available at: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan%20Riskesdas%202018%20Nasional.pd (Accessed on: 18/10/2022).

[7] Kemenkes RI. Laporan Provinsi Bengkulu Riskesdas 2018. Jakarta: Bdan Penelitian dan Pengembangan Kesehatan 2018. f Available at: https://repository.badankebijakan.kemkes.go.id/id/eprint/3855/1/LAPORAN%20RISKESDA%20BENGKULU%202018.pdf (Accessed on:18/10/2022).

[8] Ernawati A, Perencanaan B, Daerah P, Pati K. Correlation between Age and Employment Status of the Mother with the Incidence of Chronic Energy Deficiency in Pregnant Women. Journal Litbang 2018;XIV:27-37. https://doi.org/10.33658/jl.v14i1.106.

[9] Sari WK, Deltu SN. Correlation between Nutrition Knowledge Level, Anemia, and Food Consumption Level with the Incidence of Diabetes in Pregnant Women in Muara Madras Village, Merangin District, Jambi. Journal Health Lentera 'Aisyiyah 2019;4:434-9.

[10] Safitri F, Husna A. Risk Factors for Chronic Energy Deficiency (CED) in Pregnant Women in the UPTD Working Area of the Menggat Health Center, Central Kluet District, South Aceh Regency. Journal of Healthcare Technology and Medicine 2022;8:609-18. https://doi.org/2615-109X.

[11] Purwitasari D, Maryanti D. A Teacher of Nutrtion in Reproductive Health. In Yogyakarta: Nuha Medika 2014.

[12] Primasari A. Aging Process from Dentistry Aspect. Jakarta: EGC 2018.

[13] Maryam S. Nutrition in Reproductive Health. Jakarta: salemba Medika; 2015. Available at: https://repository.penerbiteureka.com/media/publications/566916-gizi-dalam-kesehatan-reproduksi-d9d39e66.pdf (Accessed on: 20/01/2023).

[14] Triatmaja NT. Factors Associated with Chronic Energy Deficiency (CED) Status of Pregnant Women in Kediri Regency. Journal Wiyata: Peneliti Sains dan Kesehatan 2017;4:137-42. https://doi.org/10.56710/wiyata.v4i2.161.

[15] Andini FR. The Relationship between Socioeconomic Factors and Pregnancy Age with the Incidence of Chronic Energy Deficiency in Pregnant Women at the Prambontergayang Community Health Center, Tuban Regency. Journal of Universitas Airlangga 2020;4:218-24. https://doi.org/10.20473/amnt.v4i3.2020.218-224.

[16] Bitty F, Asrifuddin A, Nelwan JE. Stress with the Nutritional Status of Adolescents in Manado 2 Public Junior High School. Journal KESMAS: Jurnal Kesehatan Masyarakat Unoversitas Sam Ratulangi 2018;7:1-6.

[17] Isti AN, Safitri DE, Arumsari I. Sleep Quality and Stress Associated with Nutritional Status of Adults during the Covid-19 Pandemic. Journal Gizi-Dietetik 2021;13:48-55. https://doi.org/10.47007/nut.v13i2.4053.

[18] Widyastuti SD, Sugiarto H. The Relationship between Education, Age, and Gravida with Chronic Energy Deficiency (CED) in Pregnant Women Giving Birth at Independent Midwife Practice "Y" Indramayu Regency. Nurs News. Journal Nursing Science 2021;5:124-32. https://doi.org/10.33366/nn.v5i3.2351.

[19] Ikhtirami A, Rahma AS, Tihardimanto A. The Relationship between Diet and Chronic Energy Deficiency in First Trimester Pregnant Women in the Work Area of the Kassi-Kassi Health Center in Makassar City. Journal Melucca Medica 2021;8:106-15. https://doi.org/10.30598/molmed.2021.v14.i1.11.

[20] Anggraini Y. The Influence of Demographics and Socioeconomics on the Incidence of Chronic Energy Deficiency in Pregnant Women in Metro City, Lampung Province. Journal Health 2013;4:401-7. https://doi.org/10.26630/jk.v4i2.84.

[21] Angraini DI. The Relationship between Family Factors and the Incidence of Chronic Energy Deficiency in Women of Reproductive Age in the District of Terbanggi Besar. Journak JK Unila (Jurnal Kedokteran Universitas Lampung) 2018;2:146–50. https://doi.org/10.23960/jkunila22146-150.

[22] Simbolon D, Setia A, Sembiring AC, Wahyudi A. Family Characteristics, Reproductive Health and Child Birth Size in Pregnant Women with a History of Chronic Energy Deficiency. Voice Health Research Forikes 2022;13:828-34. https://doi.org/10.33846/sf13328.

[23] Faozi BF. Parity Relationship with Chronic Energy Deficiency. Journal Nursing Science Before 2022;4:18-23.

[24] Wubie A, Seid O, Eshetie S, Dagne S, Menber Y, Wasihun Y, Petrucka P. Determinants of chronic energy deficiency among non-pregnant and non-lactating women of reproductive age in rural Kebeles of Dera District, North West Ethiopia, 2019: Unmatched case control study. PLoS One 2020;15:e0241341. https://doi.org/10.1371/journal.pone.0241341.

[25] Khayatunnisa T. The Relationship Between Chronic Energy Deficiency (CED) and the Incidence of Anemia, Infectious Diseases, and Concentration Power in Young Women. Journal Nutrition and Food, Soedirman 2021;5:46-61. https://doi.org/10.20884/1.jgipas.2021.5.1.3263.

[26] Rini RF, Herutomo T, Haryanto I. Factors Associated with Chronic Energy Deficiency (CED) in Pregnant Women in the Jatiluhur Purwakarta Health Center Work Area in 2017. Journal of Holistic and Heal Sciences 2018;2:36-43. https://doi.org/10.51873/jhhs.v2i1.23.

[27] Fitrianingtyas I, Pertiwi FD, Rachmania W. Factors Associated with Abortion Incidents. Jounal Health Media 2021;6:169-79. https://doi.org/10.33088/jmk.v6i2.209.

[28] Hafsah T, Prawitasari T, Djais JTB. Hospital Malnutrition and Pediatric Nutrition Care at Hasan Sadikin Hospital, Bandung. Journal Indonesian Clinical Nutrition 2019;16:47-57. https://doi.org/10.22146/ijcn.43090.

[29] Nurwijayanti, Radono P, Fazrin I. Analysis of Knowledge, Infectious Diseases, Dietary Patterns Against the Nutritional Status of Adolescents in the Stikes Surya aMitra Husada Kediri Diet on Nutritional Status in Adolescents at Stikes Surya Mitra Husada Kediri. Journal Health Nutrition 2019;1:70-5.

[30] Aprilianti D, Purba JSR. Relationship of Knowledge, Attitude, Energy and Protein Intake to the Risk of Chronic Energy Deficiency (CED). Pontianak Nutrition Journal 2018;1:36-9. https://doi.org/2622-1705.

[31] Telisa I, Eliza E. Macronutrient intake, iron intake, hemoglobin level and risk of chronic energy deficiency in female adolescents. Journal Action: Aceh Nutrition Journal 2020;5:80-6. https://doi.org/10.30867/action.v5i1.241.

[32] Fauziana S, Fayasari A. Relationship of Knowledge, Food Diversity, and Macro-Micro Nutrient Intake to CED in Pregnant Women. Binawan Student Journal 2020;2:191-9. https://doi.org/10.54771/bsj.v2i1.107.

[33] Nur, I. U. dan Puspitasari, D.I.Differences in Preconception Nutrition Knowledge and Protein Energy Consumption Levels in Women of Reproductive Age (WRA) Age 15-19 Years Chronic Energy Deficiency (CED) and Not CED in SMA Negeri 1 Pasawahan. Journal Health 2017;10:23-36. https://doi.org/10.23917/jurkes.v10i2.5527.14/12/2022.

[34] Putri M.C, Angraini DI, Hanriko R. The Relationship between Food Intake and Chronic Energy Deficiency (CED) in Women of Reproductive Age (WRA) in Terbanggi Besar District, Central Lampung Regency. Journal Agromedicine 2019;6:105-13.

[35] Aulia I, Verawati B, Dhilon DA, Yanto N. The relationship between nutritional knowledge, food availability, and food intake with the incidence of chronic energy deficiency in pregnant women. Journal Doppler 2020;4:106-11.

[36] Dictara AA, Angraini DI, Mayasari D, Aila K. The Relationship between Food Intake and Chronic Energy Deficiency (CED) in Pregnant Women in the Working Area of the Sukaraja Health Center, Bandar Lampung City. Journal Majority 2020;9:1-6. https://doi.org/2337-3776.12/02/2023.

[37] Kiani AK, Dhuli K, Donato K, Aquilanti B, Velluti V, Matera G, et al. Main Nutritional Deficiencies. J Prev Med Hyg 2022;63:E93-101. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2752.

[38] Alam S, Ansyar DI, Satrianegara MF. Dietary Patterns and Educational History in Women of Childbearing age Al-Sihah. The Public Health Seience Journal 2020;12:81-7. https://doi.org/10.2425/as.v12i1.14185.

[39] Dhiu E, Berek NC, Ruliati LP, Jutomo L, Ratu JM. Factors Affecting Chronic Energy Deficiency (CED) in Pregnant Women. Journal of Telenursing (JOTING) 2022;4:958-67. https://doi.org/10.31539/joting.v4i2.3897.

[40] Danini FR. Hubungan Faktor Sosio Ekonomi dan Usia Kehamilan dengan Kejadian Kekurangan Energi Kronis pada Ibu Hamil di Puskesmas Prambontergayan Kabupaten Tuban. Amerta Nutrition 2020;4:218-24. https://doi.org/10.20473/amnt.v4i3.2020.218-224.

[41] Tumanggor L, dan Siregar A. Faktor-faktor Yang Berhubungan Dengan Kejadian Kurang Energi Kronik (KEK) Pada Ibu Hamil di RSUD Kotapinang Kabupaten Labuhanbatau Selatan. Public Health Journal 2022;8:1-9.

[42] Rahayu D, dan Sagita YD. Dietary and Income Patterns of Families with Cronic Energy Deficiency (CHD) Incidence in Pregnant Mothers in the Second Trimester. Holistik Jurnal Kesehatan 2019;13:7-18.

Received on August 8, 2023. Accepted on June 6, 2024.

Correspondence: Demsa Sumbolon, Jl. Indragiri No. 3, Padang Harapan, Bengkulu City, Bengkulu, 38225 Indonesia. E-mail: demsa_ui03@yahoo.com

How to cite this article: Sumbolon D, Lorena L, Nathan O. Interaction of protein intake and number of family members as a risk factor for chronic energy deficiency in women of childbearing age. J Prev Med Hyg 2024;65:E194-E202. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3065

Non-comunicable disease

Spatial distribution and determinant factors of anemia among women age 15-49 years in Burkina Faso; using mixed-effects ordinal logistic regression model

KALEAB TESFAYE TEGEGNE[1], ELENI TESFAYE TEGEGNE[2], MEKIBIB KASSA TESSEMA[3], TADELE KASSAHUN WUDU[4], MOGES TADESSE ABEBE[5], ASMAMAW ZEGEYE WORKAEH[6]

[1] Department of Public Health, College of Health Science, Debark University, Debark, Ethiopia;
[2] School of nursing, college of medicine and health sciences, University of Gondar, Gondar, Ethiopia;
[3] Leishmania Research and Treatment Center, University of Gondar, Gondar, Ethiopia;
[4] Department of Statistics, Debark University, Debark, Ethiopia;
[5] Department of Nursing, College of Health Science, Debark University, Debark, Ethiopia;
[6] Vice president for academic research, technology transfer and community service of Debark University, Debark, Ethiopia

Keywords

Anemia • Women • Spatial analysis • Mixed-effects ordinal logistic regression

Summary

Background. *Anemia is a condition in which the number of healthy red blood cells/ hemoglobin (Hgb) level (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiologic needs. Thus, the current study is aimed to assess the spatial distribution and determinant factors of anemia among women aged 15-49 in Burkina Faso.*

Methods. *A secondary data analysis was done based on 2021 Burkina Faso; Demographic and Health Surveys. Total weighted samples of 5655 women's were included. Data processing and analysis were performed using STATA 14; ArcGIS 10.1 and SaTScan 9.6 software.*

Result. *The spatial distribution of anemia in Burkina Faso among women aged 15-49.was found to be clustered (Global Moran's I = 0.25, p value < 0.0001). In the multivariable mixed-effect ordinal regression analysis; Age 25-29 years [AOR = 1.31 ; 95% CI: 1.06 1.61], rich wealth status [AOR = 1.32 ; 95% CI: 1.08 1.62], regions Cascades [AOR = 1.62 ; 95% CI: 1.16 2.25],Hauts-bassis [AOR = 1.40; 95% CI: 1.06 1.84], Plateau central [AOR = 0.72 ; 95% CI: -0.54 0.96 and Sahel[AOR = 0.42 ; 95% CI: 0.28 0.63], were significant predictors of anemia among women aged 15-49.*

Conclusions. *A significant clustering of anemia among women aged 15-49 were found in Burkina Faso. Age, wealth index, regions Cascades, Hauts-bassins, Plateau central, and Sahel were significant predictors of anemia.*

Introduction

Anemia is a condition in which the number of healthy hemoglobin (Hgb) level (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiologic needs [1]. Anemia is diagnosed when a blood hemoglobin concentration is 120 g/dL for non-pregnant women and below 110 g/dL in pregnant women [2].

The magnitude of anemia differs according to geographic areas, Sub-Saharan Africa (SSA) and South Asia had the highest prevalence of anemia in all age groups. Women of 15-49 years are physiologically more susceptible to anemia because of continues menstrual blood loss and the demands of frequent pregnancy [3]. In eastern Africa, the prevalence of anemia in women of 15- 49 years age is higher, which ranges from 19.2% in Rwanda to 49% in Zambia [1].

According to different studies done worldwide; age [4, 5], educational level [6-8], wealth status [6, 7, 9, 10], type of toilet facility and source of drinking water [6, 10], current pregnancy status [5, 7, 10], and residence [2, 11], are associated with anemia in women of 15- 49 years.

Previous studies have reported pregnancy status [11, 12], lower nutritional status [13], repeated childbearing [14] haemoglobin < 11 g/dl for pregnant women, lactation/ breastfeeding [12], helminths infection [15] and malaria [16]frequently leading to anaemia. Plasmodium falciparum causes the most severe and profound anaemia, with a significant risk of death. This cannot be explained simply by the direct destruction of parasitized red blood cells at the time of release of merozoites, a process shared by all these species. In this review, Clara Menendez, Alan Fleming and Pedro Alonso focus on recent advances in our knowledge of the pathophysiology, epidemiology, management and prevention of anaemia from falciparum malaria. Copyright (C were found to be important causes of anemia among women age 15-49 years.

However, the progress made in decreasing the magnitude of anemia is far less than the expected and its socioeconomic burden, particularly in resource-poor countries, is still a major concern [17]. To achieve the World Health Organization global nutrition targets 2025 and nutrition targets of the Sustainable Development Goals-2030, it is important to generate adequate evidence on contextual determinants of anemia to contribute to the development of timely interventions in anemia prevention.

In addition, assessing the geographic distributions of anemia and its determinant factors across the regions in Burkina Faso can inform the national policy in designing prevention and intervention programmes to address anemia. More-over, mapping the spatial distribution of anemia by regions can help focus resources for prevention and treatment in the hot spot areas that is areas with elevated incidence or prevalence of anemia among women age 15-49 years in Burkina Faso.
Although previous studies have attempted to estimate the prevalence of anemia in Burkina Faso, no studies in Burkina Faso have utilized nationally representative data to investigate the spatial distribution and determinant factors of anemia among women age 15-49 years in Burkina Faso. Therefore, this study aims to assess the spatial distribution and determinant factors of anemia in Burkina Faso among women aged 15–49.

Methods

Study setting and data source

Burkina Faso is one of the sub-Sahara African countries which contained thirty National, Regional states: namely Boucle du mouhoun,Cascades,Centre,Centre Est,Centre Nord,Centre Ouest,Centre Sud,Est,Hauts-bassins,Nord,Plateau central,Sahel and Sud-Ouest This study was a secondary data analysis based on 2021 Burkina Faso Demographic and Health Surveys (BFDHS). The 2021 BFDHS provides reliable estimates at the national level, for urban and rural areas, and for each of the 13 regions [18]. The BFDHS 2021 applied a stratified two-stage cluster sampling technique. Stratification was realized by separating each region into urban and rural areas. In the BFDHS 2021, Blood specimens for anemia testing were collected from women aged 15-49 that voluntarily consented to be tested. Blood samples were drawn from a drop of blood taken from a finger prick and collected in a micro cuvette. Hemoglobin analysis was carried out on site using a battery-operated portable HemoCue analyzer. The full sampling procedure and the Anemia testing data are accessible in the full 2021 BFDHS report [18]. The total weighted samples of 5655 women aged 15–49 were included in this study.

Study variables

The outcome variable for this study was hemoglobin level in the blood, a key indicator for Anemia. Age, place of residence, region, wealth index, and type of toilet facility were included as independent variables in this study (Tab. I).

Operational definition

Wealth index

It is the percent distribution of population by wealth quintiles. It was classified as Poorest, Poorer, Middle, and Richer & Richest.

Improved sanitation facility

Includes flush or pours flush toilets flowing to a piped sewer system, septic tank, or latrine, ventilated pit latrine, pit latrine with slab, and compositing toilet. Based on the type of sanitation facility, a household was classified as having or not having an improved sanitation facility [19, 20].

Improved water sources

If a household used piped water (in to dwelling, compound, yard or plot, piped to neighbor, public tap/standpipe), tube well/borehole, protected well, protected spring and rain water collection for drinking purposes.it is considered as using improved water sources [20, 21].

Data source and extraction

First, authorization was obtained through online request after submitting the objectives of our study. Then, the data was accessed from the demography heath survey (DHS) program official database www.measuredhs.com and we have extracted the outcome and independent variables.

Data processing and management

Data processing and analysis were performed using STATA 14; ArcGIS 10.1 and SaTScan 9.6 software. Cross tabulations and summary statistics were conducted to describe the study population.

Ethics approval and consent to participate

The study does not contain the collection of information from subjects. We sent a one-page proposal abstract of the study to the DHS program office. They gave permission to access the data.

Spatial analysis

Spatial autocorrelation analysis

In this study, the existence of spatial autocorrelation was checked using Global Moran's index (Moran's I). Global Moran's index (Moran's I) was used to identify the presence of spatial auto correlation. Moran's I value ranges from-1 to 1 [22]. A value close to 1 shows a strong positive spatial autocorrelation (disease/event clustered), whereas a value close to -1 shows a

Tab. I. Measurement of outcome variable used in the Analysis.

Pregnancy status	Anemia status			
	Mild anaemic	Moderate anaemic	Sever anaemic	Not anaemic
Pregnant women	10.0-10.9 g/dl	7.0-9.9 g/d	< 7.0 g/dl	≥ 11.0 g/dl
Non Pregame women	11 and 11.9 g/dL	8 and 10.9 g/dL	<8 g/dL	≥ 12.0 g/dl,

strong negative spatial autocorrelation (disease/event dispersed). If Moran's I is close to 0, it indicates that there is no spatial autocorrelation. A statistically significant Moran's I ($p < 0.05$) led to the rejection of the null hypothesis (anemia is randomly distributed) and showed the presence of spatial autocorrelation. Hot- spot analysis was made using Gettis-OrdGi*statistics.

Spatial scan statistical analysis

Spatial scan statistics were applied to identify a significant Primary (most likely) and secondary cluster of anemia using Kuldorff's SaTScan software. SaTScan™ works with a moving window and requires fixing of the window size that moves across the study area. Since the dependent variable (anaemic and not anaemic) has a Bernoulli distribution, the Bernoulli model was employed for purely spatial analysis. To fit the Bernoulli model, women age 15-49 years who were anaemic (mild, moderate, and severe) were considered as cases and those who were not anaemic were considered as controls. The default maximum spatial cluster size of < 50% of the population was considered as an upper limit, which permitted both small and large clusters to be identified and ignored clusters that contained more than the maximum limit. Areas with high Log Likelihood Ratio and significant p-value were taken as high anemic areas compared to areas outside of the window.

Statistical analysis

Since the BFDHS data have a hierarchical nature, women 15-49 years age within a cluster may be more similar to each other than with women 15-49 years age in another cluster. Due to this, the assumption of independence of observations and equal variance across clusters might be violated. Therefore, an advanced statistical model is required to take into account the between cluster variability to get a reliable standard error and unbiased estimate. Furthermore, by taking the ordinal nature of the outcome variable into account, ordinal logistic regression and mixed effect ordinal logistic were fitted. Model comparison was done based on Akaike and Bayesian Information Criteria (AIC and BIC). Mixed effect model with the lowest Information Criteria (AIC and BIC) was selected**.** Adjusted Odds Ratio (AOR) with a 95% Confidence Interval (CI) and *p*-value 0.05 in the multivariable model was declared as determinant factors of anemia. The assumption of proportional odds was checked and the results tell that the assumption of proportional odds is plausible at 5% level of significance for all considered covariates in the model.

Clusters were accounted in the analysis using mixed-effect ordinal logistic regression, by including region in random effect model and all other variables in fixed effect model.

Results

Characteristics of study population

In this study, a total of 5655 women 15-49 years age were included. Among these respondent, more than half of them were uneducated (67.1%) and poorest (17.0%) in wealth index and more than half (64.7%) of them were rural residents. Four hundred ninety three (8.9%) of the study participants were in the age range of 15 to 19 years. Concerning the marital status, 5025 (90.8%) respondents were married while 100 (1.8%) respondents were never married. Five hundred eighty eight (10.6%) of the study participants were from Hauts-bassins region. 3676 (66.4%) of the respondents had improved toilet facility, whereas 3349 (60.5%) of the study participants used improved drinking water (Tab. II). Regarding, the current pregnant, majority of women (90.4%) were not pregnant or don't know whether they are pregnant or not.

Spatial analysis of anemia

Spatial distribution of anemia

The highest number of anemia cases were found in Centre and Hauts-bassins regions (Fig. 1).

The spatial distribution of anemia in Burkina Faso among women age 15-49 years was identified to be clustered (Global Moran's I = 0.25, p value < 0.0001). Given the z-score of 10.9016137606, there is a less than 1% likelihood that this clustered pattern could be the result of random chance (Fig.2).

Gettis-OrdGi statistical analysis of anemia

Based on the Gettis-OrdGi statistical analysis, this study identified hotspots and cold spot areas of anemia in Burkina Faso among women aged 15–49. Accordingly, the red colors indicate the significant hotspot area (higher cluster of anemia), which were found in Boucle du mouhoun, Centre, Hauts-bassins,Nord, Centre Ouest, Plateau central, and Centre Est regions. In contrast, the blue color indicates significant cold spot areas (low cluster of anemia), located in Sahel and Cascades regions (Fig. 3).

Interpolation of space

For the prediction of anemia prevalence in untested women age 15-49 years in different locations of, Burkina Faso. We employed standard Kriging interpolation. Based on geostatistical Kriging analysis, Boucle du mouhoun, Centre Ouest, Centre Sud, Centre and Cascades regions is 3.91-4.77 number of cases, border of Boucle du mouhoun, Hauts-bassins, border of Sahel and Plateau central regions the predicted anemia prevalence for untested women age 15-49 years is 7.35-8.21 number of cases and for inside Boucle du mouhoun, Centre Ouest, Centre and Centre Sud regions the predicted anemia prevalence for untested women age 15-49 years is highest which is 9.93-10.79 number of cases (Fig. 4).

Spatial SaTScan analysis of Anemia (Bernoulli based model)

A spatial scan statistical analysis recognized a total of 123 significant primary and secondary clusters. Among these, 116 clusters were primary (most likely) clusters

Tab. II. Characteristics of women 15-49 years age in Burkina Faso, 2021 (N = 5,655)

Variables	Anemia level (weighted frequency)				Total	Weighted percent
	Severe	Moderate	Mild	Not anemic		
Age						
15-19	5	165	102	221	493	8.9%
20-24	6	257	207	412	882	15.9%
25-29	9	238	236	476	959	17.3%
30-34	11	250	252	485	998	18.0%
35-39	12	259	211	424	906	16.4%
40-44	11	210	183	322	726	13.1%
45-49	10	185	143	233	571	10.3%
Marital; status						
Never married	3	25	21	51	100	1.8%
Married	54	1428	1219	2324	5025	90.8%
Widowed	6	86	73	157	322	5.8%
Divorced	1	25	21	41	88	1.6%
Educational level						
No education	53	1101	919	1639	3712	67.1%
Primary, secondary, Higher	11	452	411	911	1785	32.2%
Don't know	0	11	4	23	38	0.7%
Type of place of residence						
Urban	19	494	458	981	1952	35.3%
Rural	45	1070	876	1592	3583	64.7%
Region						
Boucle du mouhoun	6	141	119	214	480	8.7%
Cascades	1	70	51	183	305	5.5%
Centre	9	171	140	361	681	12.3%
Centre Est	0	150	124	236	510	9.2%
Centre Nord	8	112	95	144	359	6.5%
Centre-Ouest	4	136	113	234	487	8.8%
Centre Sud	4	102	85	188	379	6.8%
Est	5	84	76	131	296	5.3%
Hauts-bassins	5	119	151	313	588	10.6%
Nord	5	136	116	184	441	8.0%
Plateau central	5	157	109	140	411	7.4%
Sahel	8	82	47	43	180	3.3%
Sud-Ouest	4	104	108	202	418	7.6%
Wealth index						
Poorest	20	290	250	381	941	17.0%
Poorer	15	302	261	425	1003	18.1%
Middle	11	346	276	485	1118	20.2%
Richer	8	319	246	630	1203	21.7%
Richest	10	307	301	652	1270	22.9%
Type of toilet facility						
Improved	33	1029	851	1763	3676	66.4%
Not Improved	31	535	483	810	1859	33.6%
Source of drinking water						
Not Improved	27	644	522	993	2186	39.5%
Improved	37	920	812	1580	3349	60.5%
Currently pregnant						
No/don't know	57	1388	1206	2314	4965	90.4%
Yes	6	168	118	233	525	9.6%

which were located in the Plateau central, Centre Nord, half of Est, half of Nord, and Sahel regions at 14.122803 N, 0.062321 W, with 228.21 km radius, a Relative Risk (RR) of 1.32, and Log-Likelihood Ratio (LRR) of 51.483251, at p-value < 0.01 (Tab. III). This tells us that women's within the spatial window had 1.32 times higher risk of experiencing anemia as compared to women's outside the spatial window. The secondary cluster were found in half of Boucle du mouhoun, border of Centre Ouest, and border of Nord regions at

Fig. 1. Spatial distribution of anemia across regions among women age 15-49 years in Burkina Faso, 2021.

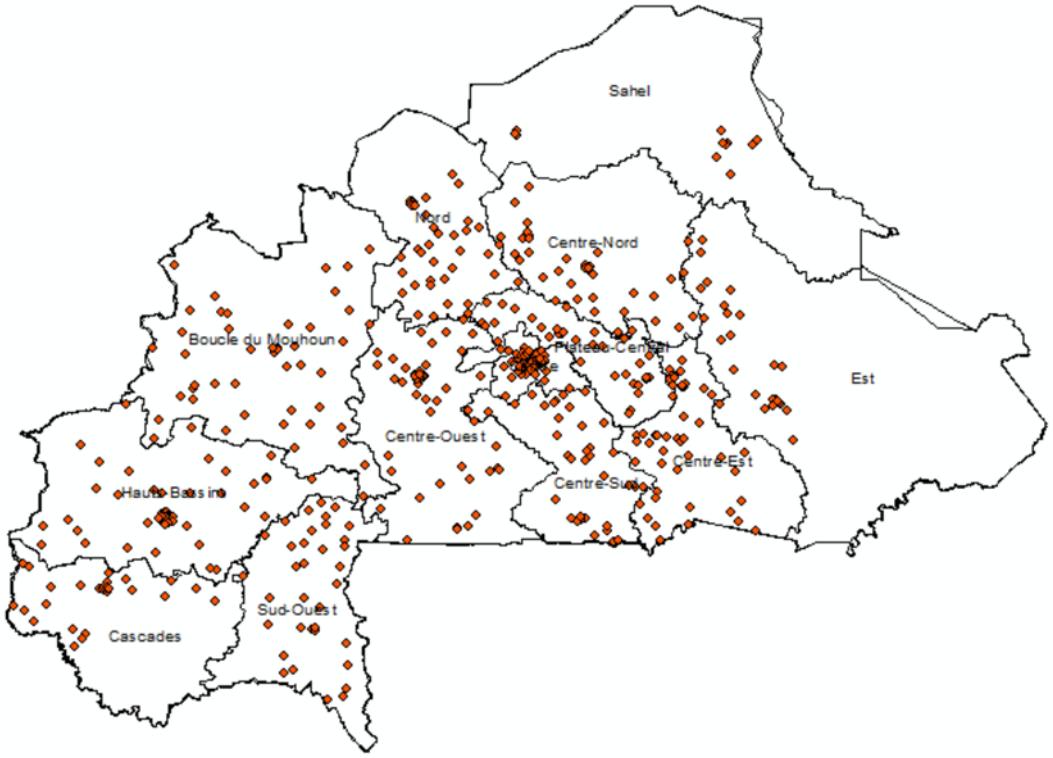


Fig. 2. Spatial autocorrelation analysis of anemia among women age 15-49 years in Burkina Faso, 2021.

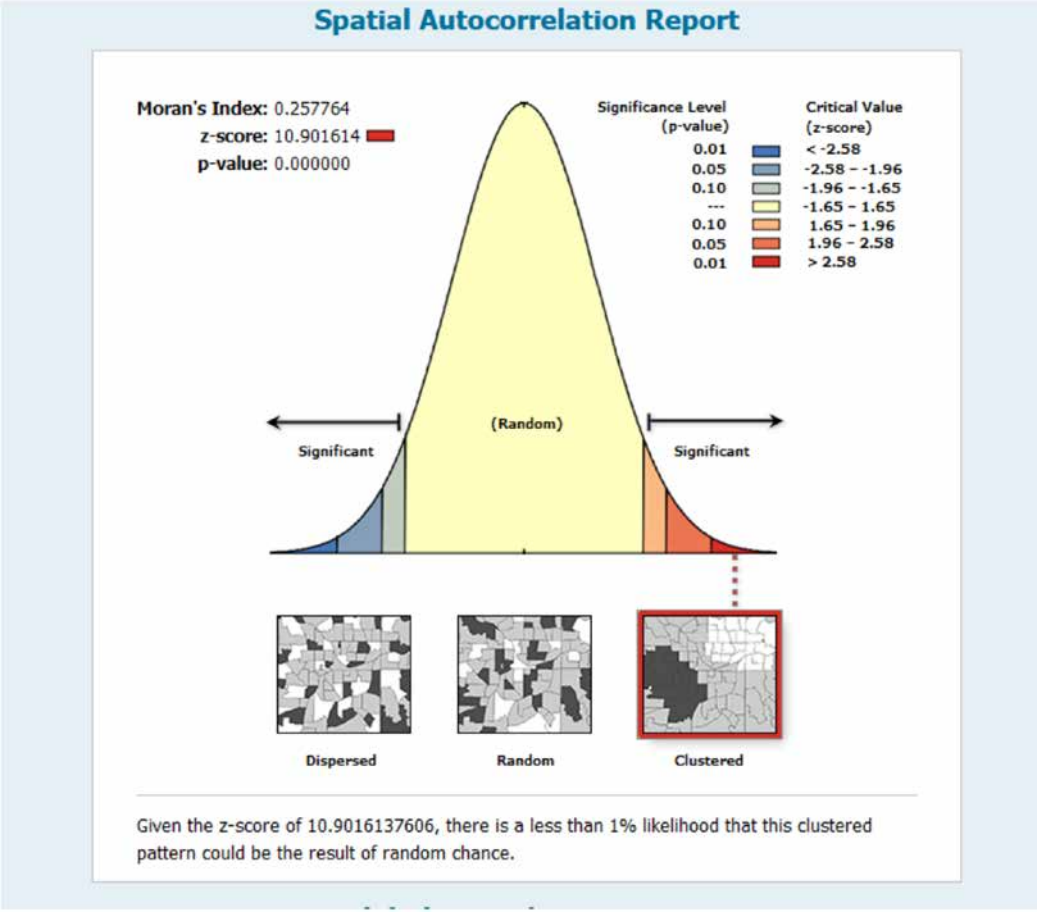


Fig. 3. Hotspot and Cold areas of anemia across regions among women age 15-49 years in Burkina Faso, 2021.

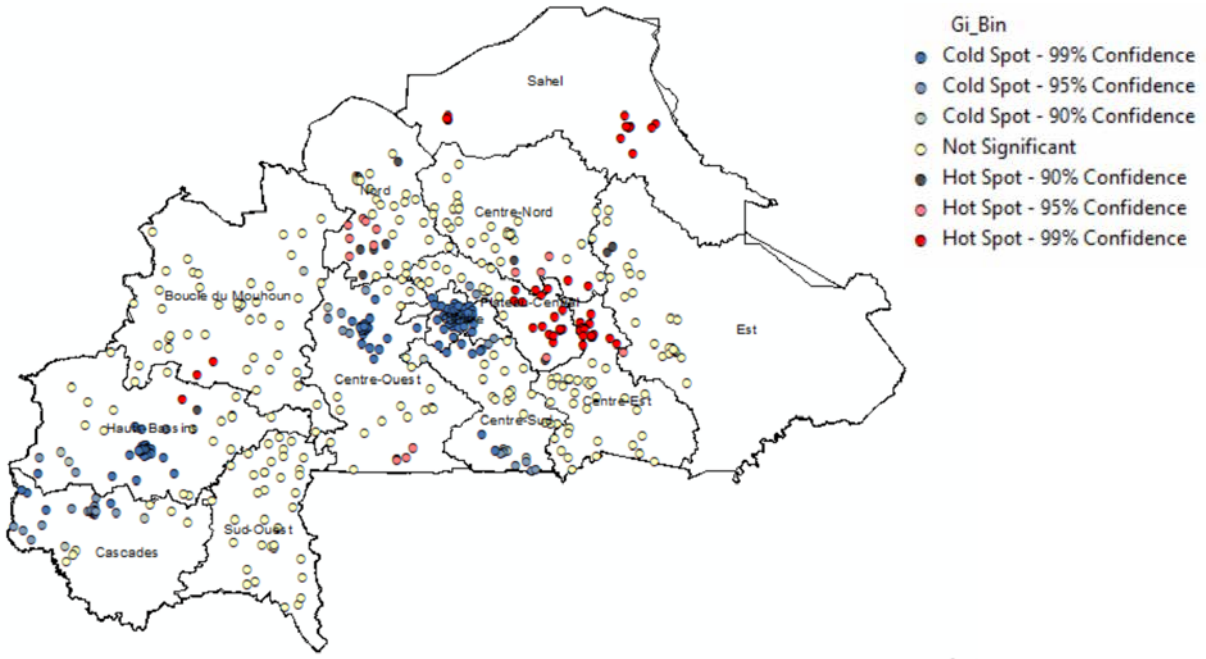
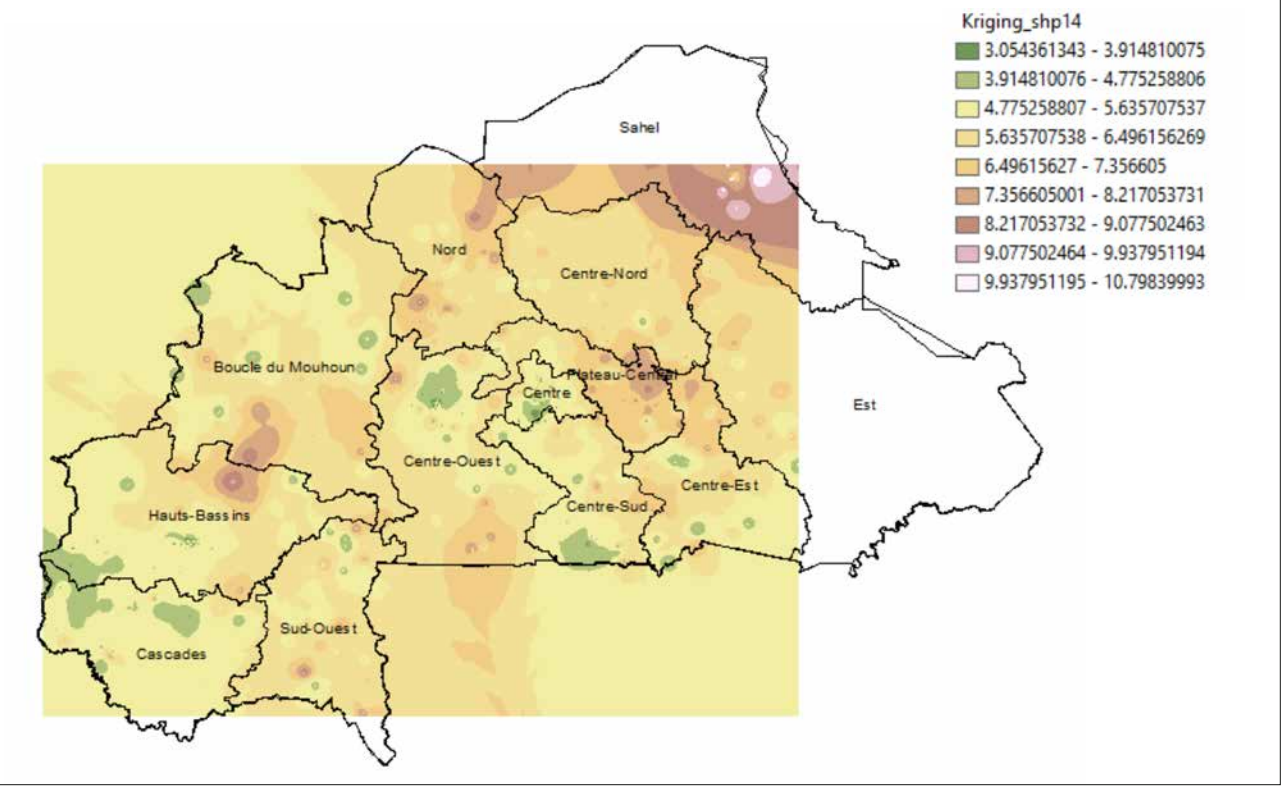


Fig. 4. Spatial interpolation of anemia across regions among women age 15-49 years in Burkina Faso, 2021.



11.845827 N, 3.836225 W), with 39.61 km radius, a Relative Risk (RR) of 1.50, and Log-Likelihood Ratio (LRR) of 12.782125, at p-value = 0.0019. This tells us that women's within the spatial window had 1.50 times higher risk of experiencing anemia as compared to women's outside the spatial window (Fig. 5).

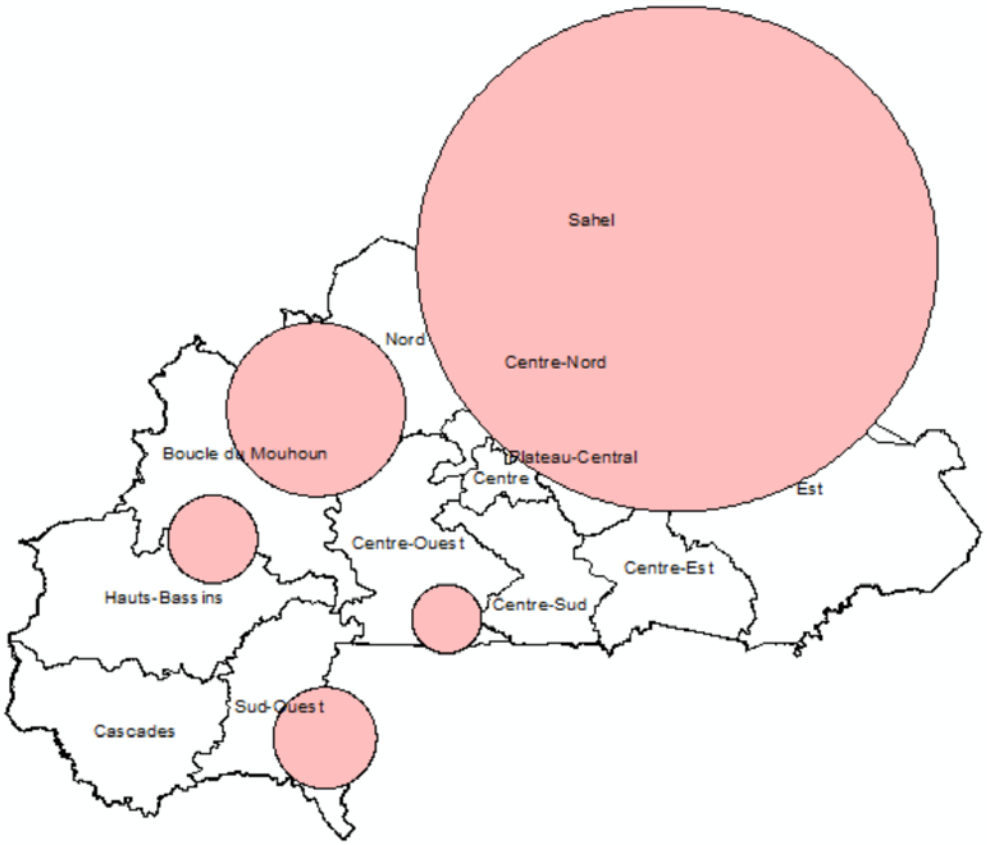
Determinant factors of anemia

Based on multivariable mixed-effects ordinal logistic regression model, Age, wealth index, regions Cascades, Hauts-bassins, and Plateau central were significantly associated with the level of anemia among women age 15-49 years in Burkina Faso at p-value 0.05 (Tab. IV).

Tab. III. Significant spatial clusters with high rate of Anemia among women age 15-49 years in Burkina Faso, 2021

	Cluster Enumeration area (cluster) identified	Coordinate (radius	Population	Case	RR	LLR	P- value
1	473, 469, 467, 466, 468,470, 474, 472, 471, 313, 315, 314, 318, 312, 204, 311, 309, 209, 310, 201, 316, 199, 306, 215, 203, 317, 216, 211, 212, 213, 205, 210, 214, 188, 208, 477, 475, 476, 78, 200,202, 221, 308, 190, 207, 307, 206, 220, 195, 192,193, 194, 432, 218, 217, 191, 197, 222, 219, 437,458, 166, 457, 189, 433,446, 196, 330, 198, 331,332, 175, 170, 439, 418 434, 438, 176, 392, 179,177, 450, 178, 456, 455, 403, 171, 453, 440, 454, 442, 414, 174, 167, 172, 444, 441, 173, 436, 419, 452, 391, 415, 448, 169, 420, 435, 449, 320, 428, 416, 443, 447, 451, 445, 115	14.122803 N, 0.062321 W) / 228.21 km	1281	843	1.32	51.483251	< 0.001
3	10, 9, 380, 367, 381, 37, 17	11.845827 N, 3.836225 W) / 39.61 km	84	67	1.50	12.782125	0.0019

Fig. 5. Primary and secondary clusters of Anemia among women age 15-49 years in Burkina Faso, 2021.



Making other variables constant, the likelihood of experiencing severe anemia among among women that were in age group of 25-29 years (relative to moderate, mild or non-anemic) were 1.31 times higher than those in the age group of 15-19 years [AOR = 1.31 ; 95% CI: 1.06 1.61]. The likelihoods of rich women aged 15 to 49 developing severe anemia (compared to moderate, mild or non-anemic) were 1.32 times higher than poor women aged 15–[AOR = 1.32 ; 95% CI: 1.08 1.62] while holding other variables constant. Regarding region, the odds of severe anaemic (opposed to moderate, mild or non-anemic) were increased by 62%, and 40% among women aged 15-49 residing in Cascades and Hauts-bassins respectively as compared with women aged 15-49 residing in Boucle du mouhoun and the odds of severe anaemic (opposed to moderate, mild or non-anemic) were decreased by 72%, and 42% in Plateau central and Sahel respectively as compared with women aged 15-49 residing in Boucle du mouhoun.

Discussion

This study is aimed to investigate the spatial distribution and determinants of anemia among women age 15-49 in

Tab. IV. Bi-variable and multivariable mixed-effects ordinal logistic regression model of anemia among women age 15-49 in Burkina Faso, 2021 (N = 5,655).

Variables		Crude odds ratio				Adjusted odds ratio			
		OR	95% CI		P-value	OR	95% CI		P-value
Region									
1)	Boucle du mouhoun	Ref	Ref		Ref	Ref	Ref		Ref
2)	Cascades	1.82	1.31	2.53	< 0.001	1.62	**1.16**	**2.25**	**0.004**
3)	Centre	1.49	1.14	1.93	0.003	1.22	0.93	1.60	0.145
4)	Centre Est	1.10	0.83	1.46	0.485	1.04	0.79	1.37	0.754
5)	Centre Nord	0.88	0.65	1.20	0.443	0.86	0.64	1.16	0.344
6)	Centre Ouest	1.11	0.84	1.47	0.442	1.10.	0.83	1.46	0.472
7)	Centre Sud	1.20	0.89	1.63	0.215	1.21	0.90	1.64	0.201
8)	Est	0.99	0.72	1.38	0.993	1.01	0.73	1.39	0.940
9)	Hauts-bassins	1.55	1.18	2.03	0.001	1.40	**1.06**	**1.84**	**0.015**
10)	Nord	0.89	0.67	1.19	0.462	0.88	0.66	1.17	0.382
11)	Plateau central	0.71	0.53	0.96	0.026	0.72	**0.54**	**0.96**	**0.027**
12)	Sahel	0.47	0.31	0.70	< 0.001	0.42	**0.28**	**0.63**	**< 0.001**
13)	Sud-Ouest	1.16	0.86	1.55	0.316	1.17	0.87	1.56	0.285
Type of place of residence									
Urban		Ref	Ref		Ref				
Rural		0.74	0.65	0.84	< 0.001	0.87	0.74	1.03	0.120
Toilet facility									
Yes		Ref	Ref		Ref				
No		0.86	0.77	0.97	0.015	1.04	0.91	1.19	0.480
Wealth index									
1)	Poorest	Ref	Ref		Ref				
2)	Poorer	1.03	0.86	1.22	0.733	1.00	0.84	1.19	0.951
3)	Middle	1.06	0.89	1.26	0.338	1.001	0.83	1.20	0.988
4)	Richer	1.48	1.25	1.77	< 0.001	1.32	**1.08**	**1.62**	**0.007**
5)	Richest	1.53	1.28	1.84	< 0.001	1.24	0.97	1.59	0.075
Age									
1)	15-19	Ref	Ref		Ref				
2)	20-24	1.13	0.91	0.24	0.243	1.09	0.88	1.34	0.403
3)	25-29	1.34	1.09	1.65	0.005	1.31	**1.06**	**1.61**	**0.011**
4)	30-34	1.19	0.97	1.47	0.088	1.16	0.95	1.43	0.140
5)	35-39	1.08	0.88	1.34	0.432	1.07	0.87	1.32	0.491
6)	40-44	1.02	0.82	1.27	0.817	1.03	0.83	1.28	0.770
7)	45-49	0.87	0.69	1.10	0.262	0.87	0.69	1.10	0.266
Random intercept									
Var (cons)		--	--		--	0.12	0.08	0.20	--

AOR: Adjusted Odd ratio; COR: Crude Odd Ratio; CI: Confidence interval.

Burkina Faso. The spatial analysis result showed that the spatial distribution of anemia among women age 15-49 was significantly varied across the country. In multivariable mixed-effect ordinal regression analysis; Age, wealth index, regions Cascades, Hauts-bassins, Plateau central, and Sahel were significant predictors of the level of anemia among women age 15-49 in Burkina Faso.

The present study documented that the spatial distribution of anemia among women age 15-49 significantly varied across the country this implies that anemia is unevenly distributed in all regions of Burkina Faso. Significant hotspot areas of anemia were identified in the Boucle du mouhoun, Centre, Hauts-bassins, Nord, Centre Ouest, Plateau central, and Centre Est regions this implies that

these regions have higher prevalence of anemia than other regions of Burkina Faso. Significant cold spot areas of anemia (low cluster of anemia), located in Sahel and Cascades regions this implies that this regions have low prevalence of anemia than other regions of Burkina Faso.

116 clusters were primary (most likely) clusters which were located in the Plateau central, Centre Nord, half of Est, half of Nord, and Sahel regions at 14.122803 N, 0.062321 W, with 228.21 km radius, a Relative Risk (RR) of 1.32, and Log-Likelihood Ratio (LRR) of 51.483251, at p-value < 0.01 (Tab. III). This tells us that women's within the spatial window had 1.32 times higher risk of experiencing anemia as compared to women's outside the spatial window. The secondary cluster were found in half of Boucle du mouhoun, border of Centre Ouest, and border of Nord regions at 11.845827 N, 3.836225 W), with 39.61 km radius, a Relative Risk (RR) of 1.50, and Log-Likelihood Ratio (LRR) of 12.782125, at p-value = 0.0019. This tells us that women's within the spatial window had 1.50 times higher risk of experiencing anemia as compared to women's outside the spatial window.

Regarding region, the odds of severe anaemic (opposed to moderate, mild or non-anemic) were increased by 62%, and 40% among women aged 15-49 residing in Cascades and Hauts-bassins respectively as compared with women aged 15-49 residing in Boucle du mouhoun (p values < 0.05) and the odds of severe anaemic (opposed to moderate, mild or non-anemic) were decreased by 72%, and 42% in Plateau central and Sahel respectively as compared with women aged 15-49 residing in Boucle du mouhoun (p values < 0.05) This spatial variation might be due to the difference in socioeconomic status, dietary diversity and food security [23]. Infectious disease like Malaria [24, 25] accounting for 18% of all deaths before five years of age. Clinical manifestations of severe falciparum malaria vary according to transmission in-tensity and typically present as one or more life-threatening complications, including: hy-perparasitemia; hypoglycemia; cerebral malaria; severe malarial anemia (SMA, HIV [23].

The likelihoods of rich women aged 15-49 developing severe anemia (compared to moderate, mild or non-anemic) were 1.32 times higher than poor women aged 15 [AOR = ;1.32; 95% CI: 1.08, 1.62, p values < 0.05] while holding other variables constant. This is in contrast with previous studies [2, 6, 7, 9-11] but similar with a study in Nepal [3] which showed that women in poorer wealth status were less likely to be anemic. The possible reasons listed in previous study conducted in Nepal is being an agrarian-based country and the same eating pattern for all. Most of the people consume iron-rich staple foods regardless of wealth status [3] and the same reason might apply to Burkina Faso. This finding may be surprising because maintaining food security is a big issue among poor families [26].

The current study revealed that the chances of women in age group of 25-29 years developing severe anemia (versus moderate, mild or non-anemic) were higher than the chances of women in age group of 15-19 years (p values < 0.05). This is similar with previous studies [4, 5]. The possible explanations for such results might be due to this specific group 25-29 years is in the phase of puberty growth spurt, when there is increasing need for the intake of iron, imposed by the expansion of cellular mass and by the growth of tissues, as well as by menstrual loss, with a direct influence on metabolism and the need for iron [4] as compared to women in age group of 15-19 years. Besides, inadequate intake of iron-rich foods and consequence of unhealthy dietary choices lead to anemia [27]. Therefore, the iron-deficiency intake – associated with menstrual losses and other factors – may lead to higher risks for adolescents to develop iron-deficiency anemia [28].

The current study has some strengths and limitations that need to be kept in mind while interpreting the result. The first strength of the current study was using large population-based data with a large sample size, which is representative at national and regional levels, so it can be generalized to women aged 15-49 years in Burkina Faso. Secondly, the combined use of both ArcGIS and Sat Scan statistical tests facilitated to identify similar and statistically significant areas with a high cluster of anemia (hot spot area). Furthermore, by considering the ordinal nature of the outcome variable and the cluster nature of data, the current study applied an advanced model (mixed effect ordinal logistic regression) to get reliable standard errors and parameter estimates. The first limitation of the present study was using secondary data, some important variable like dietary intake, Plasmodium falciparum parasite rate and hook- worm were not included in the analysis.

Conclusions

A significant clustering of anemia among women aged 15-49 were found in Burkina Faso and the significant hotspot areas with high cluster anemia were identified in Boucle du, mouhoun, Centre, Hauts-bassins, Nord, Centre Ouest, Plateau central, and Centre Est regions. Besides, Age, wealth index, regions Cascades, Hauts-bassins, Plateau central, and Sahel were significant predictors of anemia. Therefore, effective public health intervention and nutritional education should be designed for the identified hotspot areas and risk groups in order to decrease the incidence of anemia.

Acknowledgments

We would like to thank the measure DHS for providing us the data and shape files for the study area.

Authors' contributions

Conception and design of the work, acquisition of data, analysis, and interpretation of data were done by KTT.

Data curation, drafting the article, revising it critically for intellectual content, validation, and final approval of the version to be published were done by KTT, ETT, MKT, TKW, MTA and AWZ. All authors read and approved the final manuscript.

Funding

No fund was received for this work.

Availability of data and materials

The datasets supporting the conclusions of this article are available upon request to the corresponding author.

Ethics approval and consent to participate

The study does not contain the collection of information from subjects. We sent a one-page proposal abstract of the study to the DHS program office. They gave permission to access the data.

Consent for publication

Not applicable.

Conflicts of interest

All authors declare no conflicts of interest.

References

[1] Teshale AB, Tesema GA, Worku MG, Yeshaw Y, Tessema ZT. Anemia and its associated factors among women of reproductive age in eastern Africa: a multilevel mixed-effects generalized linear model. PLoS One 2020;15:e0238957. https://doi.org/10.1371/journal.pone.0238957.

[2] Tusa BS, Kebede SA, Weldesenbet AB. Spatial distribution and determinant factors of anemia among adults aged 15-59 in Ethiopia; using mixed-effects ordinal logistic regression model. BMC Nutr 2021;7:18. https://doi.org/10.1186/s40795-021-00424-4.

[3] Sunuwar DR, Singh DR, Chaudhary NK, et al. Prevalence and factors associated with anemia among women of reproductive age in seven South and Southeast Asian countries: Evidence from nationally representative surveys. PLoS One 2020;15:e0236449. https://doi.org/10.1371/journal.pone.0236449.

[4] Bezerra AGN, Leal VS, Lira PIC, et al. Anemia and associated factors in women at reproductive age in a Brazilian Northeastern municipality. Rev Bras Epidemiol 2018;21:e180001. https://doi.org/10.1590/1980-549720180001.

[5] Kandala NI, Pallikadavath S, Amos Channon A, et al. A multilevel approach to correlates of anaemia in women in the Democratic Republic of Congo: findings from a nationally representative survey. Eur J Clin Nutr 2020;74:720-31. https://doi.org/10.1038/s41430-019-0524-8.

[6] Habyarimana F, Zewotir T RS. Spatial Distribution and Analysis of Risk Factors Associated with Anemia Among Women of Reproductive Age: Case of 2014 Rwanda Demographic and Health Sur- vey Data. Open Public Health J 2018;11:425-37. https://doi.org/10.2174/1874944501811010425.

[7] Kibret KT, Chojenta C, D'Arcy E, Loxton D. Spatial distribution and determinant factors of anaemia among women of reproductive age in Ethiopia: a multilevel and spatial analysis. BMJ Open 2019;9:e027276. https://doi.org/10.1136/bmjopen-2018-027276.

[8] Lover AA, Hartman M, Chia KS, Heymann DL. Demographic and spatial predictors of anemia in women of reproductive age in Timor-Leste: implications for health program prioritization. PLoS One 2014;9:e91252. https://doi.org/10.1371/journal.pone.0091252.

[9] Hakizimana D, Nisingizwe MP, Logan J, Wong R. Identifying risk factors of anemia among women of reproductive age in Rwanda - a cross-sectional study using secondary data from the Rwanda demographic and health survey 2014/2015. BMC Public Health 2019;19:1662. https://doi.org/10.1186/s12889-019-8019-z.

[10] Nankinga O, Aguta D. Determinants of anemia among women in Uganda: further analysis of the Uganda demographic and health surveys. BMC Public Health 2019;19:1757. https://doi.org/10.1186/s12889-019-8114-1.

[11] Adamu AL, Crampin A, Kayuni N, et al. Prevalence and risk factors for anemia severity and type in Malawian men and women: urban and rural differences. Popul Health Metr 2017;15:12. https://doi.org/10.1186/s12963-017-0128-2.

[12] Lee JO, Lee JH, Ahn S, et al. Prevalence and risk factors for iron deficiency anemia in the Korean population: results of the fifth KoreaNational Health and Nutrition Examination Survey. J Korean Med Sci 2014;29:224-9. https://doi.org/10.3346/jkms.2014.29.2.224.

[13] Harding KL, Aguayo VM, Namirembe G, Webb P. Determinants of anemia among women and children in Nepal and Pakistan: an analysis of recent national survey data. Matern Child Nutr 2018;14:e12478. https://doi.org/10.1111/mcn.12478.

[14] Balarajan YS, Fawzi WW, Subramanian SV. Changing patterns of social inequalities in anaemia among women in India: cross-sectional study using nationally representative data. BMJ Open 2013;3:e002233. https://doi.org/10.1136/bmjopen-2012-002233.

[15] Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521-32. https://doi.org/10.1016/S0140-6736(06)68653-4.

[16] Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. Parasitol Today 2000;16:469-76. https://doi.org/10.1016/s0169-4758(00)01774-9.

[17] Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014;123:615-24. https://doi.org/10.1182/blood-2013-06-508325.

[18] Burkina Faso. 2021; DHS final report. Available at: https://dhsprogram.com/what-we-do/survey/survey-display-562.cfm (Access on: March 24, 2024).

[19] World Health Organization, United Nations Children's Fund. Progress on household drinking water, sanitation and hygiene 2000-2020: five years into the SDGs. WHO 2021.

[20] World Health Organization (WHO). Joint monitoring programme for water supply and sanitation. United Nations 2006.

[21] WHO/UNICEF Joint Water Supply, Sanitation Monitoring Programme. Progress on sanitation and drinking water: 2015 update and MDG assessment. WHO 2015.

[22] Waldhör T. The spatial autocorrelation coefficient Moran's I under heteroscedasticity. Stat Med 1996;15:887-92. https://doi.

org/10.1002/(sici)1097-0258(19960415)15:7/9<887::aidsim257>3.0.co;2-e.

[23] Ejigu BA, Wencheko E, Berhane K. Spatial pattern and determinants of anaemia in Ethiopia. PLoS One 2018;13:e0197171. https://doi.org/10.1371/journal.pone.0197171.

[24] Perkins DJ, Were T, Davenport GC, et al. Severe malarial anemia: innate immunity and pathogenesis. Int J Biol Sci 2011;7:1427-42. https://doi.org/10.7150/ijbs.7.1427.

[25] Quintero JP, Siqueira AM, Tobón A, et al. Malaria-related anaemia: a Latin American perspective. Mem Inst Oswaldo Cruz 2011;106:91-104. https://doi.org/10.1590/s0074-02762011000900012.

[26] Ajao KO, Ojofeitimi EO, Adebayo AA, Fatusi AO, Afolabi OT. Influence of family size, household food security status, and child care practices on the nutritional status of under-five children in Ile-Ife, Nigeria. Afr J Reprod Health 2010;14:117-26.

[27] Borges CQ, Silva Rde C, Assis AM, Pinto Ede J, Fiaccone RL, Pinheiro SM. Fatores associados à anemia em crianças e adolescentes de escolas públicas de Salvador, Bahia, Brasil. Cad Saude Publica 2009;25:877-88. https://doi.org/10.1590/s0102-311x2009000400019.

[28] Silva T dos S, Oliveira FM, Santos JM de J. Níveis de Hemoglobina e Consumo de Alimentos Fontes de Ferro em Estudantes do Ensino Médio. Rev Bras Ciências da Saúde 2018;22:307-14. https://doi.org/10.22478/ufpb.2317-6032.2018v22n4.34154.

Received on March 15, 2024. Accepted on May 14, 2024.

Correspondence: Kaleab Tesfaye Tegegne, Department of Public Health, College of Health Science, Debark University, Debark, Ethiopia. E-mail: kaleabtesfaye35@gmail.com

How to cite this article: Tegegne KT, Tegegne ET, Tessema MK, Wudu TK, Abebe MT, Workaeh AZ. Spatial distribution and determinant factors of anemia among women age 15-49 years in Burkina Faso; using mixed-effects ordinal logistic regression model. J Prev Med Hyg 2024;65:E203-E213. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3227

Non comunicable disease

Comparison of the short-term effect of intra-articular hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized clinical trial

OMID GHORBANI[1], DARYOOSH MAHDIBARZI[1], PARIA YOUSEFI-TOODDESHKI[2]
[1] Department of surgery, Faculty of Medicine, Shahed University, Tehran, Iran;
[2] Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

Keywords

Intra-Articular • Hyaluronic Acid • Platelet-Rich Plasma • Knee Osteoarthritis

Summary

Introduction. *Osteoarthritis (OA) is one of the most common degenerative joint diseases which involved all joints. It is very important to choose a treatment method with high efficiency to reduce the pain and disability of patients and also to improve their quality of life. The current study aimed to investigate the therapeutic effects of intra-articular injection of PRP and hyaluronic acid (HA) in the knee of people with knee osteoarthritis (KOA).*
Methods. *In this randomized clinical trial study, 90 patients with KOA were randomly divided into two groups of intra-articular HA and PRP. The patients of the two groups were followed up for five months and different outcomes were recorded. The McMaster index (WOMAC) evaluated all patients at rest and during movements. Measurements were taken at the beginning and after the third month of follow-up.*
Results. *Three month after the last injection (5th month) and after adjusting of baseline value using analysis of covariance, the mean of knee pain, stiffness, physical function and finally total score in the PRP group, was significantly lower than the HA group. Regarding the Osteoarthritis grade, the mean of knee pain, Stiffness, Physical function and finally total score in the PRP group was significantly lower than the HA group in all Osteoarthritis grades. Also, there were no complications in the studied groups.*
Conclusions. *The results of the current study showed that pain and stiffness reduction as well as physical function of the knee joint in the PRP group was better than in the HA group.*

Introduction

Osteoarthritis (OA) is one of the most common degenerative joint diseases, involving all joints [1]. The nature of this disease is the progressive destruction of the joint, characterized by the progressive degeneration of articular cartilage and subchondral bone involvement [2]. While knee osteoarthritis (KOA) is one of the main causes of disability in the knee joint, this manifests itself with symptoms such as knee pain and stiffness, joint inflammation and degeneration, also has a major impact on disability and reduces quality of life [3]. The risk factors of this disease, include increasing age, obesity, female sex, and inflammation of the knee joint [4,5]. The knee is the most common joint affected by arthritis among the Iranian population. The prevalence of this disorder in Iran is estimated at 15.5% [6]. According to a study, knee osteoarthritis in Iran ranks ninth in terms of disease burden after accidents, natural disasters, cardiovascular diseases, *etc.* [7].
So far, many studies have been presented on the treatment methods of osteoarthritis such drug treatments, interventional methods, and auxiliary treatment regimens [8, 9]. Non-surgical measures are the first step to control patients' knee pain, which includes weight loss, specific exercise regimens, lifestyle changes, physical therapy, use of non-steroidal anti-inflammatory drugs, painkillers, and intra-articular injections of corticosteroids, gels, *etc.* [10, 11]. Meanwhile, acetaminophen, non-steroidal anti-inflammatory drugs, and corticosteroids have analgesic and sometimes anti-inflammatory effects. However, the occurrence of common side effects in the use of such drugs limits their use in many patients. Gastrointestinal complications, aggravation of heart failure, increased blood pressure [12], liver disorders [13], kidney problems [14], exacerbation of asthma [15], and the risk of osteoporosis [16] in long-term use are common side effects of anti-inflammatory drugs.
The ability of cartilage to regenerate itself is unfortunately limited due to the lack of blood vessels and innervation, as well as its isolation from the body's systemic circulation, so the intra-articular injection of a drug or drug combination with the property of regeneration and repair of cartilage tissue has always been of interest to researchers [17]. In recent years, intra-articular injection of platelet-rich plasma (PRP) in knee osteoarthritis has attracted the attention of researchers [18, 19]. This injection contains PRP, which has a higher concentration of platelets than normal blood. PRP is an environment rich in high concentrations of cytokines and various growth factors that are obtained through blood centrifugation and can be considered a new solution to stimulate mesenchymal

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3270

cells to replicate and regenerate damaged tissues [20]. Samples from patients with knee osteoarthritis show that the number of mesenchymal cells in the synovial fluid of these people has significantly decreased compared to healthy individuals, as a result of PRP injection as a stimulating factor for the regeneration and replication of this cell can be effective in the treatment of arthritis [21]. Increasing the presence of mesenchymal cells in the synovial fluid of sick people can play a modulating role in the responses of the immune system, which accelerates the healing process [22]. The current study aimed to investigate the therapeutic effects of intra-articular injections of PRP and hyaluronic acid (HA) in patients with knee osteoarthritis.

Methods

In the current randomized clinical trial study, 90 patients with painful knee arthritis with radiological grades one to three of the Kellgren and Lawrence radiological criteria were included. More details were shown in figure1.

Inclusion criteria

Patients aged 40 to 65 years, history of knee pain for at least three months, knee osteoarthritis grade 1 to 3 based on the Kellgren and Lawrence criteria (based on knee osteoarthritis criteria of the American College of Rheumatology) were included.

Exclusion criteria

Patients suffering from diseases such as diabetes, rheumatoid arthritis, hemophilia, dysfunction of blood platelets, any infection or active wound at the injection site, taking antiplatelet or anticoagulant drugs in the last ten days before injection, taking non-steroidal anti-inflammatory drugs, having history of intra-articular corticosteroid injection in the previous three weeks or systemic corticosteroid use in the last two weeks, peripheral blood platelet count less than 150,000 per microliter, patients with drug or alcohol addiction and abnormal ESR or CRP levels were excluded.

After selection of the cases, their basic information including age, sex, height, weight, and body mass index was recorded and patients were divided into the PRP and HA groups using simple random allocation methods.

Interventions

PRP group

After taking the patients' history, examining them, and performing routine monitoring such as blood pressure, heart rate, and electrocardiogram (if necessary), 30-35 ml of the patient's venous blood was taken from the upper limb with an 18G needle under sterile conditions and placed in special centrifuge kits (produced by Royagen, Iran) containing 5 ml of acid citrate dextrose solution-A to prepare platelet-rich plasma. This solution was placed in a centrifuge for 15 minutes with a rotation speed of 1600 rpm. The Buffy coat and plasma layer of the solution inside the test tube was separated and centrifuged again for 7 minutes with a rotation speed of 2800 rpm. Finally, 5 ml PRP was prepared for intra-articular injection. Anesthetic injections may also affect platelet activation by changing the PH of the environment, so no local anesthetic was injected. Instead, patients were given a single dose of acetaminophen and codeine two hours before injection. Under sterile conditions, a 22-gauge, 50 mm needle was inserted from the upper external area of the knee patella (suprapatellar) and the outside to the inside of the knee joint and the prepared plasma was injected inside the knee joint. In our study, the frequency of intra-articular injection of PRP was three times at one-month intervals.

Hyaluronic Acid group

In this group, HA (Hyalgan®) was injected. Hyalgan produced by Fidia Farmaceutici S.p.A., Abano Terme, Italy, is a viscous solution consisting of a high molecular weight (500,000-730,000 Da) fraction of purified natural sodium hyaluronate in buffered physiological sodium chloride, having a PH of 6.8-7.5. The sodium hyaluronate is extracted from rooster combs. Hyalgan was supplied as a sterile, non-pyogenic solution in 2 mL pre-filled syringes containing 20 mg of sodium hyaluronate, 17 mg of sodium chloride, 0.1 mg of monobasic sodium phosphate, 1.2 mg of dibasic sodium phosphate, and up to 2 cc water for injection. After resting for 15-20 minutes, the patients were asked to flex and extend their knees to ensure even distribution of the HA in the joint space. The patients were monitored in the clinic for one hour after the injection and were discharged with written instructions regarding the following issues if no side effects occurred. Hyaluronic acid injections were administered three times at one-week intervals.

Study outcomes

The intensity of pain, dryness, and knee function of the patients before the first injection and three months after the last injection were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores. The WOMAC criterion consists of three parts: pain level, joint stiffness level, and knee function level. Scoring in each case is from 0 to 4 and the total score of this scale is from 0 to 96.

Statistical analysis

Descriptive statistics including mean ± standard and frequency (percentage) was used to present quantitative and qualitative findings. Data were analyzed using the independent sample t-test, paired sample t-test, Chi-square, or Fisher exact test and Analysis of covariance (ANCOVA) test. The statistical significance level was considered at: 0.05. All data were analyzed using SPSS, version 22.0, Armonk, NY, USA: IBM Corp. Released 2015.

Tab. I. Descriptive characteristics of understudied cases.

Variables	PRP (n: 41)	Hyaluronic Acid (n: 44)	p
Gender			
Females	26(63.4%)	26(59.1%)	0.682
Osteoarthritis grade			
1	14(34.1%)	15(34.1%)	
2	14(34.1%)	14(31.8%)	
3	13(31.7%)	15(34.1%)	0.961
Age	Mean ± SD	Mean ± SD	
	60.24 ± 1.97	61.90 ± 2.06	0.014
BMI			
	29.47 ± 1.52	28.78 ± 1.39	0.032

Tab. II. Comparison of different outcome scores within groups over the time.

Group	N	Outcome	Baseline	Three months after the intervention	
			Mean ± SD	Mean ± SD	p
PRP	41.00	Pain	13.66 ± 3.60	6.44 ± 1.42	0.001
	41.00	Stiffness	3.10 ± 0.80	1.80 ± 0.93	0.001
	41.00	Physical function	36.07 ± 6.71	18.85 ± 6.70	0.001
	41.00	Total	52.37 ± 9.19	27.10 ± 8.46	0.001
Hyaluronic acid	44.00	Pain	11.93 ± 1.59	10.61 ± 1.17	0.001
	44.00	Stiffness	2.91 ± 0.86	2.52 ± 0.73	0.001
	44.00	Physical function	35.36 ± 6.42	33.05 ± 6.41	0.001
	44.00	Total	50.20 ± 8.41	46.18 ± 7.90	0.001

Results

Baseline characteristics

Regarding the gender, 26(63.4%) and 26(59.1%) of cases in the PRP and Hyaluronic Acid groups were females respectively (P: 0.682). Mean of age in the PRP and Hyaluronic Acid groups were 60.24 ± 1.97 and 61.90 ± 2.06 and the difference between two groups was statistically significant (P: 0.001). The mean of BMI in the PRP and Hyaluronic Acid groups were 29.47 ± 1.52 and 28.78 ± 1.39 and the difference between two groups was statistically significant (P: 0.032) (Tab. I).

Main outcomes

Within groups comparison

PRP group

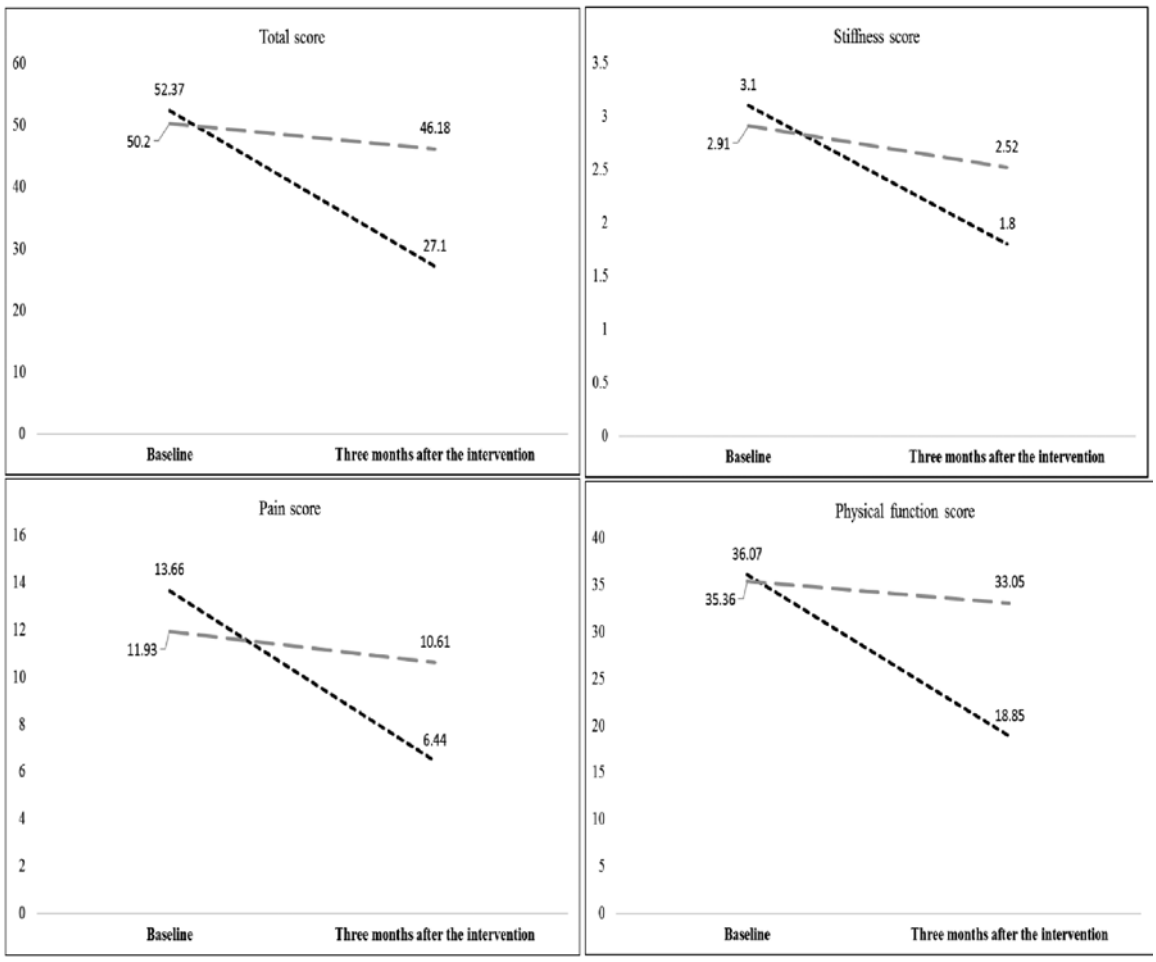
In this group, the knee pain score three months after intervention decreased significantly from 13.66 ± 3.60 to 6.44 ± 1.42(P: 0.001), also the knee stiffness score decreased from 3.10 ± 0.80 to 1.80 ± 0.93 (P: 0.001). Regarding the knee physical function score, this score decreased significantly from 36.07 ± 6.71 to 18.85 ± 6.70 (P: 0.001), and finally the total score decreased significantly from 52.37 ± 9.19 to 27.10 ± 8.46 (P: 0.001) (Tab. II, Fig. 1).

Hyaluronic Acid

In this group, the knee pain score decreased significantly from 11.93 ± 1.59 to 10.61 ± 1.17 (P: 0.001) in three months after the intervention compared to baseline.

Fig. 1. Flow diagram of the study. N: number of patients, KOA: Knee osteoarthritis; PRP: platelet-rich plasma; HA: hyaluronic acid.

Fig. 2. The trend of changes in different outcome scores in studied interventions.



Also the knee stiffness score decreased significantly from 2.91 ± 0.86 to 2.52 ± 0.73 (P: 0.001). Regarding the knee physical function score, this score decreased from 35.36 ± 6.42 to 33.05 ± 6.41 (P: 0.001), and finally the total score decreased from 50.20 ± 8.41 to 46.18 ± 7.90 (P:0.001) (Tab. II, Fig. 2).

Between groups comparison

Three months after the intervention, the mean of knee pain, stiffness, physical function and finally total score in the PRP group, was significantly lower than the Hyaluronic Acid group. More details were shown in the Table III. Regarding the Osteoarthritis grade, the mean of knee pain, Stiffness, Physical function and finally total score in the PRP group was significantly lower than the Hyaluronic Acid group in all Osteoarthritis grades (Tab. IV). Also, there were no complications in the studied groups.

Discussion

One of the effective factors in the development and progression of knee arthritis is inflammation, which aggravates the symptoms. Therefore, the use of treatments that have an anti-inflammatory effect can have an effective role in reducing the symptoms of the disease as well as the side effects of osteoarthritis of the joints. One of these treatments is the use of blood derivatives such as PRP, which can play an important role in reducing symptoms. PRP.as an anti-inflammatory factor can affect various cells, including mesenchymal stem cells, and as a result, it can modulate various cellular activities [23-25]. Another property of PRP is the absorption of other cells effective in treatment [23].

Tab. III. Comparison of different outcome scores between groups three month after the intervention.

Outcome	PRP (n: 41)	Hyaluronic acid (n: 44)	Partial eta squared	P
	Mean ±SD	Mean ± SD		
Pain	6.44 ± 1.42	10.61 ± 1.17	0.82	0.001
Stiffness	1.80 ± 0.93	2.52 ± 0.73	0.41	0.001
Physical function	18.85 ± 6.70	33.05 ± 6.41	0.95	0.001
Total	27.10 ± 8.46	46.18 ± 7.90	0.98	0.001

Tab. IV. Comparison of different outcome scores between groups three month after the intervention by Osteoarthritis grades.

Outcome	PRP (n: 41)	Hyaluronic acid (n: 44)	Partial eta squared	P
Pain				
Osteoarthritis grade	Mean ± SD	Mean ± SD		
1.00	4.93 ± 0.73	9.73 ± 0.80	0.96	0.001
2.00	6.86 ± 1.10	10.71 ± 0.73	0.81	0.001
3.00	7.62 ± 0.65	11.40 ± 1.24	0.96	0.001
Stiffness				
1.00	1.07 ± 0.73	1.93 ± 0.26	0.60	0.001
2.00	1.71 ± 0.61	2.29 ± 0.47	0.33	0.001
3.00	2.69 ± 0.63	3.33 ± 0.49	0.17	0.03
Physical function				
1.00	13.21 ± 1.97	27.60 ± 1.80	0.39	0.001
2.00	16.79 ± 1.63	31.36 ± 2.98	0.50	0.001
3.00	27.15 ± 5.08	40.07 ± 5.23	0.98	0.001
Total				
1.00	19.21 ± 1.97	39.27 ± 2.43	0.98	0.001
2.00	25.36 ± 2.71	44.36 ± 3.59	0.75	0.001
3.00	37.46 ± 5.84	54.80 ± 6.29	0.99	0.001

This multifaceted property of PRP has made this drug play an important role in reducing joint inflammation and play an important role in improving function and reducing pain in people with osteoarthritis [26, 27]. It is believed that intra-articular injection of PRP and HA can reduce pain and improve quality of life in patients with OA [28-30]. Due to the importance of the issue the current study aimed to assess the short-term effect of intra-articular hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis in a randomized clinical trial study.

Our results showed that the knee pain, knee stiffness, physical function and total WOMAC scores decreased significantly from baseline to three months after the intervention in both PRP and HA groups. Also, three months after the intervention the mean of knee pain, stiffness, physical function and finally total WOMAC scores in the PRP group, was significantly lower than the HA group. Regarding the osteoarthritis grade, the mean of knee pain, stiffness, physical function and finally total score in the PRP group, was significantly lower than the hyaluronic acid group in all osteoarthritis grades. This finding indicates that the PRP as well as HA improved OA indices, but the amount of changes in the PRP group was significantly more than HA group.

Several studies have been conducted comparing the effectiveness of PRP, and HA in the treatment of osteoarthritis [31-33]. In the study of Lana et al., they concluded that PRP has a greater effect on reducing patients' pain scores compared to HA at different times after treatment [34]. The results of Sampson et al.'s study indicated a significant reduction in pain within one year after PRP injection in patients with OA [35]. The study by Sanchez et al showed a reduction in knee pain intensity for 5 weeks after PRP [36].

The findings of the meta-analyses conducted in this field also indicate the superiority of PRP over HA, and in reducing pain [27, 37, 38]. The results of the meta-analysis showed that the greatest effectiveness of PRP in reducing WOMAC pain and VAS pain outcomes was observed 6 months after treatment [32]. The results of other studies in this field indicate that the effectiveness of drug injection is not stable and usually decreases over times [37].

The results of our study indicated that PRP is more effective in reducing the stiffness and function of patients. Also, there were no significant complications among patients, and most of the patients only experienced brief pain at the injection site, which improved within a short time after the intervention. Other studies also support this finding. The meta-analysis results showed that pain, stiffness, and WOMAC performance in the PRP group improved the most in the 12 months after injection [32]. These results have been confirmed in other studies that have shown that after PRP injection, a drug effect lasts up to 12 and even 24 months [27, 39]. Another study showed improvement in patients' quality of life in 12 months after injection of PRP and HA [30]. Tucker et al.'s study results showed that the pain stiffness and functional scores, improved significantly in the PRP group compared to the control group [40]. Therefore, as mentioned, the findings of various studies indicate that PRP is more effective in reducing knee joint pain than HA. In justification of these findings, it can be said that PRP has anti-inflammatory properties. Indeed, PRP reduces inflammation by inducing a more targeted and controlled anti-inflammatory response, modulating the immune response, and increasing angiogenesis and re-epithelialization [41]. Also, PRP can potentially reduce the impact of other underlying knee joint diseases [42-44]. In fact, by promoting tissue repair and regeneration, PRP can reduce the impact of these diseases on the progression of osteoarthritis [32].

Limitations of the study

The present study had limitations, including the small sample size and the short follow-up period of the patients.

Conclusions

The results of the study indicate a significant improvement in pain, stiffness, and physical function of the knee joint in patients with arthritis especially in the PRP group. Due to its positive effect, safety, and availability, PRP has attracted the interest of Physician in the treatment of knee arthritis and it can be concluded that PRP injection can be considered a more effective treatment than HA in patients with knee osteoarthritis.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This research approved by the ethical committee of Shahed University with approval id IR.SHAHED.REC.1399.028. The written informed consent was obtained from all participants.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the study conception and design. OG, DB: participated in the design of the study; OG, PYT: performed data collection, wrote the manuscript, and helped with statistical analysis; OG, DB: edited the manuscript. All authors read and approved the final manuscript.

References

[1] Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthritis Cartilage 2022;30:184-95. https://doi.org/10.1016/j.joca.2021.04.020.

[2] Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, Goldring SR, Jones G, Teichtahl AJ, Pelletier JP. Osteoarthritis. Nat Rev Dis Primers 2016;2:16072. https://doi.org/10.1038/nrdp.2016.72.

[3] Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee osteoarthritis: a primer. Perm J 2017;21:16-183. https://doi.org/10.7812/TPP/16-183.

[4] Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine 2020;29-30:100587. https://doi.org/10.1016/j.eclinm.2020.

[5] Peshkova M, Lychagin A, Lipina M, Di Matteo B, Anzillotti G, Ronzoni F, Kosheleva N, Shpichka A, Royuk V, Fomin V, Kalinsky E, Timashev P, Kon E. Gender-related aspects in osteoarthritis development and progression: a review. Int J Mol Sci 2022;23:2767. https://doi.org/10.3390/ijms23052767.

[6] Davatchi F, Sandoughi M, Moghimi N, Jamshidi AR, Tehrani Banihashemi A, Zakeri Z, Sadeghi Abdollahi B. Epidemiology of rheumatic diseases in Iran from analysis of four COPCORD studies. Int J Rheum Dis 2016;19:1056-62. https://doi.org/10.1111/1756-185X.12809.

[7] Naghavi M, Abolhassani F, Pourmalek F, Lakeh M, Jafari N, Vaseghi S, Mahdavi Hezaveh N, Kazemeini H. The burden of disease and injury in Iran 2003. Popul Health Metr 2009;7:9. https://doi.org/10.1186/1478-7954-7-9.

[8] Zhu B, Ba H, Kong L, Fu Y, Ren J, Zhu Q, Fang M. The effects of manual therapy in pain and safety of patients with knee osteoarthritis: a systematic review and meta-analysis. Syst Rev 2024;13:91. https://doi.org/10.1186/s13643-024-02467-7.

[9] Song X, Liu Y, Chen S, Zhang L, Zhang H, Shen X, Du H, Sun R. Knee osteoarthritis: a review of animal models and intervention of traditional Chinese medicine. Animal Model Exp Med 2024;7:114-26. https://doi.org/10.1002/ame2.12389.

[10] Allison K, Jones S, Hinman RS, Pardo J, Li P, DeSilva A, Quicke JG, Sumithran P, Prendergast J, George E, Holden MA, Foster NE, Bennell KL. Alternative models to support weight loss in chronic musculoskeletal conditions: effectiveness of a physiotherapist-delivered intensive diet programme for knee osteoarthritis, the POWER randomised controlled trial. Br J Sports Med 2024;58:538-47. https://doi.org/10.1136/bjsports-2023-107793.

[11] Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. Braz J Phys Ther 2021;25:135-46. https://doi.org/10.1016/j.bjpt.2020.08.004.

[12] Snowden S, Nelson R. The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardiol Rev 2011;19:184-91. https://doi.org/10.1097/CRD.0b013e31821ddcf4.

[13] García Rodríguez LA, Williams R, Derby LE, Dean AD, Jick H. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. Arch Intern Med 1994;154:311-6. https://doi.org/10.1001/archinte.1994.00420030117012.

[14] Winkelmayer WC, Waikar SS, Mogun H, Solomon DH. Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. Am J Med 2008;121:1092-8. https://doi.org/10.1016/j.amjmed.2008.06.035.

[15] Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ 2013;346:f3195. https://doi.org/10.1136/bmj.f3195.

[16] van Esch RW, Kool MM, van As S. NSAIDs can have adverse effects on bone healing. Med Hypotheses 2013;81:343-6. https://doi.org/10.1016/j.mehy.2013.03.042.

[17] Kon E, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, Della Villa S. Non-surgical management of early knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2012;20:436-49. https://doi.org/10.1007/s00167-011-1713-8.

[18] Garcia-Motta H, Carvalho C, Guilherme EM, de Oliveira MPB, Rossi KNZP. Effects of intra-articular injection of platelet-rich plasma on the inflammatory process and histopathological characteristics of cartilage and synovium in animals with osteoarthritis: a systematic review with meta-analysis. Adv Rheumatol 2024;64:24. https://doi.org/10.1186/s42358-024-00364-0.

[19] Patel S, Gahlaut S, Thami T, Chouhan DK, Jain A, Dhillon MS. Comparison of conventional dose versus super-dose platelet-rich plasma for knee osteoarthritis: a prospective, triple-blind, randomized clinical trial. Orthop J Sports Med 2024;12:23259671241227863. https://doi.org/10.1177/23259671241227863.

[20] Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev 2003;83:835-70. https://doi.org/10.1152/physrev.2003.83.3.835.

[21] Kohno Y, Mizuno M, Ozeki N, Katano H, Otabe K, Koga H, Matsumoto M, Kaneko H, Takazawa Y, Sekiya I. Comparison of mesenchymal stem cells obtained by suspended culture of synovium from patients with rheumatoid arthritis and osteoarthritis. BMC Musculoskelet Disord 2018;19:78. https://doi.org/10.1186/s12891-018-1998-6.

[22] Mohanraj B, Huang AH, Yeger-McKeever MJ, Schmidt MJ, Dodge GR, Mauck RL. Chondrocyte and mesenchymal stem cell derived engineered cartilage exhibits differential sensitivity to pro-inflammatory cytokines. J Orthop Res 2018;36:2901-10. https://doi.org/10.1002/jor.24061.

[23] Ishida K, Kuroda R, Miwa M, Tabata Y, Hokugo A, Kawamoto T, Sasaki K, Doita M, Kurosaka M. The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. Tissue Eng 2007;13:1103-1112. https://doi.org/10.1089/ten.2006.0193.

[24] Jeyakumar V, Niculescu-Morzsa E, Bauer C, Lacza Z, Nehrer S. Platelet-rich plasma supports proliferation and redifferentiation of chondrocytes during in vitro expansion. Front Bioeng Biotechnol 2017;5:75. https://doi.org/10.3389/fbioe.2017.00075.

[25] Olivotto E, Merli G, Assirelli E, Cavallo C, Belluzzi E, Ramonda R, Favero M, Filardo G, Roffi A, Kon E: Cultures of a human synovial cell line to evaluate platelet-rich plasma and hyaluronic acid effects. J Tissue Engin Regen Med 2018;12:1835-42. https://doi.org/10.1002/term.2704.

[26] Huang G, Hua S, Yang T, Ma J, Yu W, Chen X. Platelet-rich plasma shows beneficial effects for patients with knee osteoarthritis by suppressing inflammatory factors. Exp Ther Med 2018;15:3096-102. https://doi.org/10.3892/etm.2018.5794.

[27] Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP injections for the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Cartilage 2021;13(Suppl 1):364S-75. https://doi.org/10.1177/1947603520931170.

[28] Yoga R, Mukaram M. Intra-articular sodium hyaluronate for the treatment of osteoarthritis of the knee. A retrospective review of 45 patients. Malaysian Orthop J 2009;3:4-7. https://doi.org/10.5704/MOJ.0911.001.

[29] Haque Bhuyan MZ, Tamura Y, Sone E, Yoshinari Y, Maeda C, Takahashi M, Tabata Y, Murali R, Waki Y, Aoki K. The intra-articular injection of RANKL-binding peptides inhibits cartilage degeneration in a murine model of osteoarthritis. J Pharmacol Sci 2017;134:124-30. https://doi.org/10.1016/j.jphs.2017.05.008.

[30] Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2011;19:528-35. https://doi.org/10.1007/s00167-010-1238-6.

[31] Konana VS, Yallapura HS, Bettaswamy S, Sivaram SP, Thimmegowda DG: Comparing the Effectiveness of Intra-articular injection with autologous platelet-rich plasma vs hyaluronic acid vs platelet-derived growth factors in early osteoarthritis of knee joint. J Orthop Joint Surg 2024;6:27-34. https://doi.org/10.5005/jojs-10079-1134.

[32] Khalid S, Ali A, Deepak F, Zulfiqar MS, Malik LU, Fouzan Z, Nasr RA, Qamar M, Bhattarai P. Comparative effectiveness of intra-articular therapies in knee osteoarthritis: a meta-analysis comparing platelet-rich plasma (PRP) with other treatment modalities. Ann Med Surg 2024;86:361-72.

[33] Abdulwahab D, Lateef S, Farìs W, Al Radhwany Y. Single shot of knee intraarticular injection of platelets rich plasma versus hyaluronic acid injections for symptomatic knee osteoarthritis. an observational prospective study. Int J Disab Sports Health Sci 2004;7:342-50.

[34] Lana JF, Weglein A, Sampson SE, Vicente EF, Huber SC, Souza CV, Ambach MA, Vincent H, Urban-Paffaro A, Onodera CM, Annichino-Bizzacchi JM, Santana MH, Belangero WD. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. J Stem Cells Regen Med 2016;12:69-78. https://doi.org/10.46582/jsrm.1202011.

[35] Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. Am J Phys Med Rehabil 201;89:961-9. https://doi.org/10.1097/PHM.0b013e3181fc7edf.

[36] Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. Clin Exp Rheumatol 2008;26:910-3.

[37] McLarnon M, Heron N. Intra-articular platelet-rich plasma injections versus intra-articular corticosteroid injections for symptomatic management of knee osteoarthritis: systematic review and meta-analysis. BMC Musculoskelet Disord 2021;22:550. https://doi.org/10.1186/s12891-021-04308-3.

[38] Nie LY, Zhao K, Ruan J, Xue J. Effectiveness of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled clinical trials. Orthop J Sports Med 2021;9:2325967120973284. https://doi.org/10.1177/2325967120973284.

[39] Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res 2017;12:16. https://doi.org/10.1186/s13018-017-0521-3.

[40] Tucker JD, Goetz LL, Duncan MB, Gilman JB, Elmore LW, Sell SA, McClure MJ, Quagliano PV, Martin CC. Randomized, placebo-controlled analysis of the knee synovial environment following platelet-rich plasma treatment for knee osteoarthritis. Randomized Controlled Trial 2021;13:707-19. https://doi.org/10.1002/pmrj.12561.

[41] Xu P, Wu Y, Zhou L, Yang Z, Zhang X, Hu X, Yang J, Wang M, Wang B, Luo G, He W, Cheng B. Platelet-rich plasma accelerates skin wound healing by promoting re-epithelialization. Burns Trauma 2020;8:tkaa028. https://doi.org/10.1093/burnst/tkaa028.

[42] Jawanda H, Khan ZA, Warrier AA, Acuña AJ, Allahabadi S, Kaplan DJ, Ritz E, Jackson GR, Mameri ES, Batra A, Dornan G, Westrick J, Verma NN, Chahla J. Platelet-rich plasma, bone marrow aspirate concentrate, and hyaluronic acid injections outperform corticosteroids in pain and function scores at a minimum of 6 months as intra-articular injections for knee osteoarthritis: a systematic review and network meta-analysis. Arthroscopy 2024;40:1623-36.e1. https://doi.org/10.1016/j.arthro.2024.01.037.

[43] Mouneshwaran R, Vijayaragavan R: A comparative study of functional outcome of single dose intra-lesional platelet rich plasma injection versus single dose corticosteroid injection for plantar fasciitis. Int J Orthop 2024;10:177-81. https://doi.org/10.22271/ortho.2024.v10.i1c.3516.

[44] Kavia A, Singh J, Raina S, Sahni G, Singh M. A comparative study of single intra-articular platelet-rich plasma versus corticosteroid injection in the treatment of adhesive capsulitis of the shoulder. Nat J Physiol Pharm Pharmacol 2024;14:10-10. https://doi.org/10.5455/njppp.2023.13.03153202331052023.

Received on May 1, 2024. Accepted on June 19, 2024.

Correspondence: Omid Ghorbani, Department of surgery, Faculty of Medicine, Shahed University, Tehran, Iran. E-mail: omidghorbanidr@gmail.com

How to cite this article: Ghorbani O, Mahdibarzi D, Yousefi-Tooddeshki P. Comparison of the short-term effect of intra-articular hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized clinical trial. J Prev Med Hyg 2024;65:E214-E220. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3270

NON COMUNICABLE DISEASE

Machine learning techniques to identify risk factors of breast cancer among women in Mashhad, Iran

ATIEH KHALEGHI[1], SEYYED MOHAMMAD TABATABAEI[2,3], ZEINAB SADAT HOSSEINI[4], MOSLEM TAHERI SOODEJANI[5], EHSAN MOSA FARKHANI[6], MARYAM YAGHOOBI[3,7]

[1] Data Scientist at AFRY AB, Sweden; [2] Department of Medical Informatics, Faculty of Health Mashhad University of Medical Sciences, Mashhad, Iran; [3] Clinical Research Development Unit, Imam Reza Hospital, University of Medical Sciences, Mashhad, Iran; [4] Faculty of Medicine, Islamic Azad University of Mashhad, Mashhad, Iran; [5] Research Center of Prevention and Epidemiology of Non-Communicable Disease, Department of Biostatistics and Epidemiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [6] Department of Epidemiology, Faculty of Health Mashhad University of Medical Sciences, Mashhad, Iran; [7] Department of Epidemiology, Faculty of Public Health, Iran University of Medical Sciences, Tehran, Iran

Keywords

Random forest • Logistic regression • Decision tree • Principal component analysis • Breast cancer

Summary

Background. *Low survival rates of breast cancer in developing countries are mainly due to the lack of early detection plans and adequate diagnosis and treatment facilities.*
Objectives. *This study aimed to apply machine learning techniques to recognize the most important breast cancer risk factors.*
Methods. *This case-control study included women aged 17-75 years who were referred to medical centers affiliated with Mashhad University of Medical Science between March 21, 2015, and March 19, 2016. The study had two datasets: one with 516 samples (258 cases and 258 controls) and another with 606 samples (303 cases and 303 controls). Written informed consent has been observed. Decision Tree (DT), Random Forest (RF), Logistic Regression (LR), and Principal Component Analysis (PCA) were applied using R studio software.*
Results. *Regarding the DT and RF, the most important features that impact breast cancer were family cancer, individual history of breast cancer, biopsy sampling, rarely consumption of a dairy, fruit, and vegetable meal, while in PCA and LR these features including family cancer, pregnancy number, pregnancy tendency, abortion, first menstruation, the age of first childbirth and childbirth number.*
Conclusions. *Machine learning algorithms can be used to extract the most important factors in the diagnosis of breast cancer in developing countries such as Iran.*

Introduction

The most prevalent malignancy of women in the world is breast cancer [1]. Globally, there were 2.3 million new instances of breast cancer in 2020, and this disease claimed 685,000 lives [2]. By 2040, it is expected that there will be more than 3 million new cases and 1 million deaths due to breast cancer worldwide [3]. Breast cancer has been identified as the fifth-leading cause of mortality among Iranian women [4]. In Iran, 15,492 new cases of breast cancer were diagnosed in 2022, making up 11.3% of all new cancer cases [5]. The exact causes of breast cancer are still unknown, but there are both modifiable and non-modifiable risk factors associated with this malignancy [6]. Some of the main non-modifiable risk factors include aging [7], being a woman [8], having a family history of breast cancer [9], possessing certain genetic mutations [10], late menopause, and early menarche [11]. On the other hand, modifiable risk factors for breast cancer include obesity [8], alcohol, smoking [12], postmenopausal hormone therapy [13], and being single [14].
Early detection of breast cancer can lead to lower treatment costs and more effective treatment. Thus, knowledge about the main risk factors that affect this mysterious cancer is a crucial task [15].

Machine learning algorithms have a significant impact on the healthcare system by analyzing large data sets, and assisting to make decisions about a patient's health status, disease progression, and optimal treatment plans [16]. Several machine learning algorithms are used in the medical field for prediction and classification including Decision Trees (DTs), Logistic Regression (LR), random forests (RFs), Principal Component Analysis (PCA), and Support Vector Machines (SVMs) [16]. Decision trees use a tree-like structure to represent decisions and their potential outcomes [17], while logistic regression predicts the probability of an observation belonging to a specific class [18]. Random forest is a method that improves the accuracy and robustness of predictions by combining multiple decision trees [19]. Principal component analysis is an algorithm that reduces the number of dimensions in large datasets with many features, making the data simpler to analyze and interpret [20]. By accounting for time-varying information and managing multiple predictors, interactions, and missing values, these models can improve the accuracy of clinical risk predictions [21].
Unfortunately, the majority of women in developing countries know little about the principal factors that escalate the risk of breast cancer. Moreover, breast

cancer is diagnosed at a younger age in many developing countries such as Iran, Tunisia, and Pakistan [22, 23]. Determining the inhibitory policies and decisions from responsible people to diminish the occurrence of breast cancer requires having knowledge of the risk factors of this cancer. Reviews on risk factors of breast cancer from various published articles in developed countries may not provide a practical solution, since the findings of these studies cannot be applied to women in developing countries. To the best of our knowledge, despite the importance of risk factors associated with this disease, few studies have been conducted in Iran using machine learning methods. Thus, the aim of this study was to determine the most important risk factors of breast cancer using machine learning algorithms in Mashhad, northeastern Iran.

Materials and methods

Study population

In this case-control study, data was collected from two different data sets. All women aged 17-75 years who were referred to medical centers affiliated with Mashhad University of Medical Science (MUMS) between March 21, 2015, and March 19, 2016, were enrolled. From these women, the case group was composed of individuals who had positive mammography and were confirmed to have breast cancer through histology. Women without breast cancer were selected as the control group. The smaller data set contained 516 samples, divided into 258 cases and 258 controls. The larger data set contained 606 samples, divided into 303 cases and 303 controls. To account for the effect of age, frequency matching was performed for group matching. However, other factors were not matched in order to measure their effects [24].

Data preprocessing

Data preprocessing involves several steps. In the parsing step, individual data elements were identified in the source files and isolated in the target files. These parsed data elements were then corrected using sophisticated data algorithms in R, and the data was standardized and transformed into its preferred format.

To handle missing data, imputation methods such as mice in R were used to fill in missing values. The missing data was also removed to compare the results of these two approaches, and the results were found to be the same. As a result, removing the missing data was chosen as the preferred method for proceeding with the analysis.

Breast cancer prediction models

This paper proposes a method that combines feature selection techniques with machine learning methods to predict prospective cases. Four different methods were used to extract features. The first method is the information.gain decision tree algorithm, which selects the best combination of features based on their correlation with class attributes using a function based on entropy. The second method is the Elastic net algorithm, which balances between LASSO and ridge penalties to address over-regularization. This is achieved by setting a hyper-parameter called Alpha, where Alpha = 1 results in a LASSO model and Alpha = 0 results in a ridge model. This technique, known as Elastic net, is a regularization regression that uses the cv.glmnet function with the family set to 'binomial'.

The third method used in this paper is Random Forest, which uses the built-in random Forest function to extract important variables using the importance function. This feature selection method falls under the category of embedded methods. Each random forest contains 4 to 12 hundred decision trees, each built using a random sample of observations and features from the dataset. Each individual tree consists of a sequence of yes-no questions based on single or combined features.

The fourth method used is principal component analysis, which is a widely recommended method for reducing a dataset with many variables. This is achieved by projecting the data onto fewer variables using linear combinations of the original variables, using the prcomp function in the latest version of R Studio software.

Results

When using the Information.gain algorithm on a small sample size of the data set, the 10 most important factors that had an effect on breast cancer were identified and ranked according to their coefficients. These factors, in order of importance, were: family cancer, scancerb (Individual history of breast cancer), sampling B (Biopsy sampling), rarely consumption of a dairy meal, fruit meal, and vegetable meal daily, table salt, fast food consumption, oil consumption and type of job. As shown in Figure 1, the results for this method using a large sample size of the data set are the same as those for a small sample size, with the exception of the type of job. For the larger sample size, age with a coefficient of 0.05 was identified as an important factor instead of type of job.

As shown in Figure 2, the Elastic net results identified the 10 most effective factors on breast cancer as family cancer, pregnancy number, pregnancy tendency, first menstruation, abortion, childbirth (the age when they gave birth to the first child), childbirth number, stillbirth, scancerb (Individual history of breast cancer), sampling B (Biopsy sampling).

The results for the Elastic net algorithm were the same for both large and small sample sizes of the dataset.

According to the Random Forest algorithm, for the small sample size, the 10 most important factors that affected breast cancer were identified as family cancer, sampling B, scancerb, rarely consumption of dairy, fruit, and vegetable meals daily, job type, table salt, fast food consumption, and first menstruation (Fig. 3).

Fig. 1. The 10 most important risk factors of breast cancer in the larger sample selected by Information.gain function from the Decision Tree algorithm.

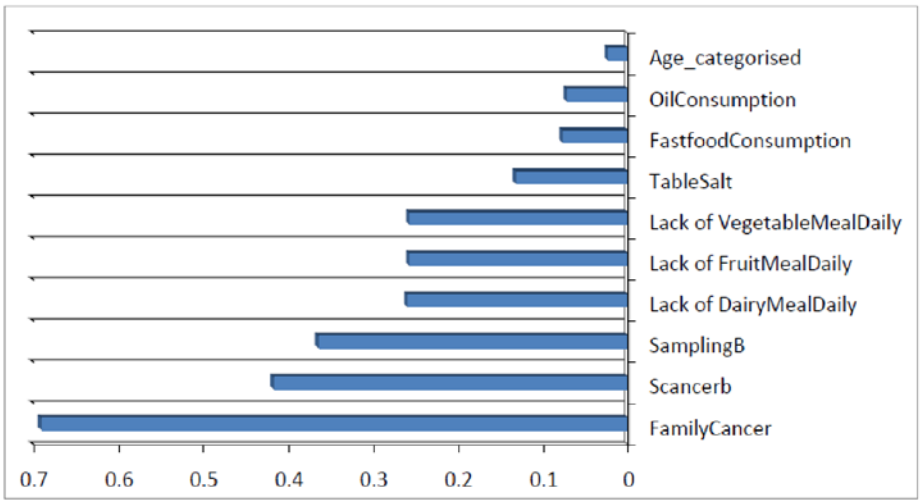
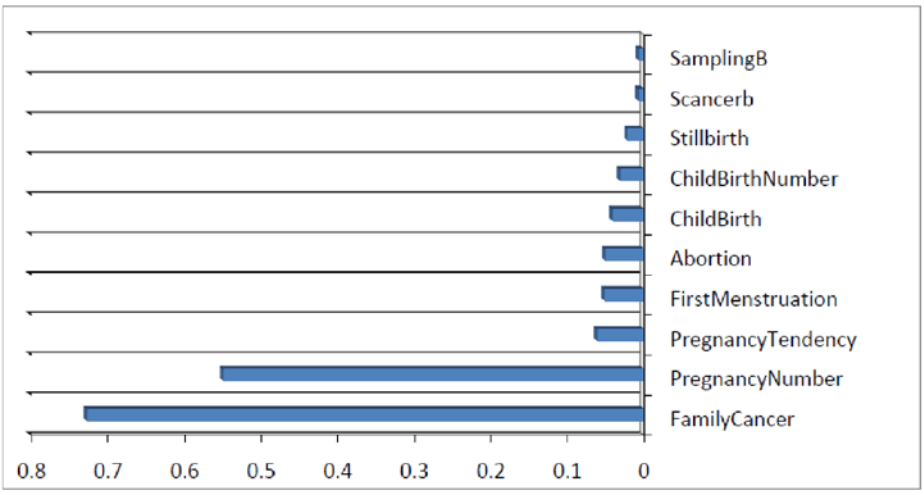


Fig. 2. The 10 most important risk factors of breast cancer selected by the Elastic Net algorithm.



For the large sample size of the dataset using the Random Forest algorithm, two different factors were identified as important: age and number of pregnancies, instead of type of job and age at first menstruation.

When using Principal component analysis, as shown in Figure 4, the 10 most important risk factors for breast cancer were identified as the same in both sample sizes including pregnancy tendency, first menstruation, pregnancy number, childbirth number, childbirth (the age of first giving birth), abortion, stillbirth, scancerb, sampling B and family cancer (Fig. 4).

Discussion

This case-control study investigated the most important risk factors associated with breast cancer among Iranian women. Four machine learning methods were performed in this study including Decision Tree (DT), Random Forest (RF), Logistic Regression (LR), and Principal Component Analysis (PCA). Based on all 4 machine learning algorithms, family history of cancer, biopsy sampling, and individual history of breast cancer were the most important risk factors for breast cancer.

A case-control study indicated that family and personal history of breast cancer were the most important risk factors for breast cancer [25]. Women with two or more persons of breast cancer in their family among women younger than 50 years, or three or more persons at any age, but who do not have BRCA mutations, are about 4 times more likely to have breast cancer [26]. These studies are consistent with the findings of all four machine learning methods in our research. Thakur P et.al found that early menstruation increases the risk of breast cancer by more than two times [27]. Numerous other studies have also corroborated this finding [28, 29]. Based on the RF, LR, and PCA in our study, early menarche was among the top 10 associated risk factors of breast cancer. However, a cohort study found no association between early menstruation age and the risk of breast cancer [30].

Fig. 3. The 10 most important risk factors of breast cancer selected by the Random Forest algorithm.

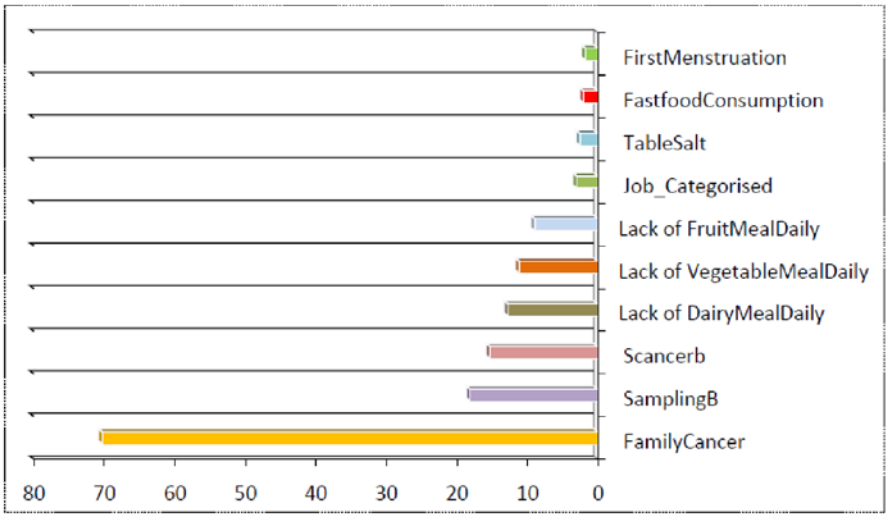
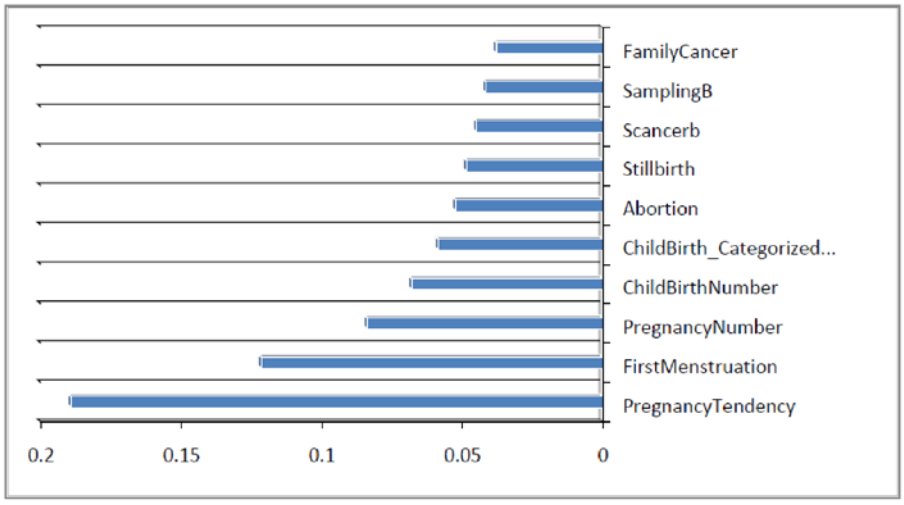


Fig. 4. The 10 most important risk factors of breast cancer selected by the Principal Component Analysis algorithm.



According to a case-control study, the risk of breast cancer is inversely related to the number of children born. Women who have had five or more children have a 50% lower risk of developing breast cancer compared to women who have never given birth [31]. Also, a systematic review and meta-analysis in the Eastern Mediterranean region found that having no history of live birth was among the factors that had the largest odd ratios for breast cancer [32]. Our observations showed that the number of pregnancies was only in LR and PCA models among the 10 risk factors associated with breast cancer.

Diet can play an important role in the prevention and management of many diseases, including breast cancer. A systematic review and meta-analysis showed that there was only an association between milk consumption and breast cancer among dairy products. Consumption of more than 450 grams of milk per day was associated with an increased risk of breast cancer. Also, a diet rich in vegetables, fruits, and soy products, and low in red meats, has been associated with a lower risk of breast cancer [33]. Our DT and RF models showed that low consumption of dairy products, fruits, and vegetables was associated with breast cancer risk. However, Patricia M et al. found that there was no significant relationship between dairy consumption and the risk of breast cancer [34].

It is important to note that this study has some limitations that should be considered. First, we only used four machine learning models in our study. Second, the data for this study was collected from hospitals affiliated with Mashhad University of Medical Sciences. As a result, there is uncertainty about whether the prediction model developed in this study can be applied to other datasets from different populations or regions.

Conclusions

Our study showed that the use of machine learning methods can play an effective role in predicting breast

cancer risk factors in Iranian population with large sample size and different characteristics. Future research could involve using classification techniques to train machine learning models on the data. These models could then be used to make predictions or classifications based on the patterns and relationships identified in the data.

Acknowledgements

We would like to thank the Clinical Research Development Unit, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, for their collaboration in conducting this study.

Conflict of interest statement

The authors declare that they have no conflicting interests.

Funding

This study had no specific funding and was done with the authors' interest.

Ethical statement

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, *etc.*) have been completely observed by the authors.
The study has ethical approval from Mashhad University of Medical Sciences (ID: IR.MUMS.REC.1397.125).

Author's contributions

MT-S, E-MF, Z-SH, AK, S-MT, MY: study conception and design; MY, Z-SH: data collection; AK, S-MT: analysis and interpretation of results; AT, S-MT: draft manuscript preparation; MT-S, Z-SH, E-MF, AK, S-M, T, MY: reviewed the results and approved the final version of the manuscript.

References

[1] Najaf Najafi M, Salehi M, Ghazanfarpour M, Hoseini ZS, Khadem-Rezaiyan M. The association between green tea consumption and breast cancer risk: a systematic review and meta-analysis. Phytother Res 2018;32:1855-64. https://doi.org/10.1002/ptr.6124.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.https://doi.org/10.3322/caac.21660.

[3] Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, Vignat J, Gralow JR, Cardoso F, Siesling S, Soerjomataram I. Current and future burden of breast cancer: global statistics for 2020 and 2040. Breast 2022;66:15-23. https://doi.org/10.1016/j.breast.2022.08.010.

[4] Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Ann Oncol 2009;20:556-63. https://doi.org/10.1093/annonc/mdn642.

[5] InternationaAgency for Research on Cancer. Cancer Day. World Health Organization. Data visualisation tools for exploring the global cancer burden in 2022. Available at: https://gco.iarc.fr/today/data/factsheets/populations/364-iran-islamic-republic-of-fact-sheets.pdf (Accessed on: 13/7/2024).

[6] Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer-epidemiology, risk factors, classification, prognostic markers, and current treatment strategies-an updated review. Cancers (Basel) 2021;13:4287. https://doi.org/10.3390/cancers13174287.

[7] Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, Zeng H, Zhou J, Wei W. Global patterns of breast cancer incidence and mortality: a population-based cancer registry data analysis from 2000 to 2020. Cancer Commun (Lond) 2021;41:1183-94. https://doi.org/10.1002/cac2.12207.

[8] Youn HJ, Han W. A review of the epidemiology of breast cancer in asia: focus on risk factors. Asian Pac J Cancer Prev 2020;21:867-80. https://doi.org/10.31557/APJCP.2020.21.4.867.

[9] Terry MB, Liao Y, Whittemore AS, Leoce N, Buchsbaum R, Zeinomar N, Dite GS, Chung WK, Knight JA, Southey MC, Milne RL, Goldgar D, Giles GG, McLachlan SA, Friedlander ML, Weideman PC, Glendon G, Nesci S, Andrulis IL, John EM, Phillips KA, Daly MB, Buys SS, Hopper JL, MacInnis RJ. 10-year performance of four models of breast cancer risk: a validation study. Lancet Oncol 2019;20:504-17. https://doi.org/10.1016/S1470-2045(18)30902-1.

[10] Ibrahim SS, Hafez EE, Hashishe MM. Presymptomatic breast cancer in Egypt: role of BRCA1 and BRCA2 tumor suppressor genes mutations detection. J Exp Clin Canc Res 2010;29:1-10. https://doi.org/10.1186/1756-9966-29-82.

[11] Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141-51. https://doi.org/10.1016/S1470-2045(12)70425-4.

[12] Zeinomar N, Knight JA, Genkinger JM, Phillips KA, Daly MB, Milne RL, Dite GS, Kehm RD, Liao Y, Southey MC, Chung WK, Giles GG, McLachlan SA, Friedlander ML, Weideman PC, Glendon G, Nesci S; kConFab Investigators; Andrulis IL, Buys SS, John EM, MacInnis RJ, Hopper JL, Terry MB. Alcohol consumption, cigarette smoking, and familial breast cancer risk: findings from the Prospective Family Study Cohort (ProF-SC). Breast Cancer Res 2019;21:128. https://doi.org/10.1186/s13058-019-1213-1.

[13] Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394:1159-68. https://doi.org/10.1016/S0140-6736(19)31709-X.

[14] Li M, Han M, Chen Z, Tang Y, Ma J, Zhang Z, Liu Z, Zhang N, Xi C, Liu J, Tian D, Wang X, Huang X, Chen J, Wang W, Zhai S. Does marital status correlate with the female breast cancer risk? A systematic review and meta-analysis of observational studies. PLoS One 2020;15:E0229899. https://doi.org/10.1371/journal.pone.0229899.

[15] Ekici S, Jawzal H. Breast cancer diagnosis using thermography and convolutional neural networks. Med Hypotheses 2020;137:109542. https://doi.org/10.1016/j.mehy.2019.109542.

[16] Javaid M, Haleem A, Singh RP, Suman R, Rab S. Significance of machine learning in healthcare: features, pillars and applica-

tions. Int J Intell Netw 2022;3:58-73. https://doi.org/10.1016/j.ijin.2022.05.002.

[17] Von Winterfeldt D, Edwards W. Decision analysis and behavioral research. (No Title) 1986.

[18] Worth AP, Cronin MT. The use of discriminant analysis, logistic regression and classification tree analysis in the development of classification models for human health effects. Journal of Molecular Structure: THEOCHEM 2003;622:97-111. https://doi.org/10.1016/S0166-1280(02)00622-X.

[19] Shaikhina T, Lowe D, Daga S, Briggs D, Higgins R, Khovanova N. Decision tree and random forest models for outcome prediction in antibody incompatible kidney transplantation. Biomed Signal Process Control 2019;52:456-62. https://doi.org/10.1016/j.bspc.2017.01.012.

[20] Jolliffe IT, Cadima J. Principal component analysis: a review and recent developments. Philos Trans A Math Phys Eng Sci 2016;374:20150202. https://doi.org/10.1098/rsta.2015.0202.

[21] Shipe ME, Deppen SA, Farjah F, Grogan EL. Developing prediction models for clinical use using logistic regression: an overview. J Thorac Dis 2019;11(Suppl 4):S574-84. https://doi.org/10.21037/jtd.2019.01.25.

[22] Nguyen H, Bui X-N. Predicting blast-induced air overpressure: a robust artificial intelligence system based on artificial neural networks and random forest. Natural Resources Research 2019;28:893-907. https://doi.org/10.1007/s11053-018-9424-1.

[23] Shaukat U, Ismail M, Mehmood N. Epidemiology, major risk factors and genetic predisposition for breast cancer in the Pakistani population. Asian Pac J Cancer Prev 2013;14:5625-9. https://doi.org/10.7314/apjcp.2013.14.10.5625.

[24] Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. Am J Epidemiol 1992;135:1019-28. https://doi.org/10.1093/oxfordjournals.aje.a116396.

[25] Rosner B, Tamimi RM, Kraft P, Gao C, Mu Y, Scott C, Winham SJ, Vachon CM, Colditz GA. Simplified breast risk tool integrating questionnaire risk factors, mammographic density, and polygenic risk score: development and validation. Cancer Epidemiol Biomarkers Prev 2021;30:600-7. https://doi.org/10.1158/1055-9965.EPI-20-0900.

[26] Metcalfe KA, Finch A, Poll A, Horsman D, Kim-Sing C, Scott J, Royer R, Sun P, Narod SA. Breast cancer risks in women with a family history of breast or ovarian cancer who have tested negative for a BRCA1 or BRCA2 mutation. Br J Cancer 2009;100:421-5. https://doi.org/10.1038/sj.bjc.6604830.

[27] Thakur P, Seam RK, Gupta MK, Gupta M, Sharma M, Fotedar V. Breast cancer risk factor evaluation in a Western Himalayan state: a case-control study and comparison with the Western World. South Asian J Cancer 2017;6:106-9. https://doi.org/10.4103/sajc.sajc_157_16.

[28] Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. Asian Pac J Cancer Prev 2015;16:2857-70. https://doi.org/10.7314/apjcp.2015.16.7.2857.

[29] Clavel-Chapelon F, Launoy G, Auquier A, Gairard B, Brémond A, Piana L, Lansac J, Renaud R. Reproductive factors and breast cancer risk. Effect of age at diagnosis. Ann Epidemiol 1995;5:315-20. https://doi.org/10.1016/1047-2797(95)00099-s.

[30] Khalis M, Charbotel B, Chajès V, Rinaldi S, Moskal A, Biessy C, Dossus L, Huybrechts I, Fort E, Mellas N, Elfakir S, Charaka H, Nejjari C, Romieu I, El Rhazi K. Menstrual and reproductive factors and risk of breast cancer: a case-control study in the Fez region, Morocco. PLoS One 2018;13:E0191333. https://doi.org/10.1371/journal.pone.0191333.

[31] Lambe M, Hsieh CC, Chan HW, Ekbom A, Trichopoulos D, Adami HO. Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden. Breast Cancer Res Treat 1996;38:305-11. https://doi.org/10.1007/BF01806150.

[32] Namiranian N, Moradi-Lakeh M, Razavi-Ratki SK, Doayie M, Nojomi M. Risk factors of breast cancer in the Eastern Mediterranean Region: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2014;15:9535-41. https://doi.org/10.7314/apjcp.2014.15.21.9535.

[33] Kazemi A, Barati-Boldaji R, Soltani S, Mohammadipoor N, Esmaeilinezhad Z, Clark CCT, Babajafari S, Akbarzadeh M. Intake of various food groups and risk of breast cancer: a systematic review and dose-response meta-analysis of prospective studies. Adv Nutr 2021;12:809-49. https://doi.org/10.1093/advances/nmaa147.

[34] Moorman PG, Terry PD. Consumption of dairy products and the risk of breast cancer: a review of the literature. Am J Clin Nutr 2004;80:5-14. https://doi.org/10.1093/ajcn/80.1.5.

Received on July 27, 2023. Accepted on March 18, 2024.

Correspondence: Maryam Yaghoobi, Clinical Research Development Unit, Imam Reza Hospital, University of Medical Sciences, Mashhad, Iran. E-mail: myaghooobi@yahoo.com

How to cite this article: Khaleghi A, Tabatabaei Sm, Sadat Hosseini Z, Taheri Soodejani M, Farkhani Em, Yaghoobi M. Machine learning techniques to identify risk factors of breast cancer among women in Mashhad, Iran. J Prev Med Hyg 2024;65:E221-E226. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3045

Non comunicable disease

Impact of gender and education on cervical cancer knowledge amongst students: implications for health policies and public health strategies in Wiesbaden, Germany

HARRY GYMAH GYAMFI[1]
[1] Fresenius University of Applied Sciences

Keywords

Cervical cancer • Human papillomavirus (HPV) • Screening • Health policies

Summary

Introduction. *Cervical cancer is a global health concern primarily caused by human papillomavirus (HPV). It has a significant impact in Germany, with thousands of new diagnoses and deaths annually. Despite advancements in screening and treatment leading to improved survival rates of 65% for invasive cervical tumors, the financial burden remains substantial.*
Aims. *The study aims to assess the impact of gender and education of Wiesbaden students towards cervical cancer and its associated health policies. Data was collected through an online questionnaire distributed with 54 students in Wiesbaden, Germany participating in the study. Statistical analysis was performed using SPSS, including one-way ANOVA, t-tests, Kruskal-Wallis, and chi-square tests. The respondents' average age was 28.24 years, with a higher female participation.*
Results. *Education level did not significantly influence perceptions of ideal vaccination age ($p < 0.581$). Females and males perceived a lower number of vaccine doses (< 3) required compared to the standard. Education level showed a moderate association with knowledge of long-term complications, and gender had a moderate correlation with information sources ($rho = 27$, $p = 0.090$).*
Conclusion. *Gender disparities did not significantly impact knowledge of cervical cancer. Public health programs should consider education levels and tailor interventions to all age groups and genders.*

Introduction

Cervical cancer is a significant global health concern characterized by the abnormal growth of cells in the cervix. The primary risk factor associated with its development is the human papillomavirus (HPV), mainly transmitted through sexual contact [1]. Moreover, HPV and its associated diseases impact both males and females, manifesting frequently in males as warts on various organs, including the penis and oropharyngeal tract [2]. Less commonly, HPV can lead to cancers of the penis, anus, and oral cavity [2]. The role of HPV in causing cervical cancer is attributed to dysplasia, an uncontrolled proliferation of cells surrounding the cervix [1]. Among the various HPV strains, HPV 16 and HPV 18 account for 70% of cervical malignancies [1, 3]. Several other factors also contribute to the risk of cervical cancer, including a history of multiple sexual partners, a family history of the disease, smoking, and early initiation of sexual activity, among others [4]. However, the early stages of cervical cancer often present without noticeable symptoms, making it challenging to detect. As the disease progresses and metastasizes, visible symptoms such as vaginal bleeding and changes in vaginal discharge become more apparent [5].

To combat the spread of HPV and facilitate early detection, various screening techniques are employed, including the Pap smear, Visual Inspection with Acetic Acid (VIA), and HPV-DNA [6]. The Pap smear has been widely used for screening purposes, particularly in Germany [7]. Additionally, HPV vaccinations are available and recommended, with higher effectiveness demonstrated when administered at an earlier age [8].

Despite advancements in screening and treatment, cervical cancer remains a significant global health burden, with approximately 529,800 new cases and 275,100 deaths reported each year [9]. Importantly, there is a considerable disparity in incidence rates between industrialized and developing countries. Developed nations have witnessed a gradual decline in cervical cancer incidence and mortality rates due to effective screening programs and HPV vaccination campaigns [9]. In Germany, cervical cancer screening has undergone changes over the years. From 1971 to 2019, annual opportunistic Pap test screenings were supported by the statutory health insurance system for women aged 20 and above. Since January 1, 2020, a coordinated screening program has been implemented, involving annual Pap testing for women aged 20-34 and co-testing (Pap test + HPV test) every three years for women aged 35 and older [10].

The impact of cervical cancer in Germany is profound, with thousands of new diagnoses and deaths annually. However, advancements in screening and treatment have

led to improved survival rates, with a relative 5-year survival rate of 65% for invasive cervical tumors [11]. Nonetheless, the financial burden of cervical cancer remains substantial, with costs ranging from 1,055 euros to over 10,000 euros, depending on the stage of the disease [12]. There is therefore the need to assess how sociodemographic background like gender and education affects policies implemented to tackle the disease.

The study aims to assess the impact of gender and education of Wiesbaden students towards cervical cancer and its associated health policies. This will aid to contribute to the development of cost-effective strategies for public health budgets and inform the evaluation of essential elements for an effective public health policy for the Hessen state in Germany.

Methods

Study design

The study was a cross-sectional survey. Data was collected through an online questionnaire hosted on "SurveyPlanet." To ensure the questionnaire's comprehensibility and effectiveness, a trial sample of 5 questionnaires was initially tested among potential participants. Following adjustments based on feedback, the final questionnaire was distributed, consisting of 21 questions grouped into three categories: demographic background, cervical cancer awareness, and knowledge of treatment and screening programs. The online survey was active for a duration of 30 days, from July 4, 2022.

Study population and area

The study involved 54 participants from 12 to 38 years old. The study targeted students in Wiesbaden, located in the German state of Hessen. To comprehensively assess knowledge disparities, the study refrained from imposing limitations based on other demographic parameters, such as age and gender.

Data entry and analysis

Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 28. To address the research questions and test hypotheses, various statistical tests were employed, including one-way ANOVA, one-sample t-test, Kruskal-Wallis, and chi-square tests. These tests were used to assess associations and determine statistical significance, with a significance level set at $p < 0.05$.

Ethical consideration

Participants were voluntary and provided informed consent. The purpose and processes of the study were explained on the first page of the questionnaire. Participants remained anonymous, ensuring confidentiality, and their data could not be linked to individual submissions. The study posed no social risk to participants.

Results

The average age of respondents (N = 54) who took part in the survey was 28.24 years (SD = 4.73) with the age ranging from 12 years to a maximum of 51 years. Of the population, half of the population's age was less than 27 years, and the other half was more than 27 years. The distribution of the age wasn't normally distributed with skewness of -0.18 (SE = 0.33) and kurtosis of 1.596 (SE = 0.12). With regards to gender, there were more female respondents (n = 34) than that of male respondents (n = 20). The male respondents had an average age of about 28 years (SD = 5.88) which was similar to that of the females average age of 28 years (SD = 4.00). The most occurring age for males was 1 year lesser (25 years) than that of the female respondents (26 years) as seen in Table I.

As highlighted in Figure 1 below, a one-way analysis of variance (ANOVA) shows that there was no significant difference in terms of respondents' level of education and perception of ideal age one should start taking the HPV vaccine. With respondents with high school education (n = 5) choosing an average of 20 years (SD = 17.49), respondents with bachelors (n = 22) choosing an average age of 17 years (SD = 5) and respondents with a postgraduate (n = 25) choosing an average of 19 years (SD = 8.39), $F(2,49) = 0.55$, $p < 0.581$.

In comparison to the recommended 3 doses of the HPV vaccine, there was a significant difference in the perception of the number of doses amongst females and males as shown in Figure 2. Female respondents (n = 32), on average, chose 2.6 doses (SD = 0.62), $t(31) = 3.74$, $p < 0.001$, $d = 0.66$. Similarly, among male respondents (n = 22), there was a significant difference in their perception of the number of doses required compared to the standard of 3. Male respondents chose an average of 2.4 doses (SD = 0.68), $t(18) = 4.03$, $p < 0.001$, $d = 0.92$. A Kruskal Wallis test indicates that there is no significant difference between respondents' level of education and their response to how often one should take a pap smear screening df = 1, p = 0.173 (two-tailed), Kruskal-Wallis H = 3.51. A chi-square test statistic indicates that for females, there was no difference between their response to which gender cervical cancer affects and the body

Tab. I. Age distribution of respondents.

Participants	Description	Statistic	Std. Error
All respondents	Mean (years)	28.24 (SD = 4.73)	0.64
	Minimum(years)	12.00	
	Maximum (years)	38.00	
	Mean (years)	28.35 (SD = 3.99)	0.69
Females	Minimum(years)	22.00	
	Maximum (years)	38.00	
	Mean (years)	28.05 (SD = 5.88)	1.32
Male	Minimum(years)	12.00	
	Maximum (years)	38.00	

Fig. 1. Bar chart showing educational level of participants and their average response to vaccination age.

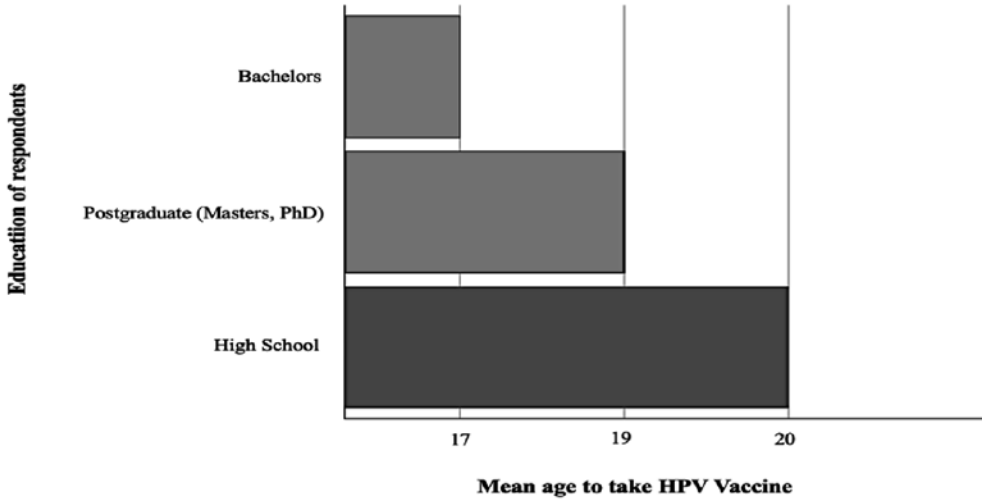
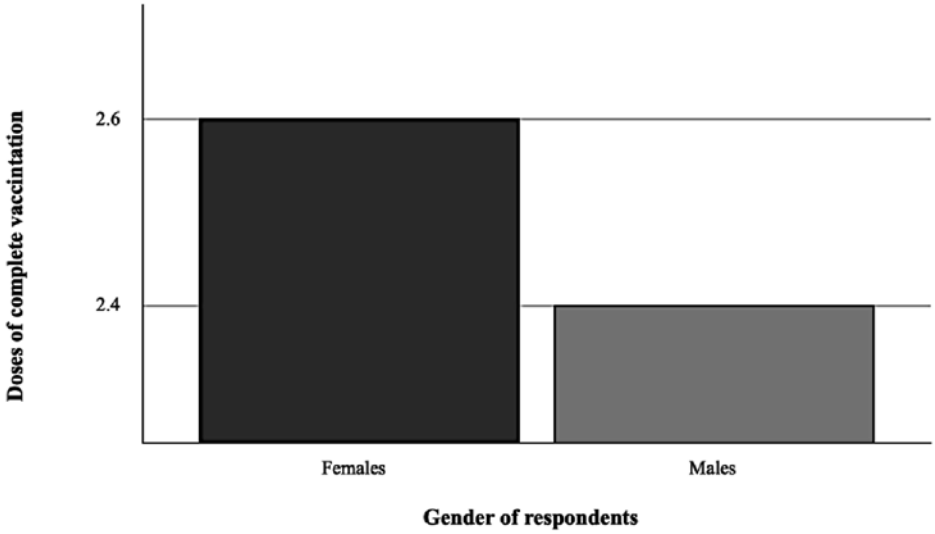


Fig. 2. Histogram of gender and their average response to doses to complete vaccination.



part it affects (X2(1, N = 34) = 0.14, p = 0.711). Similar significance of difference was also observed for males (X2(1, N = 20) = 1.25, p = 0.264).

There was also an observed moderate association between respondents' level of education and their knowledge of the long-term complications of cervical cancer, Spearman's Rho (53) = -0.27, p = 0.090. Similarly, for gender, there was a moderate correlation between their response on where they heard of cervical cancer, Contingency Coefficient (53) = 0.32, p = 0.439. Although with regards to gender, most males and females chose health personnel as their source of knowledge, there were differences with regards to the other sources of information (shown in Tab. II). In response to knowledge on age one is supposed to take the HPV vaccine, the study showed a weak positive association of respondent's knowledge on age for HPV vaccination and their age, Pearson's R (53) = 0.20, p = 0.144.

Tab. II. Respondents source of information on learning about cervical cancer.

Source of Information	Female	Male	Total
Health Personnel (HP)	8	8	16
Tv Programs (TV)	4	1	5
Internet (IT)	3	3	6
Friends/Relatives (FR)	5	3	8
2 of either HP, TV, IT,FR	4	2	6
3 of either the HP, TV, IT,FR	6	0	6
All of HP, TV, IT,FR	4	2	6
Total	34	19	53

IT: Internet; HP: Health Personnel; TV: Television; FR: Friends/Relative.

Discussion

The observation that more women than men responded to the survey suggests that women exhibit a greater concern for cervical cancer and related issues. This finding aligns

with other studies that reported a similar observation regarding women's higher interest in reproductive health [13]. Consequently, it is important to design campaigns aimed at improving reproductive health in a way that also addresses men's interests, thus increasing their participation in reproductive health surveys. This inclusive approach will help inform governmental policymaking to reflect the diverse gender groups.

The tests of significance revealed that there was no significant difference between respondents' education level and their beliefs regarding the appropriate age for vaccination and awareness of routine pap smear screening. This indicates that when developing public health programs focused on education, lower levels of education should be taken into consideration. It is noteworthy that vaccination knowledge does not vary significantly with education level. Therefore, HPV vaccination programs' education and sensitization in Wiesbaden should encompass all tiers of education.

Despite the German government efforts to promote HPV vaccination through mass education campaigns and absorbing the vaccination cost for state insurers, the study revealed a significant difference between genders, in terms of the perception of the maximum number of vaccine doses, which is three [14]. This finding suggests that men and women hold differing views on the recommended dosage for HPV vaccination. Additionally, a weak relationship was found between respondents' age and their knowledge about the age for cervical cancer vaccination. The implications of this disparity are crucial for designing targeted public health initiatives to ensure comprehensive vaccine understanding and uptake across all genders and age groups.

The study found no significant difference in gender with regards to general knowledge about cervical cancer, including understanding of the gender at risk and the affected biological body part. This indicates that gender has no impact on the assimilation of cervical cancer information. In Wiesbaden, Germany, public health initiatives for awareness seem to effectively reach various gender subgroups of the student community.

Lastly, the study highlighted that health personnel are the most common source of information for both males and females. This highlights the effectiveness of providing health personnel with enhanced cervical cancer education materials. Furthermore, the study indicated that other sources of information, such as television programs and the internet, are underutilized, resulting in lower promotion rates. Therefore, additional campaigns utilizing these sources should be employed to increase their effectiveness in disseminating knowledge about cervical cancer.

Limitations of the study include the relatively small sample size of 54 participants from a specific student population in Wiesbaden limits the generalizability of the results to a broader context. Additionally, the voluntary nature of participation might introduce selection bias, as participants with a higher interest or awareness of cervical cancer could have been more likely to respond. Furthermore, the self-reported nature of data collection through an online questionnaire may lead to recall bias and social desirability bias.

Conclusions

The study found that disparities in various subgroups, such as gender, do not make a significant difference in students' knowledge of cervical cancer in Wiesbaden, Germany. This is also true for educational level and age. According to the findings of the study, student disparities are not a major factor in knowledge and awareness barriers. As a result, promotional materials should always be curated to be representative of all subgroups in society. In terms of effective promotion sources, health personnel are the most effective source of public health promotion on cervical cancer. Other sources of information, such as the internet and television programs, are currently underutilized. In the long-term, education and other public health promotion interventions should be tailored to various societal subgroups. Furthermore, such promotions should use other sources, such as the internet and television programs, to accommodate changes in societal trends.

Acknowledgements

The author would like to extend his sincere gratitude to Patrick Amponsah Frempah, MSc., and Priscilla Anyimiah, MSc., for their expertise and assistance in reviewing the questionnaire and providing feedback on the draft manuscript.

Funding

None.

Data availability/supplemental material

The data presented in this study are from the responses in the questionnaire. To access questionnaire, click here.

Conflict of interest statement

The author declares no conflict of interest.

Authors' contributions

GGH: contributed to the conceptualization and design of the study, development of the questionnaire, methodology design, data analysis, and writing of the manuscript.

References

[1] Okunade KS. Human papillomavirus and cervical cancer. J Obstet Gynaecol 2020;40:602-8. https://doi.org/10.1080/01443615.2019.1634030.

[2] Canepa P, Orsi A, Martini M, Icardi G. HPV related diseases in males: a heavy vaccine-preventable burden. J Prev Med Hyg 2013;54:61-70.

[3] Robadi A, Pharaon M, Ducatman BS. The importance of high-risk human papillomavirus types other than 16 and 18 in cervical neoplasia. Arch Pathol Lab Med 2018;142:693-5. https://doi.org/10.5858/arpa.2017-0563-ra.

[4] Sindiani M, Alshdaifat EH, Alkhatib AJ. Investigating cervical risk factors that lead to cytological and biopsy examination. Med Arch 2020;74:294-7. https://doi.org/10.5455/medarh.2020.74.294-297.

[5] Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet 2019;393:169-82. https://doi.org/10.1016/s0140-6736(18)32470-x.

[6] Chung MH, McKenzie KP, De Vuyst H, Richardson BA, Rana F, Pamnani R, Njoroge JW, Nyongesa-Malava E, Sakr SR, John-Stewart GC, Mugo NR. Comparing Papanicolau smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy. AIDS 2013;27:2909-19. https://doi.org/10.1097/01.aids.0000432472.92120.1b.

[7] Sroczynski G, Schnell-Indert P, Mühlberger N, Lang K, Aidelsburger P, Wasem J, Mittendorf T, Engel J, Hillemanns P, Petry KU, Krämer A, Siebert U. Decision-analytic modeling to evaluate the long-term effectiveness and cost-effectiveness of HPV-DNA testing in primary cervical cancer screening in Germany. GMS Health Technol Assess 2010;6:Doc05. https://doi.org/10.3205/hta000083.

[8] Kamolratanakul S, Pitisuttithum S. Human Papillomavirus Vaccine Efficacy and Effectiveness against Cancer. Vaccines 2021;9:1413. https://doi.org/10.3390/vaccines9121413.

[9] Hu Z, Ma D. The precision prevention and therapy of HPV-related cervical cancer: new concepts and clinical implications. Cancer Med 2018;7:5217-5236. https://doi.org/10.1002/cam4.1501.

[10] Jentschke M, Lehmann R, Drews N, Hansel A, Schmitz M, Hillemanns P. Psychological distress in cervical cancer screening: results from a German online survey. Arch Gynecol Obstet 2020;302:699-705. https://doi.org/10.1007/s00404-020-05661-9.

[11] Krebs - Cervical cancer. Available at: https://www.krebsdaten.de/Krebs/EN/Content/Cancer_sites/Cervical_cancer/cervical_cancer_node.html (Accessed on: 22/08/2022).

[12] Armstrong SF, Guest JF. Cost-Effectiveness and cost-benefit of cervical cancer screening with liquid based cytology compared with conventional cytology in Germany. Clin Outcomes Res 2020;12:153-66. https://doi.org/10.2147/ceor. s234385.

[13] Harlow F, Zheng A, Nordberg J, Hatch EE, Ransbotham S, Wise LA. A qualitative study of factors influencing male participation in fertility research. Reprod Health 2020;17:186. https://doi.org/10.1186/s12978-020-01046-y.

[14] Hense S, Hillebrand K, Horn J, Mikolajczyk R, Schulze-Rath R, Garbe E. HPV vaccine uptake after introduction of the vaccine in Germany. Hum Vaccin Immunother 2014;10:1729-33. https://doi.org/10.4161/hv.28450.

Received on August 30, 2023. Accepted on March 29, 2024.

Correspondence: Harry Gyimah Gyamfi, Gerhart-Hauptmann strasse 25, 66564 Otweiller, Germany. E-mail: gyimah333@gmail.com

How to cite this article: Gymah Gyamfi H. Impact of gender and education on cervical cancer knowledge amongst students: Implications for health policies and public health strategies in Wiesbaden, Germany. J Prev Med Hyg 2024;65:E227-E231. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3077

HEALTH CARE MANAGEMENT

Monitoring emergency and urgent surgery: an improvement in a Healthcare Management Unit at a third-level hospital in Italy

LUCIA INGLESE[1], ILARIA BARBERIS[2], MARIIA KORSHUNOVA[3], ROSA AMATO[1], FRANCESCA ZANGRILLO[2], LUCIA ARATA[2], VALENTINO TISA[4], RICCARDO PAPALIA[2], MAURIZIO SANTO[2], GABRIELLA TIBERIO[2], ALESSANDRA MORANDO[2], GIOVANNI ORENGO[5]

[1] Department of Health Sciences (Dissal), University of Genoa, Genoa, Italy;
[2] U.O. Governo Clinico e Organizzazione Ospedaliera, Ospedale Policlinico San Martino-IRCCS, Genoa, Italy;
[3] University of Piemonte Orientale, Novara, Italy; [4] Dipartimento di Prevenzione S.C. Igiene e Sanità Pubblica ASL2 savonese, Italy;
[5] Direzione Sanitaria, Ospedale Policlinico San Martino-IRCCS, Genoa, Italy

Keywords

Emergency • Urgent surgery • Monitoring • Surgeon list

Summary

Introduction. *At San Martino IRCCS Hospital in Genoa, Italy, emergency and urgent surgery is classified according to the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classification, whereby cases are divided into two categories and colour-coded accordingly: - EMERGENCY – (Colour-code: RED) "Surgery to be performed within minutes"; - URGENCY – (colour-code: YELLOW) "Surgery to be performed within hours". In this context, it is essential that the emergency surgical team gets clear and complete information from the proposing surgeon, in order to complete the surgical list.*

Methods. *Between 14th April 2023 and 23th July 2023, a new method of requesting urgent and emergency surgery by filling out an online form was tested.*

Results. *A total of 406 online requests were made, resulting in 367 E/U surgeries. The greatest number of emergency operations concerned thoracic-abdominal surgery (45%), followed by urology (19%). The requests analysed classified 18% of cases as red and 71% as yellow. The remaining 11% contained compilation errors. Moreover, 11% of the interventions were not performed within the time limits defined according to the severity code.*

Conclusions. *By means of this new tool, San Martino IRCCS Hospital's Healthcare Management Unit can monitor requests for surgery in real time, thereby achieving greater efficiency and implementing corrective measures in the use of Operating Room resources.*

Introduction

Emergency and urgent surgery accounts for an increasing proportion of surgical activities performed in hospitals and requires a significant commitment from hospital staff to meet clinical needs [1, 2]. In daily practice, general and specialist surgeons deal with many surgical emergencies, scheduling and providing care both for patients arriving at the emergency room and for those admitted to the various units for elective surgery [3]. San Martino IRCCS Hospital in Genoa, Italy, is the regional tertiary adult acute-care reference hospital. It has 1,400 beds and two daytime operating theatres for emergency surgery. In the absence of a universal classification defining the timing of emergency and urgent surgery, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classification [4], which is applicable to all surgical disciplines, is adopted. According to this classification, surgical cases are divided into the following two categories, to which a colour –code is assigned [5]:

- EMERGENCY – (Colour code: RED) "Emergency surgery to be performed within minutes". This category comprises life-saving, organ-saving or limb-saving interventions or critical situations in which surgery is concurrent with resuscitation manoeuvres (performed within 1 hour);
- URGENCY – (Colour code: YELLOW) "Urgent surgery to be performed within hours". This includes situations with acute onset or clinical deterioration or situations that potentially threaten the life, organ or limb of the patient, or conditions that require surgery for fracture fixation, relief of pain or other stressful symptoms (performed within 6-12 hours) [6].

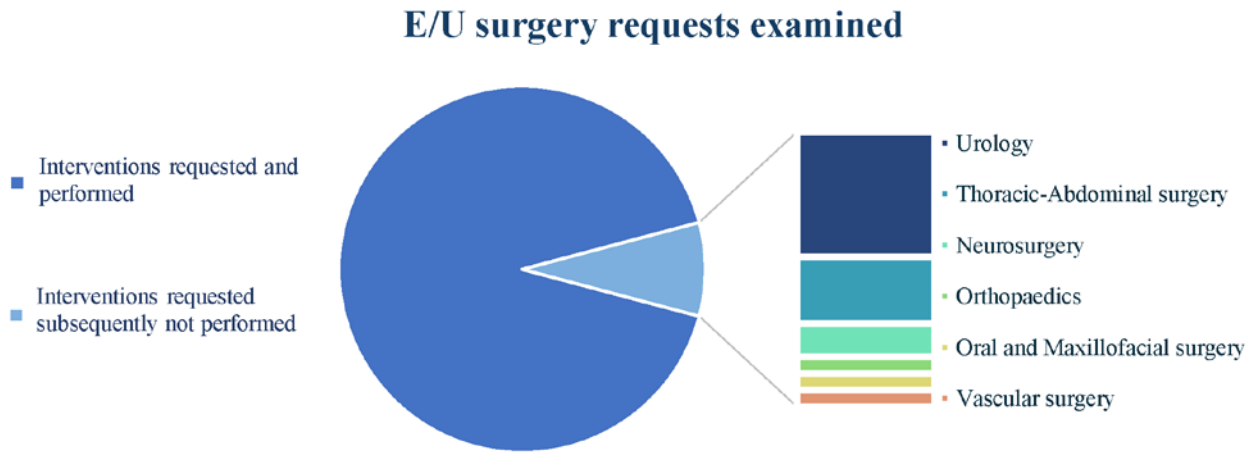
In this context, it is essential that the emergency surgical team gets clear and complete information from the proposing surgeon [7, 8]. It is therefore necessary to ensure rapid and effective communication, in order to minimize the time between referral and surgery [9].

Methods

Up until April 2023, requests for E/U surgery at the San Martino IRCCS Hospital were based exclusively on the information provided on a paper form; text fields had to be handwritten by the proposing surgeon and the form was sent to the anaesthetist and the surgeon on call. In order to meet the demand for E/U intervention quickly

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3161

Fig. 1. E/U surgery requests submitted in the period between 14th April 2023 and 23th July 2023. The distribution of the surgical disciplines that sent requests for E/U surgery which was subsequently not performed is also shown.



and efficiently, the paper form contained the following information: the patient's personal details, suspected diagnosis and planned surgery, severity code (colour code class), date and time of report, proposing surgical unit, and the name and signature of the proposing surgeon. Subsequently, a new method of requesting urgent and emergency surgery was introduced; this involved filling out an online form. The clinical information reported on the online form is the same as that previously handwritten on the paper form. This online form is filled in by the proposing surgeon, but is promptly accessible to other crucial healthcare personnel, such as anaesthesiologists, other surgeons and nurses. The surgical team can access the form through the IT application used to compile the surgical register.

A three-month period of analysis and monitoring followed the introduction of the online form, with the aim of testing the new method and identifying any major criticalities and shortcomings. From April to July 2023 an experimental period was run, during which both communication methods, *i.e.* both paper and online forms, were available at the same time and used in parallel.

Results

E/U surgery requests submitted in the period between 14th April 2023 and 23th July 2023 were analysed: a total of 406 requests were made, resulting in 367 E/U surgeries (Fig. 1).

Some of the remaining patients were rescheduled for elective surgery, after medical re-evaluation, while others experienced a deterioration of their clinical conditions, prompting the decision that surgery was no longer appropriate for them.

Analysis of the data collected enabled us to identify the percentage distribution of the surgical disciplines involved. Thoracic-abdominal surgery accounted for the greatest number of emergency operations (45%), followed by urology (19%), neurosurgery (13%),

Fig. 2. E/U surgery requests submitted in the period between 14th April 2023 and 23th July 2023 in San Martino IRCCS Hospital in Genoa, categorized by surgical disciplines.

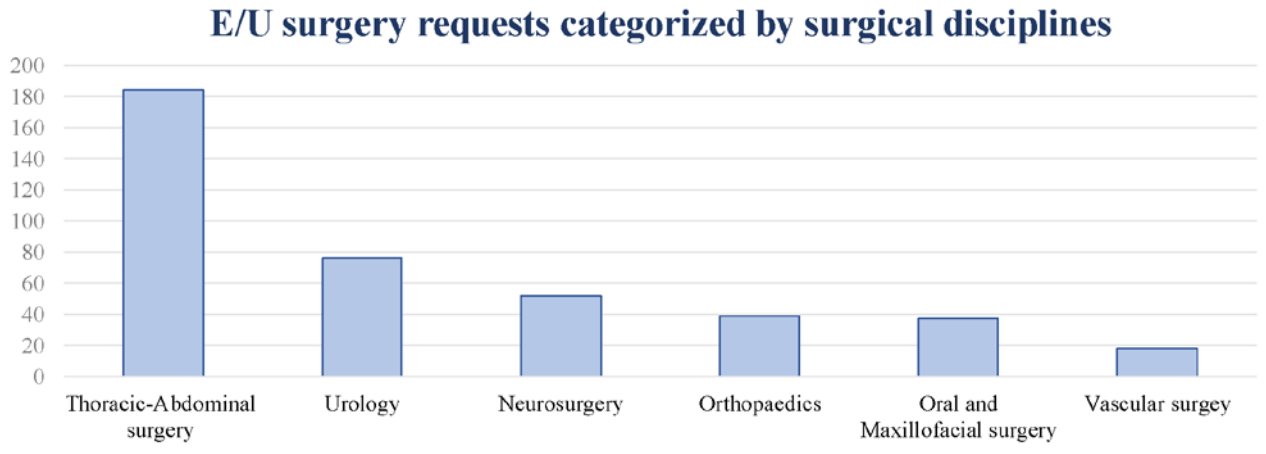
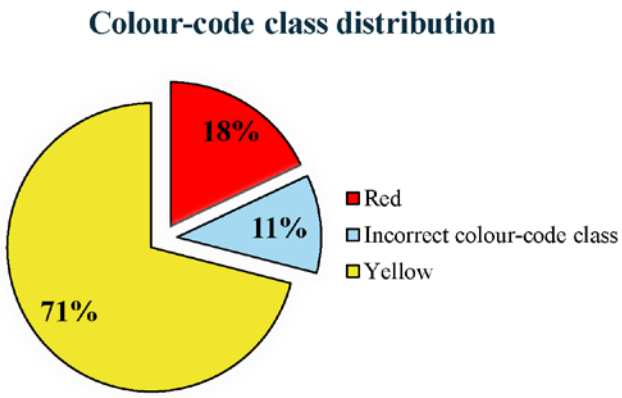


Fig. 3. Percentage distribution of E/U requests by colour-code classes submitted in the period between 14th April 2023 and 23th July 2023 at the San Martino IRCCS Hospital in Genoa.



orthopaedics (10%), oral and maxillofacial surgery (9%), and vascular surgery (4%) (Fig. 2).
The requests analysed reported colour-code classes with the following frequency: 18% were classified as red, and 71% as yellow. The remaining 11% of requests contained compilation errors (Fig. 3). The most frequent compilation errors were: omission of the colour-code class field on the paper form, changes or deletions on the form, and selection of an invalid colour-code class.
Analysis of the data obtained revealed the following critical issues:

- 11% of requests incorrectly reported the severity code (colour-code class);
- 11% of the surgical interventions were not performed within the time limits defined according to the severity code (colour-code class).

Discussion

The main limit of using paper forms is that information is available only to a small number of health workers; moreover, incomplete and/or illegible forms may give rise to doubts in interpretation or analysis [10]. This does not allow an accurate global picture of the number of requests for E/U interventions as well as the number of cases with similar colour-code class presented in the same time [11].
In order to avoid any misunderstandings and ensure proper interpretation, it is essential to limit handwritten healthcare data and to use electronic tools and standardized data management systems [12]. Indeed, if all emergency surgery workers use the same reporting system, the effectiveness of communication may improve and delays in the management of patients may be reduced [1].
To the best of our knowledge, similar digitalization trials have been conducted in other Italian hospitals, for example at the Azienda Ospedaliera Universitaria Integrata (AOUI) in Verona. In that facility, a digital request form for elective surgery was introduced in order to track the request and ensure that all mandatory fields were filled in [13].

Conclusions

In order to solve the problems observed, a dedicated tab for emergency/urgency operations was introduced into the online form in May 2023; this obliges users to enter the essential information contained in the previously used paper forms.
After a three-month experimental period, during which both reporting tools were used in parallel, paper forms were entirely replaced by online forms.
This latter tool ensures the standardisation and accuracy of the data reported and allows traceability of the E/U pathway. Indeed, San Martino IRCCS Hospital's Healthcare Management Unit can monitor requests for surgery in real time, thereby achieving greater efficiency and implementing corrective measures in the use of Operating Room resources.

Acknowledgements

The authors would like to thank the colleagues of U.O. ICT at San Martino IRCCS Hospital for their support and contribution.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Conflicts of interest statement

None declared.

Authors' contributions

AM and GO: conceived the study. LI and MK: drafted the manuscript. IB: revised the manuscript. LI, MK and IB: performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

References

[1] Coelho MA, Lourenção PLTA, Weber ST, Ortolan EVP. Implementation of a surgical screening system for urgent and emergent cases in a tertiary hospital. Rev Col Bras Cir 2019;46:e2211. Portuguese, https://doi.org/10.1590/0100-6991e-20192211.

[2] NSW Emergency Surgery Guidelines and Principles for Improvement. NSW Government, 2021. Available at: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2021_007.pdf (Accessed on:16/04/2024).

[3] De Simone B, Kluger Y, Moore EE, Sartelli M, Abu-Zidan FM, Coccolini F, Ansaloni L, Tebala GD, Di Saverio S, Di Carlo I, Sakakushev BE, Bonavina L, Sugrue M, Galante JM, Ivatury R, Picetti E, Chirica M, Wani I, Bala M, Sall I, Kirkpatrick AW, Shelat VG, Pikoulis E, Leppäniemi A, Tan E, Broek RPGT, Gurmu Beka S, Litvin A, Chouillard E, Coimbra R, Cui Y, De' Angelis N, Sganga G, Stahel PF, Agnoletti V, Rampini A; WSES TACS panel of experts; Testini M, Bravi F, Maier RV, Biffl WL, Catena F. The new timing in acute care surgery (new TACS) classification: a WSES Delphi consensus study. World J Emerg Surg 2023;18:32. https://doi.org/10.1186/s13017-023-00499-3.

[4] The NCEPOD Classification of Intervention. Classification of Intervention, 2004. Available at: https://www.ncepod.org.uk/classification.html (Accessed on:16/04/2024).

[5] Leppäniemi A, Jousela I. A traffic-light coding system to organize emergency surgery across surgical disciplines. Br J Surg 2014;101:e134-140. https://doi.org/10.1002/bjs.9325.

[6] Kluger Y, Ben-Ishay O, Sartelli M, Ansaloni L, Abbas AE, Agresta F, Biffl WL, Baiocchi L, Bala M, Catena F, Coimbra R, Cui Y, Di Saverio S, Das K, El Zalabany T, Fraga GP, Gomes CA, Gonsaga RA, Kenig J, Leppäniemi A, Marwah S, Junior GA, Sakakushev B, Siribumrungwong B, Sato N, Tranà C, Vettoretto N, Moore EE. World society of emergency surgery study group initiative on Timing of Acute Care Surgery classification (TACS). World J Emerg Surg 2013;8:17. https://doi.org/10.1186/1749-7922-8-17.

[7] Jawaid M, Raza SM, Alam SN, Manzar S. On-call emergency workload of a general surgical team. J Emerg Trauma Shock 2009;2:15-8. https://doi.org/10.4103/0974-2700.44677.

[8] Koivukangas V, Saarela A, Meriläinen S, Wiik H. How well planned urgency class come true in the emergency surgery? Timing of Acute Care Surgery. Scand J Surg 2020;109:85-8. https://doi.org/10.1177/1457496919826716.

[9] Van Essen JT, Hans EW, Hurink JL, Oversberg A. Minimizing the waiting time for emergency surgery - Operations Research for Health Care 2012;1:34-44. https://doi.org/10.1016/j.orhc.2012.05.002.

[10] Coccolini F, Sartelli M, Kluger Y, Osipov A, Cui Y, Beka SG, Kirkpatrick A, Sall I, Moore EE, Biffl WL, Litvin A, Pisano M, Magnone S, Picetti E, de Angelis N, Stahel P, Ansaloni L, Tan E, Abu-Zidan F, Ceresoli M, Hecker A, Chiara O, Sganga G, Khokha V, di Saverio S, Sakakushev B, Campanelli G, Fraga G, Wani I, Broek RT, Cicuttin E, Cremonini C, Tartaglia D, Soreide K, Galante J, de Moya M, Koike K, De Simone B, Balogh Z, Amico F, Shelat V, Pikoulis E, Di Carlo I, Bonavina L, Leppaniemi A, Marzi I, Ivatury R, Khan J, Maier RV, Hardcastle TC, Isik A, Podda M, Tolonen M, Rasa K, Navsaria PH, Demetrashvili Z, Tarasconi A, Carcoforo P, Sibilla MG, Baiocchi GL, Pararas N, Weber D, Chiarugi M, Catena F. The LIFE TRIAD of emergency general surgery. World J Emerg Surg 2022;17:41. https://doi.org/10.1186/s13017-022-00447-7.

[11] Howe TE, Varley I, Allen JE, Glossop A, McKechnie A. Scheduling terminology for oral and maxillofacial surgery. Are we speaking a universal language? Br J Oral Maxillofac Surg 2017;55:407-9. https://doi.org/10.1016/j.bjoms.2016.10.025.

[12] Adane K, Gizachew M, Kendie S. The role of medical data in efficient patient care delivery: a review. Risk Manag Healthc Policy 2019;12:67-73. https://doi.org/10.2147/RMHP.S179259.

[13] Marigo F, Poli R, Tardivo S, et al. Liste d'attesa chirurgiche: il processo di informatizzazione del percorso del paziente chirurgico nell'Azienda Ospedaliera Universitaria Integrata di Verona. ANMDO 2019. Available at: https://www.anmdo.org/wp-content/uploads/2019/07/MARIGO-Francesco-min-1.pdf (Accessed on:16/04/2024).

Received on December 26, 2023. Accepted on May 9, 2024.

Correspondence: Lucia Inglese, Department of Health Sciences (Dissal), University of Genoa, Genoa, Italy. E-mail: lucia.inglese@hsanmartino.it

How to cite this article: Inglese L, Barberis I, Korshunova M, Amato R, Zangrillo F, Arata L, Tisa V, Papalia R, Santo M, Tiberio G, Morando A, Orengo G. Monitoring emergency and urgent surgery: an improvement in a Healthcare Management Unit at a third-level hospital in Italy. J Prev Med Hyg 2024;65:E232-E235. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3161

HEALTH CARE MANAGEMENT

A new organizational model of primary healthcare in Liguria, Italy. Insights and implications

FILIPPO ANSALDI[1,2], MATTEO ASTENGO[2], ALBERTO BATTAGLINI[2], FEDERICO GRAMMATICO[2], FRANCESCA MARCHINI[2], ANDREA FIORANO[1,2], SILVIA ALLEGRETTI[1], IRENE SCHENONE[2], DANIELA AMICIZIA[1,2]
[1] Department of Health Sciences, University of Genoa, Italy; [2] Regional Health Agency of Liguria (A.Li.Sa.), Genoa, Italy

Keywords

National resilience and recovery • Plan • Regional • Models • Community • Hospital • Community • House

Summary

After years of cost-containment policies, the Italian National Health Service (NHS) has now the chance to change and improve, especially thanks to the National Recovery and Resilience Plan (NRRP). The plan serves as a catalyst for reform, allocating substantial funds to reinforce proximity networks, facilities, and telemedicine for territorial healthcare. Mission 6, specifically dedicated to health, focuses on integrating primary healthcare, hospital, and specialty care networks, underscoring the importance of a robust primary healthcare system.In alignment with NRRP objectives, the Ligurian model introduces innovative structures, such as Community Houses (CdCs), Community Hospitals (OdCs), and Territorial Operation Centres (COTs). These interconnected components form a dynamic network designed to enhance healthcare accessibility, prevent inappropriate hospital admissions, and facilitate efficient patient transitions. The model prioritizes multidisciplinary collaboration, community engagement, and the integration of socio-healthcare services. Despite substantial NRRP funding for infrastructure, challenges related to staffing and human resources persist. The social and epidemiological context highlights concern about the economic feasibility of the reform, potential workforce shortages, and the imperative for updated regulatory frameworks. The strategic reallocation of personnel from acute hospitals to new facilities is crucial, requiring meticulous workforce planning, role definitions, and trainingIn conclusion, the Ligurian model emerges as a proactive response to the structural vulnerabilities exposed by the pandemic, aligning with international trends in emphasizing primary care, prevention, and community-based services.

Introduction

The recent COVID-19 pandemic has highlighted critical limitations and challenges within the Italian National Health Service (NHS), especially regarding disparities in access for the most fragile and vulnerable population groups. To mitigate these issues and improve overall health outcomes, primary healthcare (PHC) has proven to be a key tool, due to its inclusiveness, equity, and cost-effectiveness in achieving universal health coverage. Strengthening PHC could bolster the resilience of the healthcare system, enabling it to better prepare for, respond to, and recover from future shocks and crises [1]. The World Health Organization (WHO) emphasizes the importance of PHC in consolidating and strengthening national health systems, bringing health services closer to communities [2]. The existing literature demonstrates that health systems with robust primary and proximity care services tend to exhibit better population health outcomes [3]. This comprehensive approach enables health systems to support person-centred health needs in various settings: from health promotion to disease prevention, treatment, rehabilitation, palliative care, *etc*. [2].

After a decade of cost-containment policies, the Italian NHS is in evident need of reform, in order to address the above-mentioned challenges effectively [1, 4]. In this regard, proximity structures and telemedicine for territorial healthcare assistance could help to reduce inequalities in healthcare access and improve overall healthcare services.

In the context of rethinking and redesigning the NHS and building on the critical role of primary healthcare, the National Recovery and Resilience Plan (Piano Nazionale di Ripresa e Resilienza, NRRP), which is embedded in the Next Generation EU (NGEU) programme, plays a pivotal role in shaping new organizational models that are consistent with the health needs and preferences of citizens [1, 4]. The programme is divided into six missions and has a duration of six years, from 2021 to 2026, with provisions for grants. One mission focuses specifically on "Health" (Mission 6), while the others address: 1) Digitalisation, Innovation, Competitiveness, Culture and tourism; 2) The "Green Revolution" and Ecological Transition; 3) Infrastructure for Sustainable Mobility; 4) Education and Research, and 5) Inclusion and Cohesion.

For Mission 6, a total of € 18.5 billion (€ 15.6 billion from the Recovery and Resilience Facility and € 2.9 billion from the Fund) is allocated to reinforcing proximity networks, facilities, and telemedicine for territorial healthcare [5]. The aim is to enable more effective management of social care needs and better identify priorities for action, which are closely related to the integration of primary healthcare, hospitals and specialist care networks.

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3145

The reform is targeted at reinforcing the primary healthcare system, and focuses specifically on enhancing the district, which is the territorial branch of the Local Health Agency (LHA) and is now responsible for the local management and coordination of health services. The LHA works towards promoting integration among healthcare facilities and providing a continuous response to the evolving healthcare needs of the population, as well as guaranteeing equality in access to care and ensuring uniformity of Essential Levels of Assistance (Livelli Essenziali d'Assistenza, LEAs). These latter are the services that the Italian NHS is required to provide for all citizens, either free of charge or on payment of a fee (ticket), using public resources obtained from general taxation [6].

In May 2022, the Italian health minister issued a new Decree (DM77 - "Defining models and standards for the development of primary care in the national health service"), to address some of the major challenges outlined by the National Recovery and Resilience Plan [1], which emphasizes the need for an innovative "regional care pathway system". While concerns persist regarding structuring and implementing a single model in a highly diversified regional landscape like Italy's, standards have been defined for some of the cornerstone structures of this new model.

Among those, Territorial Operation Centres ("Centrali Operative Territoriali" in Italian, COTs) coordinate patient care by establishing connections between the services and professionals involved in the various care settings, while Community Houses ("Case della Comunità", CdC) and Community Hospitals ("Ospedali di comunità", OdC) are among the sites of response to the issues addressed by the Italian government through the NRRP. These facilities are interconnected with hospices and other hospital-related structures and manage selected patients in need of specialist hospital services, particularly those with complex chronic conditions that necessitate frequent hospitalizations [7].

The care pathway must be articulated across the various settings, which are closely interconnected to allow flexible transitions according to the individual's needs and stage of life. The goal is not only to keep patients at home and to delay or prevent institutionalization, but also to ensure uniformity and appropriateness throughout the regional territory. Additionally, it is essential to improve digital interconnection with the territorial and hospital socio-healthcare system.

This overview aims to shed light on the primary healthcare model in Liguria, a region in North-western Italy, and its evolutions. It delves into critical considerations such as structural components, financing, increased costs, the current state of advancement, human resource requirements and training priorities for district managers.

The ligurian territorial healthcare model

As of January 1, 2023, the resident population of the Liguria Region was 1,502,624 (723,806 males and 778,818 females), with a general trend of declining births and gradual ageing of the population. The average age of Ligurians is 49.3 years, and the percentage of individuals aged 65 and over is 28.8% of the total population (23.5% in Italy). The current sociodemographic structure and its future projection highlight a prevalence of chronic-degenerative pathologies. The socio-healthcare system will therefore be increasingly called upon to respond to the health needs of Ligurians; this will require profound changes in its organizational model.

The territorial network

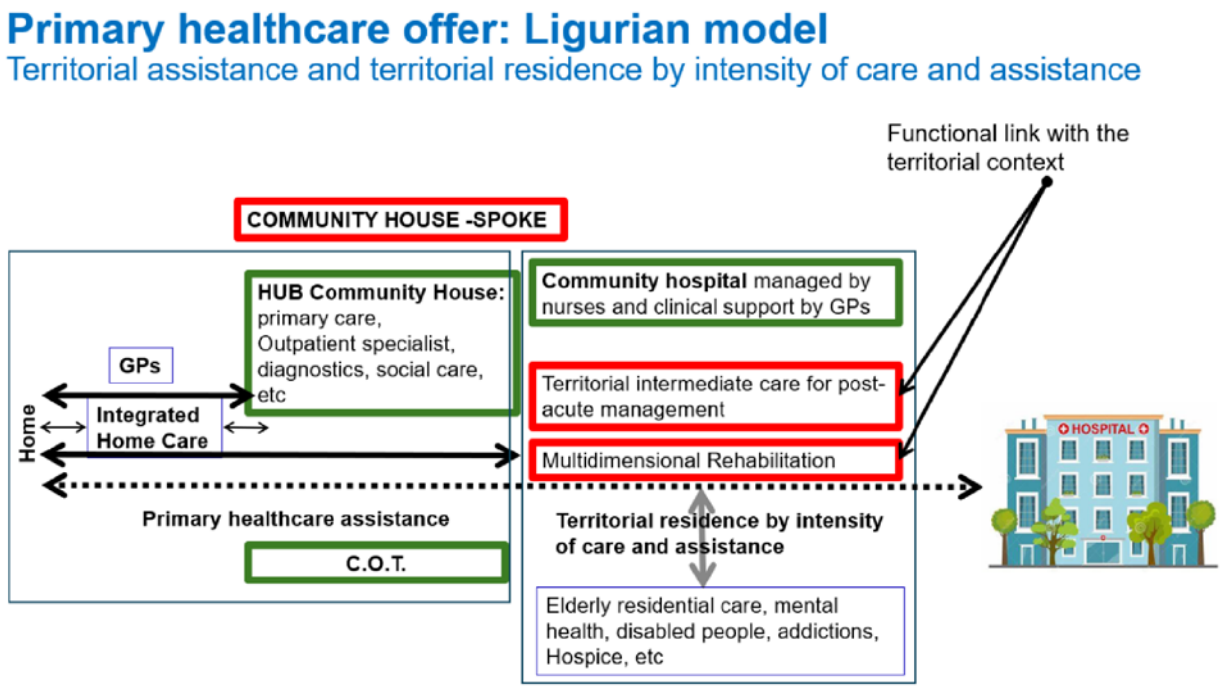
In recent decades, in Liguria, like other places [8,9], an increasing interest in improving the organization of primary care was seen, with particular emphasis being placed on reducing unnecessary visits to the emergency department (ED) for non-severe conditions and hospital admissions of chronically ill patients. Initiatives to reinforce the healthcare network have included extending the opening hours of general practitioners' (GPs) group practices and out-of-hours care and considering expanding the range of facilities to offer a broader spectrum of acute and chronic medical services. The National Recovery and Resilience Plan offers a significant opportunity to improve integration and strengthen the healthcare framework. Regional Government Resolution 1223/2022 incorporates the directives of the NRRP and DM77, providing a revision of the territorial network of various professionals, including Family or Community Nurses (IFoC), whose collaboration is necessary for the functioning of Community Houses, Community Hospitals and Territorial Operation Centres to promote "proximity prevention". In this way, the community ceases to be a passive spectator and, thanks to empowerment processes, becomes an active subject in building proposals to improve the health conditions of the community and evaluate local socio-health policies.

The advance of telemedicine emerges as a critical element in the reorganization of territorial care. Indeed, telemedicine can:

- reduce the distance between healthcare providers and patients and among healthcare providers themselves;
- enable the early diagnosis of acute events and timely intervention for patients treated at home and/or in emergency situations;
- streamline care services in remote or disadvantaged areas, optimizing resources by offering proximity services that enhance appropriateness and therapeutic adherence;
- coordinate interventions for integrated care between the hospital and primary care settings, thereby facilitating de-hospitalization processes;
- promote collaboration among professionals belonging to different hospital and territorial care networks, particularly in contexts where multidisciplinarity is essential for the proper care and management of the patient.

Figure 1 shows the offer of primary care, the facilities envisioned by the new model and their functional connections.

Fig. 1. Scheme of the primary healthcare system in the Liguria Region (Community House, Community Hospital).



Community house

In accordance with the NRRP, Community Houses serve as hubs in a reorganized territorial network, and act as reference points for proximity medicine, reception and orientation to primary care services [10]. Indeed, the overall integration of social, and health care services for the promotion of health and the comprehensive care of the community is enhanced through the implementation of physically identifiable facilities. These serve as points of reference for proximity assistance and as hubs for receiving and orienting citizens to primary healthcare services of a health, socio-health and social nature; they ensure interdisciplinary interventions through the spatial contiguity of services and the integration of professional communities (multi-professional and interdisciplinary teams) that operate according to integrated models, both within healthcare services (territory-hospital) and between health and social services.

The reference standard mandates the presence of at least 1 CdC for every 50,000 inhabitants [1]. These facilities generally offer a range of services, including medical examinations, reception, services for continuity of care, general medicine, polyclinics, first aid, first-line diagnostic services, sampling points, rehabilitation, home care services, primary care paediatricians, vaccination centres, screening, social healthcare services and telemedicine [5].

The mission of the CdCs is multi-faceted, encompassing standardizing healthcare pathways, promoting prevention and health among individuals and in the community, managing chronic conditions, conducting comprehensive assessments of individual needs, and ensuring coordination with local health services for continuity of care [11]. Their activities include inter-professional and multidisciplinary work and the coordination of interventions among General Practitioners (GPs), Paediatricians (PLSs), Outpatient Specialists, Family and Community Nurses, social workers and other healthcare and social professionals. As the multi-professional team involves Family Nurses and GPs and PLSs working in group practices, the skills of these professionals are enhanced, and professional isolation is avoided [12].

In Liguria, the recently approved 2023-2025 regional health and social plan outlines the roles and functions of Hub and Spoke CdCs. One of the main goals is to enhance citizens' access to services by identifying the "doorways" to a unified pathway of health and social assistance. Specifically, the organization of the CdCs envisioned in the Ligurian model aims to ensure the maximum proximity and capillarity and is characterized by the presence of the NHS Hub CdCs and Level I (basic) and Level II Spoke CdCs.

Level I Spokes are individual GP ambulatories; their reference centre within their district is the Hub CdC, with which they are interconnected through the COT. GPs guarantee the availability of services according to the time commitment envisaged by the evolving regulatory framework. Additionally, GPs can negotiate the allocation of the remaining hours directly with the District Director; these hours may be dedicated to district activities, including activities within the Hub CdC. The District Director will evaluate whether to extend the opening hours of the medical practice, or to allocate these hours either to covering neighbouring areas that may be experiencing shortages or to

Tab. I. Regional CdCs envisaged by the NRRP.

Minimum target	30
Maximum target	33
Needs	Regional AGENCY / N° of CdCs to be built / N° of CdCs to be renovated / Total LHA1: 0 / 5 / 5 LHA2: 0 / 6 / 6 LHA3: 0 / 13 / 13 LHA4: 0 / 3 / 3 LHA5: 2 / 3 / 5 H EVANGELICO: 0 / 1 / 1 Total: 2 / 31 / 33 The need must be detailed in terms of the number of community houses (distinguishing between those to be built and those to be renovated) per referring agency.
Funds allocated	€44,030,926.66 from NRRP to the Region No additional amount is foreseen by the regional budget.

collaboration with other professionals within the CdC. Level II Spoke centres must guarantee the presence of GPs, specialist outpatient services and basic-level home care services. Their aim is to take care of 5% of the over-65s assisted by each GP belonging to the Level II Spoke. Table I reports the regional objectives for CdCs.

Community hospital

Along with the Community House, the Community Hospital will play a pivotal role in the healthcare network by empowering the community to engage in prevention, proximity, and management functions. This approach aims to prevent inappropriate hospital admissions of patients with complex and urgent conditions, while ensuring appropriate responses to their needs [13].

The OdC is an intermediate care health facility designed for short hospital stays. It caters for patients who require a period of clinical stabilization or monitoring and remodulation of therapy after discharge from acute departments, as well as individuals coming from home who present worsening of a chronic pathology and/or the need for a clinical-diagnostic and therapeutic pathway that cannot be managed on an outpatient basis.

Effective networking with other care settings and a functional connection with hospitals and territorial services are thus crucial. Prompt activation of home care services and caregiver training are essential for safe patient transitions home. This necessitates well-defined operational procedures to ensure continuity of care, in which the coordinating role played by the COT is fundamental.

It must be emphasized that the Community Hospital neither duplicates nor replaces existing structures for patient care; it is not one of the residential facilities covered by the essential levels of assistance approved in 2017 (DPCM 12/01/2017) [14]. Instead, it complements other healthcare models.

The reference standard requires the presence of at least 1 Community Hospital with 20 beds per 50,000 - 100,000 inhabitants that operates 7 days a week. One or two further modules, each with 15-20 beds, may be added to ensure consistency with the purposes, recipients, and management methods of the OdC [1].

The OdC is designed to receive those patients who require low-intensity treatments following a minor or acute episode of worsening of chronic pathologies; while these treatments are potentially available at home, the patient is admitted on account of the (structural and/or familial) unsuitability of the home setting. OdCs offer continuous nursing care, including overnight surveillance, that is not available at home [15].

These healthcare facilities are affiliated to the local territorial area and carry out an intermediate function between home/community-based care and hospitalization, catering for short-term admissions for low- to moderate-intensity care. Unlike other health structures, OdCs are territorial facilities where stays should not exceed 30 days. Daily tariffs fall between

those of hospitals and socio-sanitary residential facilities. OdCs are intended to deliver health care for patients with functional deficits and/or stable chronic conditions, who may come from hospitals, residential care facilities, or their own homes. Subjects that may benefit from admission to an OdC include: elderly individuals with multiple chronic conditions who experience a sudden worsening of symptoms at home and require close monitoring and management, but not acute hospitalization, and patients receiving a new therapy (such as those with a spinal cord injury who are discharged home with a urinary catheter and medications for pain management, or those for whom peritoneal dialysis has recently been prescribed) who need training and support in order to adhere to catheter care and medication. In summary, the main categories of eligible patients are:

a) frail and/or chronic patients coming from home who experience worsening of a pre-existing clinical condition and for whom hospital admission is inappropriate;
b) patients (mainly with multiple morbidities) requiring continuous nursing care after being discharged from hospital facilities following acute or rehabilitative treatment;
c) patients requiring assistance in administering medications or managing aids and devices, and who require support and patient and caregiver training before returning home;
d) patients in need of support for rehabilitation/re-education involving assessments and proposals of strategies for maintaining functions and residual capacities; those requiring therapeutic support, and those with motor, cognitive or physical disabilities who need training. Physiotherapy interventions are part of protocols already activated in the department of origin to facilitate return home.

While Community Hospitals constitute a model of Intermediate Care, there remains a need for monitoring and assessment processes, to evaluate patient characteristics and care effectiveness. This will involve the continuous monitoring of the quality of healthcare services and the timely detection of any critical issues that may arise. In this regard, e-health and telemedicine services will be fundamental to improving the quality of care and access to care and will reduce costs by favouring the treatment of chronic diseases outside hospitals, which can then be dedicated to the treatment of acute cases [16].

Table II reports the regional objectives for OdCs.

Territorial operation centre (COT)

The design outlined elucidates the functioning of the organizational model implemented by the Territorial Operations Centre (COT) – a back-office service that facilitates the activation and continuity of care through a common platform integrated with key corporate management applications and interconnected with all entities/structures within the territory. The COT ensures coordination and alignment between the nodes of different networks and professionals; it therefore serves as a crucial "organizational hub" for the efficient management of continuity of care during patients' transition from the hospital to the territory. The COT provides digital and logistical support for healthcare workers, coordinating the various healthcare services

Tab. II. Regional OdCs broken down by LHA.

<table>
<tr><td>Minimum target</td><td>10</td></tr>
<tr><td>Maximum target</td><td>11</td></tr>
<tr><td>Needs</td><td>
<table>
<tr><th>Regional Agency</th><th>N° of CdCs to be built</th><th>N° of CdCs to be renovated</th><th>Total</th></tr>
<tr><td>LHA1</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>LHA2</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>LHA3</td><td>2</td><td>2</td><td>4</td></tr>
<tr><td>LHA4</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>LHA5</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>Total</td><td>2</td><td>9</td><td>11</td></tr>
</table>
The need must be detailed in terms of the number of community hospitals (distinguishing between those to be built and those to be renovated) per referring agency.
</td></tr>
<tr><td>Funds allocated</td><td>€24,016,869.09 from the NRRP to the Region

No additional amount is foreseen by the regional budget.</td></tr>
</table>

offered by the District and integrating social healthcare activities in the various settings. Its activities are linked to the registration of data on health needs and communication with the emergency network.
DM77 specifically suggests the creation of an Operations Centre (*i.e.* 116 117), a regional structure that facilitates the population's access to non-urgent medical care. It provides patients with telephone assistance, directs them to local assistance structures by transferring their calls to the COT, and transmits urgent requests for medical assistance to the emergency number (118). DM 77/2022 designates the unique number 116 117 as one of the channels that will progressively become an ordinary mean of access to the NHS. It serves various purposes, including obtaining information, receiving initial guidance on services, ensuring continuity of care and accessing socio-sanitary services. Regional Government Resolution 715/2023 has approved the "Project for the gradual activation of the Harmonized European Number (NEA) for social purposes 116 117 in the Liguria Region". Table III reports the regional objectives for the COTs, broken down by LHA.

Human resources dedicated to primary care services

The NRRP calls for a substantial transformation of primary and community care, in order to offer patients more accessible services closer to home and to allow hospitals to focus only on acute care. Indeed, expensive technologies and professional expertise need to be concentrated in hospitals to exploit clinical and organizational learning and economies of scale. However, while the new facilities require staff and other resources to become operational, the NRRP lacks provisions for extra funding in this regard, as it only funds capital expenditure (buildings, technologies, digital infrastructure) [17]. The most feasible strategy, despite resistance from most professionals, involves reallocating a portion of the staff working in acute hospitals to these new facilities. Thus, it is very important to decide how to deploy the proximity network workforce and how to specifically coordinate the activities of primary care professionals, hospital professionals, GPs, Paediatricians and new professionals.

Tab. III. Regional COTs, broken down by LHA.

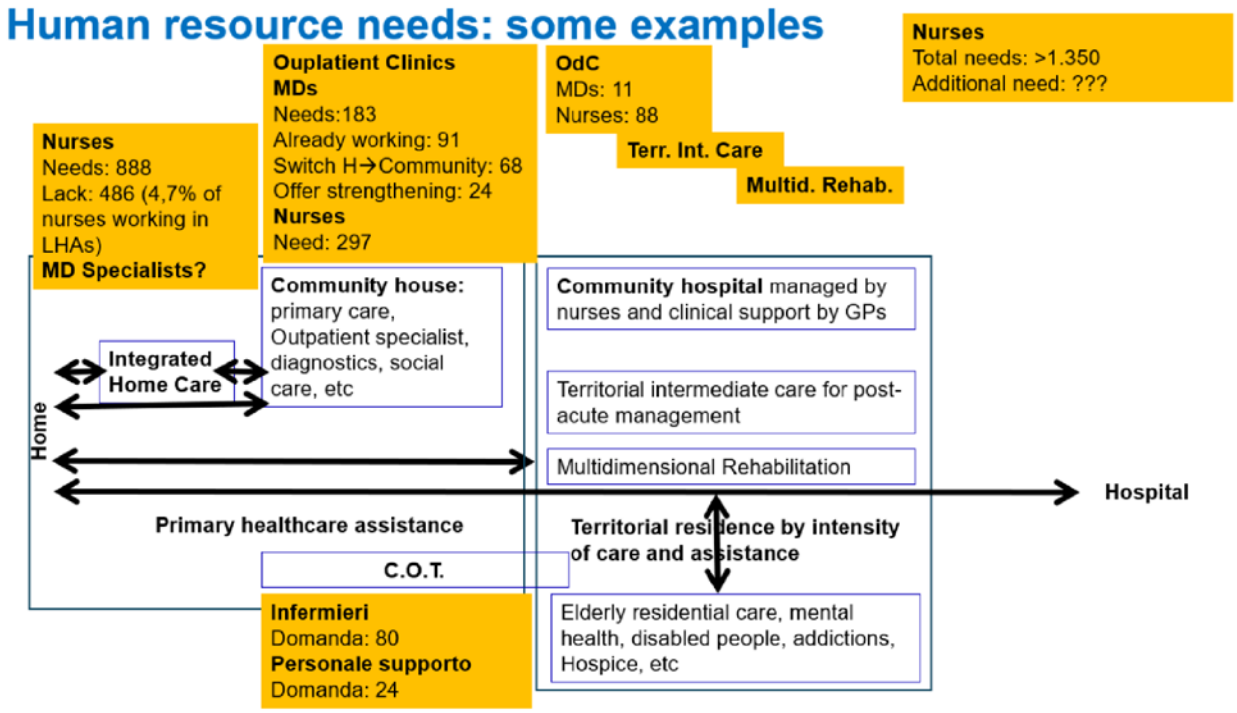
<table>
<tr><td>Minimum target</td><td>15</td></tr>
<tr><td>Maximum target</td><td>16</td></tr>
<tr><td>Needs</td><td>
<table>
<tr><td>Regional Agency</td><td>N° of COTs</td></tr>
<tr><td>LHA1</td><td>2 (n°1 San Remo, n°1 Imperia)</td></tr>
<tr><td>LHA2</td><td>3 (n°1 Savona, n°1 Cairo Montenotte, n°1 Finale Ligure)</td></tr>
<tr><td>LHA3</td><td>6 (n° 6 Genova)</td></tr>
<tr><td>LHA4</td><td>2 (n°1 Sestri Levante, n°1 Chiavari)</td></tr>
<tr><td>LHA5</td><td>3 (n°1 Brugnato, n°1 La Spezia, n°1 Sarzana)</td></tr>
<tr><td>Total</td><td>16</td></tr>
</table>
The need must be detailed in terms of the number of COTs (distinguished between those to be built and those to be renovated) per referring agency.
</td></tr>
<tr><td>Allocated ammount</td><td>€2.596.125 from NRRP to the Region (COT resources)

€1.066.071,88 from NRRP to the Region (interconnection resources)

€1.450.742,83 from NRRP to the Region (devices resources)

No additional amount is foreseen by the regional budget.</td></tr>
</table>

Fig. 2. Some examples of human resource needs.



In this regard, several questions remain unanswered: What is the staffing standard for the new territorial organization? Are there shortages of professionals? What roles and training are required? Is a shift from hospitals to the territory truly feasible?

Figure 2 shows some examples of human resource needs (or workforce requirements).

On average, Italy has a higher number of physicians than other EU countries. The number of practising physicians has steadily increased since the 2000s, reaching 412 per 100,000 population in 2021 (the EU average is 397) [16]. However, the number of public hospital physicians and GPs is declining, potentially leading to future shortages. Notably, shortages are more pronounced in specific sectors, particularly in emergency/urgency/on-call activities. Moreover, it is noteworthy that more than half of the physicians working in the public system are aged over 55 years, a value that is among the highest in the EU. In 2020 and 2021, the COVID-19 pandemic necessitated a rapid increase in the recruitment of medical and other support staff, to meet the needs of the emergency. In Italy, however, comprehensive planning for the training of health professionals, especially physicians and nurses, has generally been suboptimal. In order to tackle the problem of staff shortages, the number of medical specialization contracts for a full cycle of studies (5 years) has been increased by approximately 4200 since the academic year 2020/2021 by allocating funds from the NRRP.

However, the utilisation of NRRP funds for this purpose has sparked a renewed discussion on task-shifting, a concept overlooked for decades in Italy. Indeed, the Italian regulatory framework on the division of tasks among health professions (*e.g.* doctors, nurses, pharmacists) is obsolete and does not reflect changes in technologies and professional training. This regulation should be updated in the light of the best international experiences. Such a shift could also increase the appeal of nursing as a profession and would generate savings for the NHS, given the differences in salaries between nurses and doctors [17].

Primary care services are a fundamental part of the healthcare network of assistance, prevention, and health promotion [18]. Apart from a few regions, the Italian NHS has no functioning CdCs or OdCs yet. Where to carry out 1st and 2nd level outpatient activities remains a pertinent question and could be informed by studies aimed at investigating optimal locations for outpatient services in healthcare systems that face similar challenges.

Discussion and conclusion

The global response to the COVID-19 pandemic presented a unique opportunity to tackle the structural weaknesses of the Italian economy and guide the country towards an ecological and environmental transition. The pandemic highlighted the necessity for preventive and proactive measures, as well as a supply system capable of integrating health and social services.

In this context, implementing new organizational models for territorial health care becomes crucial. Such models ensure a unified socio-health assistance pathway, multidimensional care, and continuity of interventions across various care settings. The recent

reform approved in Italy aims to establish an integrated primary healthcare model nationwide, by transitioning primary care to community care, thereby reducing geographical disparities and enhancing service effectiveness [1].

After years of focusing on cost rationalization and efficiency, the current emphasis is on innovation and new, more integrated, and digital organizational models supported by increased resources and investments. Investing in the health system is seen as crucial to socioeconomic development, although using EU funds, and investment funds in general, presents challenges, particularly as the technical capacities to design and implement sound projects are lacking; it is therefore essential to invest in these capacities [17].

The NRRP has allocated € 2 billion to the creation of 1288 CdCs by the first half of 2026. However, economic resources, especially within the NRRP, do not adequately cover current spending, and general funding will not increase significantly in the future.

A very relevant issue is the need to monitor and assess patient characteristics and the effectiveness of care in the new facilities [19]. Indeed, there is a risk of increasing the inter-regional gap in terms of the ability to provide timely high-quality care, with some regional clinical-organizational models being rewarded and others being penalised, according to how far their outcome/process indicators are from the benchmark.

Further unresolved questions concern the needs of the new territorial organization, potential shortages of healthcare professionals, training requirements and pathways of the shift from hospital to community care. A critical point concerns the number and type of professionals required for the new structures, given the overall shortage of well-trained healthcare professionals. The difficulty of retaining nurses and physicians in service poses potential challenges in implementing the new territorial healthcare model [18].

The current budget allocation might prove insufficient, given Italy's GP shortage and the ageing population of healthcare professionals. Consequently, there may be insufficient personnel to staff CdCs and, especially, OdCs. The economic feasibility of the territorial healthcare reform is therefore questionable unless additional budget expenditures are allocated.

Achieving an equitable distribution of medical practitioners for the entire population is paramount. E-health and telemedicine services will play a fundamental role in enhancing the quality of care, facilitating access to assistance and reducing costs [20]. These services will support the treatment of chronic diseases outside hospitals, thereby allowing hospitals to focus on acute cases [21, 22].

Conflict of interest statement

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

Not applicable.

Author contributions

FA and DA: conceived and supervised the work. National and regional documents were reviewed by DA and IS. MA, AB, FG, FM and IS: wrote the first draft of the manuscript. DA and IS: had the final responsibility for deciding to submit for publication. All authors reviewed and edited the manuscript, contributed to the article, and approved the version submitted.

References

[1] Mauro M, Giancotti M. The 2022 primary care reform in Italy: Improving continuity and reducing regional disparities? Health Policy 2023:135:104862. https://doi.org/10.1016/j.healthpol.2023.104862.

[2] WHO. Primary health care. Available at https://www.who.int/health-topics/primary-health-care#tab=tab_1 (Accessed on: 8 December 2023).

[3] Rifkin SB. Alma Ata after 40 years: primary health care and health for all-from consensus to complexity. BMJ Glob Health 2018;3(Suppl 3):e001188. https://doi.org/10.1136/bmjgh-2018-001188.

[4] Filippini T, Vinceti SR. Italian National Recovery and Resilience Plan: a Healthcare Renaissance after the COVID-19 crisis? Acta Biomed 2021;92(Suppl 6):e2021463. https://doi.org/10.23750/abm.v92iS6.12339.

[5] European, Commission. National Recovery and Resilience Plan. 2021. http://www.politicheeuropee.gov.it/media/5651/pnrr-definitivo.pdf (Accessed on: 8 December 2023).

[6] Milani C, Naldini G, Baggiani L, Nerattini M, Bonaccorsi G. How to promote changes in primary care? The Florentine experience of the House of Community. Front Public Health 2023;11:1216814. https://doi.org/10.3389/fpubh.2023.1216814.

[7] Gola M, Brambilla A, Barach P, Signorelli C, Capolongo S. Educational challenges in healthcare design: training multidisciplinary professionals for future hospitals and healthcare. Ann Ig 2020;32:549-66. https://doi.org/10.7416/ai.2020.2375.

[8] Roberts E, Mays N. Can primary care and community-based models of emergency care substitute for the hospital accident and emergency (A & E) department? Health Policy 1998;44:191-214. https://doi.org/10.1016/s0168-8510(98)00021-9.

[9] Pinchbeck EW. Convenient primary care and emergency hospital utilisation. J Health Econ 2019;68:102242. https://doi.org/10.1016/j.jhealeco.2019.102242.

[10] Odone A, Saccani E, Chiesa V, Brambilla A, Brianti E, Fabi M, Curcetti C, Donatini A, Balestrino A, Lombardi M, Rossi G, Saccenti E, Signorelli C. The implementation of a Community Health Centre-based primary care model in Italy. The experience of the Case della Salute in the Emilia-Romagna Region. Ann Ist Super Sanita 2016;52:70-7. https://doi.org/10.4415/ANN_16_01_13.

[11] 1Ugolini C, Leucci AC, Nobilio L, Bertè G. Reorganizing territorial healthcare to avoid inappropriate ED visits: does the spread of Community Health Centres make Walk-in-Clinics redundant? BMC Health Serv Res 2020;20:807. https://doi.org/10.1186/s12913-020-05648-x.

[12] Buffoli M, Gola M, Rostagno M, Capolongo S, Nachiero D. Making hospitals healthier: how to improve sustainabil-

ity in healthcare facilities. Ann Ig 2014;26:418-25. https://doi.org/10.7416/ai.2014.2001.

[13] Pianori D, Avaldi VM, Rosa S, Lenzi J, Ialonardi M, Pieri G, Rossi A, Fantini MP. How do Community Hospitals respond to the healthcare needs of elderly patients? A population-based observational study in the Emilia-Romagna Region. Ann Ig 2018;30:317-29.

[14] Ministero della Salute. Servizio Sanitario: i LEA. Available at https://www.salute.gov.it/portale/lea/dettaglioContenutiLea.jsp?lingua=italiano&id=4773&area=Lea&menu=vuoto) (Accessed on: 8 December 2023).

[15] AGENAS. Documento di indirizzo per il metaprogetto dell'Ospedale di Comunità. Available at https://www.agenas.gov.it/comunicazione/primo-piano/2160-documento-di-indirizzo-per-il-metaprogetto-dell-ospedale-di-comunit%C3%A0 (Accessed on: 8 December 2023).

[16] Mauro M, Giancotti M. The 2022 primary care reform in Italy: Improving continuity and reducing regional disparities? Health Policy 2023;135:104862. https://doi.org/10.1016/j.healthpol.2023.104862.

[17] Giulio de Belvis A, Meregaglia M, Morsella A, Adduci A, Perilli A, Cascini F, Solipaca A, Fattore G, Ricciardi W, Maresso A, Scarpetti G. Italy: Health System Review. Health Syst Transit 2022;24:1-236.

[18] Capolongo S, Brambilla A, Girardi A, Signorelli C. Validation Checklist for Massive Vaccination Centers. Ann Ig 2021;33:513-7. https://doi.org/10.7416/ai.2021.2460.

[19] 19. Di Girolamo C, Leucci AC, Sforza S, Moro ML, Berti E. Effectiveness of community hospital post-acute care on mortality, re-admission, institutionalization, and activation of a home care programme in Emilia-Romagna region, Italy. Aging Clin Exp Res 2023;35:367-74. https://doi.org/10.1007/s40520-022-02298-3.

[20] De la Torre-Díez I, López-Coronado M, Vaca C, Aguado JS, de Castro C. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: a systematic review. Telemed J E Health 2015;21:81-5. https://doi.org/10.1089/tmj.2014.0053.

[21] Donald M, Jackson CL, Byrnes J, Vaikuntam BP, Russell AW, Hollingworth SA. Community-based integrated care versus hospital outpatient care for managing patients with complex type 2 diabetes: costing analysis. Aust Health Rev 2021;45:42-50. https://doi.org/10.1071/AH19226.

[22] De Marchi F, Contaldi E, Magistrelli L, Cantello R, Comi C, Mazzini L. Telehealth in Neurodegenerative Diseases: Opportunities and Challenges for Patients and Physicians. Brain Sci 2021;11:237. https://doi.org/10.3390/brainsci11020237.

Received on December 13, 2023. Accepted on June 6, 2024.

Correspondence: Irene Schenone, Regional Health Agency of Liguria (A.Li.Sa.), Genoa, Italy. E-mail: irene.schenone@alisa.liguria.it

How to cite this article: Ansaldi F, Astengo M, Battaglini A, Grammatico F, Marchini F, Fiorano A, Allegretti S, Schenone I, Amicizia D. A new organizational model of primary healthcare in Liguria, Italy. Insights and implications. J Prev Med Hyg 2024;65:236-E244. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3145

HEALTH CARE MANAGEMENT

Pandemic influenza preparedness plan in Liguria, Italy: a valuable tool for Public Health

DANIELA AMICIZIA[1,2,3], IRENE SCHENONE[2], CAMILLA STICCHI[2], FEDERICO GRAMMATICO[2], MATTEO ASTENGO[2], ALBERTO BATTAGLINI[2], FRANCESCA MARCHINI[2], MARIA FRANCESCA PIAZZA[2], SILVANO RUFFONI[2], GIOVANNI BATTISTA ANDREOLI[2], FILIPPO ANSALDI[1,2,3]

[1] Department of Health Sciences, University of Genoa, Italy; [2] Regional Health Agency of Liguria (Azienda Ligure Sanitaria - A.Li.Sa.), Genoa, Italy[3]; [3] CIRI-IT, University of Genoa Italy

Keywords

Influenza • Epidemiological surveillance • Pandemic preparedness • Influenza pandemic plan

Summary

As known, influenza presents a multifaceted challenge to public health, causing disease that ranges from mild cases to severe pandemics with significant morbidity and mortality. Effective pandemic preparedness demands a comprehensive strategy that integrates research, surveillance, response coordination and community engagement, to mitigate the impact of future health emergencies. The pandemic preparedness cycle involves dynamic, cyclical phases of preparation and response aimed at enhancing response capacity. Italy's 2021-2023 National Strategic-Operational Plan for Pandemic Influenza (PanFlu) incorporates lessons learned from past pandemics and serves as a framework for regional plans, such as Liguria's. The Ligurian plan delineates governance structures, surveillance strategies, healthcare services and communication measures necessary for effective pandemic management. It emphasizes the need to strengthen links between emergency structures, to avoid duplication and to adopt flexible approaches to scale actions appropriately and highlights the need for risk/benefit analysis to support evidence-based decision-making as well as clear guidance on data collection and communication activities. By integrating these elements, the region's overall readiness and resilience against influenza pandemics are expected to be reinforced.

Introduction

Influenza, a leading cause of upper and lower respiratory tract infections, holds significant epidemiological, clinical and socioeconomic implications for public health [1]. The seasonal epidemic trend of influenza is well-documented and the disease ranges from mild, self-limiting forms to acute respiratory conditions requiring hospitalization and, in critical cases, assisted ventilation [2].

There are four types of viruses (A, B, C, and D), with A and B causing acute disease in humans. Type A viruses, which are capable of major antigenic shifts, have been responsible for severe global pandemics and, as they cause high levels of morbidity and mortality, have the potential to pose a significant health risk and disrupt the community both socially and economically [3].

Both type A and, to a lesser extent, type B, can accumulate mutations, leading to variations in surface glycoproteins and resulting in the emergence of immunologically distinct viral strains (antigenic drift). Consequently, seasonal epidemics recur, and vaccines need to be updated according to the circulating mutated strain [4].

While type C viruses cause sporadic human cases, the more recently identified type D viruses infect swine and cattle; their involvement in human infections is unclear [5], though a study on human serum samples found an increase in the prevalence of antibodies against virus D following epidemics in animals [6].

Given its mutable nature and pandemic history, influenza poses a significant threat to all of us. Indeed, experts predict that a major influenza pandemic is likely to occur in the future, prompting global efforts in pandemic preparedness [7]. Moreover, the World Health Organization (WHO) has noted that the pandemic risk has increased, owing to population growth, closer human-animal proximity, and more frequent travel. Thus, in addition to establishing definitions to classify pandemic phases, since the late 1990s the WHO has urged member countries to develop pandemic response plans [8, 9].

Three major influenza pandemics occurred in the 20th century: in 1917, 1957 and 1968. The latest influenza pandemic, in 2009-2010, and the COVID-19 pandemic have further highlighted the ongoing risk and the unpredictability of pandemic events, emphasizing the need for comprehensive preparedness at local, national and global levels. The availability of a pandemic response plan offers the opportunity to strengthen preparations for the management of influenza and similar health threats. Coordinated regional actions and national communication are essential during a pandemic, as emphasized by the European Centre for Disease Prevention and Control [10].

A pandemic vaccine is crucial to reducing the impact of the disease, alongside interventions such as hand hygiene and the use of personal protective equipment, the primary goal being to prevent severe and complicated forms

of influenza and reduce premature mortality among individuals at risk of severe disease [11]. Moreover, several antiviral drugs that reduce symptom duration, infectious complications and influenza-associated mortality are available [12] and can be stocked by governments for use in the event of a pandemic.

Recently, Italy drew up its 2021-2023 National Strategic-Operational Plan for Pandemic Influenza (PanFlu) to replace previous pandemic influenza plans. Since then, each region, including Liguria, has had to contextualize the national document and formulate its own regional pandemic influenza plan. Here, we briefly present Liguria's regional pandemic influenza preparedness plan. Although not updated before COVID-19, it has now undergone revisions to address the ongoing risk and enhance regional readiness for future pandemics.

Influenza preparedness

In recent decades, there has been an increase in both smaller-scale outbreaks and large-scale pandemics caused by emerging infectious diseases, and scientists anticipate a rise in such events in the coming years [13]. Some evidence suggests that the probability of another pandemic occurring within our lifetime is about 17% and may increase to 44% within the next couple of decades [14].

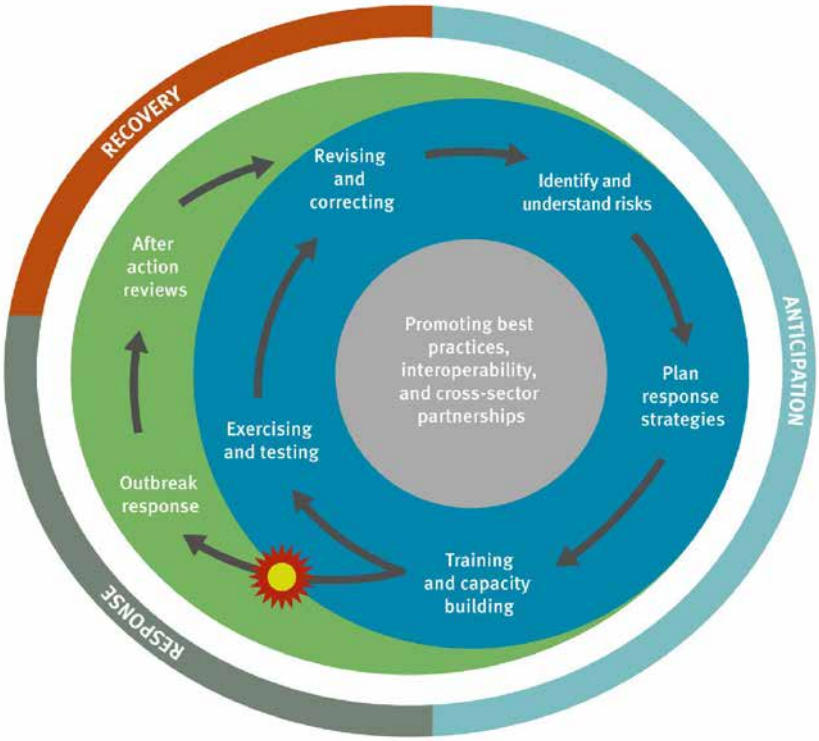
Hospitals and health professionals are accustomed to dealing with emergencies every day. However, sudden surges in the number of people seeking help, either from mass-casualty events or from outbreaks of infectious disease, are challenging to manage. Therefore, all hospitals and health agencies have established emergency plans to deal with such events. The possibility of a pandemic adds an extra dimension to emergency planning, potentially affecting the whole of society and requiring national coordination.

The WHO has initiated a global scientific process to update the list of priority pathogens/agents that can cause outbreaks or pandemics, in order to guide global investment, research and development, especially with regard to vaccines, tests and treatments. Targeting priority pathogens and virus families for research and the development of countermeasures is essential for a rapid and effective epidemic and pandemic response [15], although researchers agree that it is difficult to determine what pathogen will cause the next pandemic [16].

A pandemic will increase the demand for specialist skills, particularly in acute care, emergency medicine, patient transport services and intensive care, and will require dedicated staff, such as anaesthetists, emergency medicine specialists and intensive care nurses. There could also be an increased demand for specialist equipment, such as extracorporeal membrane oxygenation (ECMO). In the event of a pandemic, the demand for basic healthcare will also rise.

Pandemic preparedness, tailored to infectious disease emergencies of interest to Public Health, includes activities aimed at minimizing the risks posed by infectious diseases and mitigating their impact during a public health emergency, regardless of the extent of the event (local, regional, national, international). The pandemic preparedness cycle is a dynamic, cyclical

Fig. 1. Pandemic preparedness cycle from ECDC.



Tab. I. The main activities of the preparedness and response phases.

PREPAREDNESS	Interpandemic	• Definition of operational agreements/procedures for the development and maintenance of the plan • Apply sound strategies for the identification and management of pandemic influenza • Ensure ready availability for quick response • Monitor the emergence of diseases with pandemic potential, and investigate possibile outbreaks • Training of healthcare workers
RESPONSE	Alert	• Identify and characterize the nature of the disease, confirm the design of its governance • Train health workers • Communicate and raise awareness
	Pandemic	• Initial activities (when information about the disease is scarce): - Prepare and support the Regional Health System (SSR) - Manage initial cases - Identify and characterize the virus circulating in the area - Provide information to support best healthcare practices and enable the community and healthcare workers to manage their risk of exposure - Support effective governance • Targeted activities (when you have enough information about the disease to take specific measures): - Support and maintain quality care - Ensure an adequate response based on the pandemic phase - Provide a coordinated and coherent approach - Conduct immunization interventions with the pandemic vaccine preparation - Communicate to engage, empower and build trust in the community
	Transition	• Support and mantain quality care • Cessation of activities no longer necessary and transition to pre-emergency • Monitor a potential second wave of the epidemic • Monitor the development of antiviral resisteance • Communicate effectively • Evaluate systems and review plans and procedures

pathway of preparation for and response to emergencies. It involves the implementation of specific activities in the various pre- and post-emergency phases in order to improve response capacity (Fig. 1).

This continuous cycle is part of a broader system of prevention, response, recovery and mitigation of the emergency event. In each country, planning, coordination, timely diagnosis, assessment, investigation, response, and communication skills are required during a public health infectious emergency [17]. Indeed, pandemic preparedness requires comprehensive efforts right from the earliest stages of research to enable the effective development of countermeasures, monitor pandemic threats and coordinate the pandemic response in real time. Influenza pandemics are characterised by the global spread of a novel type of virus and may cause unusually high morbidity and mortality for an extended period [18]. A severe pandemic can overwhelm the resources of a society, owing to the exceptional number of people affected. However, it is crucial that action be initiated during non-pandemic times, as this enables a more effective response in subsequent phases of emergency [19]. The WHO defines four phases of the progression of an epidemic: inter-pandemic, alert, pandemic and transition phases. Each phase involves specific activities and responses.

In the inter-pandemic phase, normal epidemiological surveillance of influenza-like syndromes and influenza virology activities are expected. In the alert phase, once a new subtype of influenza virus has been identified in humans, higher levels of epidemiological and virological surveillance and careful risk assessment are required. If a potentially pandemic strain is not detected, such activities may be stepped down to the level of the inter-pandemic phase.

The transition between the inter-pandemic, alert and pandemic phases may occur rapidly or gradually, as indicated by global risk assessment, which is primarily based on virological, epidemiological and clinical data. The pandemic phase corresponds to the period of global spread of human influenza caused by a new subtype and requires precise actions.

The transition phase occurs with the decrease in global risk, and allows a de-escalation of actions, a reduction in national epidemic response activities and a shift towards recovery actions, based on country-specific risk

assessments. Table I reports the main activities, broken down by phases.

The COVID-19 pandemic revealed the need for clear, consistent, and reliable communications, especially in periods when misinformation goes viral. If people refuse vaccines or ignore public-health safety precautions, all other preparations become ineffectual. Thus, in order to ensure an effective, coordinated response to the next pandemic, it is necessary to foster public trust in the authorities that manage pandemic responses and in scientific and medical leaders. Those in power must therefore implement better, clearer and more coordinated communications than they did during the COVID-19 pandemic. Equally important is gaining broad agreement among policymakers that responding to public health crises requires working in partnership. The building of trust requires funding, commitment, intention and time, and must begin immediately if there is to be an effective response to the next pandemic [20, 21].

The impact of a pandemic on the community depends on factors such as clinical severity, transmissibility, and the healthcare system's ability to respond efficiently. Planning and coordination are therefore crucial to ensuring an effective response [22, 23]. In this context, the State-Regions Conference, in its session of January 25, 2021, sanctioned the agreement between the Government, the Regions and the autonomous Provinces of Trento and Bolzano on the national strategic-operational plan for preparation and response to an influenza pandemic (PanFlu 2021-2023) [24].

The overall goal of the Pandemic Influenza Plan is to enhance preparedness at the national and local levels so to protect the population, healthcare workers, essential services and economic activities. The plan updates and replaces previous Pandemic Influenza Plans and was prepared in conformity with the WHO recommendations. At the national level, it is based on the 2020-2025 National Prevention Plan and the 2017-2019 National Vaccine Prevention Plan.

To implement the plan, an extensive multidisciplinary and multi-sector institutional working group was formally established. Subsequently, considering the lessons learned from the 2009 pandemic and the COVID-19 pandemic, the document was collectively re-evaluated and revised by the main actors involved. This activity produced the final form of the document [24].

The 2021-2023 Pandemic Influenza Plan identifies the key actions to be implemented in the various operational areas over three years and defines the roles and responsibilities of the National Health Service in preparing for and responding to an influenza pandemic. This plan focuses on preparing for pandemic scenarios caused by influenza viruses. Four scenarios are envisaged: $Rt < 1$, $Rt = 1$, $Rt > 1.4$, $Rt > 1.7$.

This is an innovative, transitional plan that operates within a pandemic context in which international guidelines for pandemic preparedness are evolving; it therefore sets up new networks and introduces new ways of working. The regional pandemic plans derived from it are also recent.

The Liguria Region's plan is based on the recommendations laid down in the national plan [25]. The experience gained during the health emergency caused by COVID-19 constituted the basis of the regional plan to prepare the response to an influenza pandemic. To support decision-makers, the document specifies the key public health measures to be applied in Liguria during the various phases.

Since knowledge of any new influenza virus will be acquired over a variable timeframe, and the epidemiological scenario will be influenced by both the evolution of the epidemiological framework and the availability of new vaccines and effective technologies for detecting the new pathogen, these areas of primary interest will be periodically reviewed in order to ensure updated and comprehensive information.

Among the actions recommended, the epidemiological surveillance of influenza syndrome cases plays a crucial role in monitoring the pandemic's impact on the population and its evolving characteristics. This involves adopting the most effective control measures and assessing their efficacy. Equally important are the utilization and enhancement of the regional health system (RHS) and governance mechanisms and the exploitation of existing systems of prompt response to seasonal influenza.

The key principles guiding the plan are: (i) the strengthening of links between all the structures dedicated to emergencies by capitalizing on existing systems and avoiding unnecessary duplication; (ii) application of the plan in case the burden on healthcare facilities due to seasonal influenza increases), in order to preserve the RHS; (iii) the adoption of a flexible approach, whereby actions are scaled according to the phases and modulated to adapt to contingent needs; (iv) the implementation of risk/benefit analysis of the main public health measures that could be applied during the pandemic phase to support "evidence-based" decision-making; (v) the adoption of clear and detailed guidance on the collection of epidemiological and virological surveillance data, with particular emphasis on communication as a major component of response management.

A One Health approach to surveillance includes a dedicated focus on pathogens in wildlife, livestock and pets. Such surveillance provides early warnings of pathogens that have a pandemic potential and which could jump from animals to humans. In this regard, comprehensive monitoring systems need to provide accurate, timely and comprehensive information [26].

To support an integrated and coordinated response, the plan provides guidance on the roles and responsibilities of key health sectors. Additionally, it constitutes a reference for decision-makers and will be used to develop local operational plans.

Ligurian Plan

The regional technical committee for the "Strategic Operational Plan for the Preparation and Response to an Influenza Pandemic (PanFlu) 2021-2023" was established (A.Li.Sa. Resolution N° 165/2021) to contextualize the

actions to be implemented in Liguria and to draw up the regional influenza planning document [25].
Through A.Li.Sa. (Ligurian Health Agency), Liguria Region conducts activities of coordination and guidance for the various local health agencies (Aziende Sanitarie Locali, ASL), which are responsible for providing services throughout the Region in accordance with common guidelines. Additionally, it makes use of the activities of the Inter-Agency Regional Department (D.I.A.R.), which serves as the organizational tool for strategic planning, inter-organization integration and various activities of healthcare and social assistance.
The Regional Pandemic Committee coordinates the activities outlined in the 2021-2023 National Strategic Operational Plan for the Preparation and Response to an Influenza Pandemic (PanFlu) at the local level through constant cooperation with the Health Directors and General Directors of the Health Agencies.
For each phase, macro-areas of action, references, and types of activities have been defined, including governance, epidemiological and virological surveillance, preventive healthcare services, territorial healthcare assistance services, clinical management, hospital healthcare services, infection prevention and control measures, training and communication activities, and research and development [26].
After the adoption of Liguria Regional Plan, revision phases are expected. The preparedness cycle is a dynamic, cyclical process of preparation and response to emergencies and involves specific activities aimed at enhancing readiness in various pre- and post-emergency phases [12]. The WHO defines readiness as the ability to respond promptly and effectively to emergencies by implementing previously prepared actions. A simulation exercise, as defined by the European Centre for Disease Prevention and Control, is an activity guided by an evolving scenario, designed to practice the response, or elements of response, to an emergency event. PanFlu simulations are therefore carried out within the preparedness cycle. These simulation exercises are integral to the preparedness cycle, with the objective of assessing the 2021-2023 strategic-operational plan for preparation and response to an influenza pandemic.
The “Mosaico” simulation exercise is the first national, pandemic and public health simulation exercise of its kind in Italy and is expected to yield valuable insights for the future. Between January 16 and 19, 2023, the first of two simulation exercises (SIMEX), "Mosaico", took place, involving regional delegates, including those from Liguria. This was a national command-post simulation exercise (also known as functional) which enabled participants to remotely access and test existing systems, such as communications and computer tools. The goal of the simulation was to test the mechanisms for activating pandemic alerts and the functions of situation analysis and risk assessment. The “Mosaico” exercise allowed protocols to be revised and will result in a revision of the plan itself.
International guidelines for pandemic preparedness are evolving, with the WHO shifting its focus from influenza to respiratory pathogens. Although PanFlu remains valuable even in the event of pandemics caused by other X viruses, given the many overlaps, protocols are expected to evolve according to this new focus.

Conclusions

In conclusion, effective pandemic preparedness requires a comprehensive approach, ranging from the initial stages of research for the development of countermeasures to the continuous monitoring of potential pandemic threats and real-time coordination of response efforts.
Enhancing pathogen surveillance and monitoring is crucial for enabling early warnings and timely interventions The surveillance infrastructure should facilitate accurate, rapid and harmonised global reporting of data concerning novel viruses. As seen in the case of the COVID-19 pandemic, the benefits of global collaboration and data sharing around an emerging virus must be preserved and strengthened.
Epidemic risk monitoring will be achieved through the integration of surveillance systems that deal with epidemiological and virological data, healthcare service-related flows and positive-case mapping.
Proactive measures during non-pandemic periods are imperative to ensure a more robust response during emergencies. Accurate planning for primary healthcare, hospital response, the procurement of personal protective equipment, and comprehensive training and communication strategies is fundamental. Many of the recommendations may also apply to local and regional responses to other health emergencies, from smaller-scale disease outbreaks to biosecurity threats and weather-related catastrophes.

Conflict of interest statement

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

Not applicable.

Authors' contributions

FA and DA conceived and supervised the work. The review of international, national and regional documents was carried out by DA and IS. MA, AB, FG, FM and IS wrote the first draft of the manuscript. DA and IS had the final responsibility for the decision to submit for publication. All authors reviewed and edited the manuscript, contributed to the article and approved the version submitted.

References

[1] Calabrò GE, Boccalini S, Panatto D, Rizzo C, Di Pietro ML, Abreha FM, Ajelli M, Amicizia D, Bechini A, Giacchetta I, Lai PL, Merler S, Primieri C, Trentini F, Violi S, Bonanni P, de Waure C. The new Quadrivalent Adjuvanted Influenza Vaccine for the Italian elderly: a health technology assessment. Int J Environ Res Public Health 2022;19:4166. https://doi.org/10.3390/ijerph19074166.

[2] Gasparini R, Amicizia D, Lai PL, Panatto D. Influenza vaccination: from epidemiological aspects and advances in research to dissent and vaccination policies. J Prev Med Hyg 2016;57:E1-4.

[3] Taubenberger JK, Morens DM. Influenza: the once and future pandemic. Public Health Rep 2010;125(Suppl 3):16-26.

[4] Kim H, Webster RG, Webby RJ. Influenza Virus: Dealing with a Drifting and Shifting Pathogen. Viral Immunol 2018;31:174-83. https://doi.org/10.1089/vim.2017.0141.

[5] Trucchi C, Paganino C, Amicizia D, Orsi A, Tisa V, Piazza MF, Icardi G, Ansaldi F. Universal influenza virus vaccines: what needs to happen next? Expert Opin Biol Ther 2019;19:671-83. https://doi.org/10.1080/14712598.2019.1604671.

[6] Trombetta CM, Marchi S, Manini I, Kistner O, Li F, Piu P, Manenti A, Biuso F, Sreenivasan C, Druce J, Montomoli E. Influenza D Virus: Serological Evidence in the Italian Population from 2005 to 2017. Viruses 2019;12:30. https://doi.org/10.3390/v12010030.

[7] Dzau V, Yadav P. The influenza imperative: we must prepare now for seasonal and pandemic influenza. Lancet Microbe 2023;4:e203-e205. https://doi.org/10.1016/S2666-5247(23)00013-7.

[8] Spernovasilis N, Markaki I, Papadakis M, Tsioutis C, Markaki L. Epidemics and pandemics: Is human overpopulation the elephant in the room? Ethics Med Public Health 2021;19:100728. https://doi.org/10.1016/j.jemep.2021.100728.

[9] WHO. Available at https://www.who.int/health-topics/health-security#tab=tab_1 (Accessed on: 1/12/2023).

[10] European Centre for Disease Prevention and Control. Pandemic influenza. Available at: https://www.ecdc.europa.eu/en/pandemic-influenza (Accessed on: 11/12/2023).

[11] Fauci AS. Pandemic influenza threat and preparedness. Emerg Infect Dis 2006;12:73-7. https://doi.org/10.3201/eid1201.050983.

[12] WHO. Pandemic influenza. Global Influenza Programme. Pandemic influenza preparedness. Available at: https://www.who.int/teams/global-influenza-programme/public-health-preparedness (Accessed on: 11/12/2023).

[13] Williams BA, Jones CH, Welch V, True JM. Outlook of pandemic preparedness in a post-COVID-19 world. NPJ Vaccines 2023;8:178. https://doi.org/10.1038/s41541-023-00773-0.

[14] Marani M, Katul GG, Pan WK, Parolari AJ. Intensity and frequency of extreme novel epidemics. Proc Natl Acad Sci USA 2021;118:e2105482118. https://doi.org/10.1073/pnas.2105482118. Erratum in: Proc Natl Acad Sci USA 2023;120(12):e2302169120.

[15] WHO. WHO to identify pathogens that could cause future outbreaks and pandemics. Available at: https://www.who.int/news/item/21-11-2022-who-to-identify-pathogens-that-could-cause-future-outbreaks-and-pandemics (Accessed on: 11/12/2023).

[16] Williams BA, Jones CH, Welch V, True JM. Outlook of pandemic preparedness in a post-COVID-19 world. NPJ Vaccines 2023;8:178. https://doi.org/10.1038/s41541-023-00773-0.

[17] European Centre for Disease Prevention and Control. Why is pandemic preparedness planning important? Available at: https://www.ecdc.europa.eu/en/seasonal-influenza/preparedness/why-pandemic-preparedness (Accessed on: 2/12/2023).

[18] Oshitani H, Kamigaki T, Suzuki A. Major issues and challenges of influenza pandemic preparedness in developing countries. Emerg Infect Dis 2008;14:875-80. https://doi.org/10.3201/eid1406.070839.

[19] Dzau V, Yadav P. The influenza imperative: we must prepare now for seasonal and pandemic influenza. Lancet Microbe 2023;4:e203-e205. https://doi.org/10.1016/S2666-5247(23)00013-7.

[20] Creating a Communication Strategy for Pandemic Influenza. Creating a Communication Strategy for Pandemic Influenza. Available at: https://www.paho.org/en/file/25285/download?token=OFlngfvy (Accessed on: 11/12/2023).

[21] WHO. Outbreak communication: Best practices for communicating with the public during an outbreak. Available at: https://www.who.int/publications/i/item/outbreak-communication-best-practices-for-communicating-with-the-public-during-an-outbreak (Accessed on: 11/12/2023).

[22] Ridenhour B, Kowalik JM, Shay DK. Unraveling R0: considerations for public health applications. Am J Public Health 2014;104:e32-41. https://doi.org/10.2105/AJPH.2013.301704.

[23] Tan X, Yuan L, Zhou J, Zheng Y, Yang F. Modelling the initial transmission dynamics of influenza A H1N1 in Guangdong Province, China. Int J Infect Dis 2013;17:e479-84. https://doi.org/10.1016/j.ijid.2012.11.018.

[24] Minister of Health. Pandemic Influenza Plan 2021-2023. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_3005_allegato.pdf (Accessed on: 11/12/2023).

[25] Delibera di Giunta regionale n. 139/2022. "Approvazione Piano Regionale di preparazione e risposta ad una pandemia influenzale (PanFlu) 2021-2023". Available at: https://decretidigitali.regione.liguria.it/ArchivioFile/AMM2022139/REG_AMM_A_139_2022.pdf (Accessed on: 20/03/2024).

[26] US Centers for Disease Control and Prevention. One Health. Available at: https://www.cdc.gov/onehealth/index.html (Accessed on: 12/12/2023).

Received on December 14, 2023. Accepted on May 9, 2024.

Correspondence: Irene Schenone, Piazza della Vittoria 15 16121 Genova (GE), Italy. E-mail: irene.schenone@alisa.liguria.it

How to cite this article: Amicizia D, Schenone I, Sticchi C, Grammatico F, Astengo M, Battaglini A, Marchini F, Piazza MF, Ruffoni S, Andreoli GB, Ansaldi F. Pandemic influenza preparedness plan in Liguria, Italy: a valuable tool for Public Health. J Prev Med Hyg 2024;65:E245-E250. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3146

HEALTH CARE MANAGEMENT

Rethinking patient flows in a changing healthcare system: a unified approach

MARCO SCATTAGLIA[1], MICHELE MORANDI[1], MARIA GRAZIA VARÌ[2], FABRIZIO BERT[2]
[1] San Giovanni Bosco Hospital, Asl Città di Torino, Turin, Italy;
[2] Department of Public Health Sciences and Paediatrics, University of Turin, Turin, Italy

Keywords

Hospital • Patient flows • Appropriateness

Summary

Introduction. *The management of chronic diseases poses a challenge to the National Health Service (NHS), but it can also offer an opportunity for a radical renovation of healthcare provision. To improve the appropriateness of healthcare settings, it is essential to adopt integrated approach in all healthcare settings.*
Methods. *This study was conducted at San Giovanni Bosco Hospital, in the area of the "Città di Torino" Local Health Authority, between June 2021 and December 2022. Its main goal was to manage hospital patient flows in an integrated manner in order to improve the efficiency of the entire healthcare system. The data were examined in terms of effectiveness in optimizing hospital flows.*
Results. *The data indicated that hospital outpatient activities can become more specialized by leveraging the greater technological potential that a hospital possesses. At San Giovanni Bosco Hospital, the hub of the "Città di Torino" Local Health Authority (ASL), differential patient pathways were established in order to enhance the efficiency of the entire system by deploying hospital staff in a community setting. Implementation of the Otorhinolaryngology pathway avoided the hospitalization of 249 patients, who would otherwise have added strain to the overall organization of the hub hospital, which is currently short of space.*
Conclusions. *A significant effort is needed in order to build an integrated network that provides patients with reliable and stable references. The approach adopted at San Giovanni Bosco Hospital resulted in an improvement in the use of both hospital and territorial facilities.*

Introduction

Italy, like other developed countries, has an aging population [1, 2]. Moreover, in Northern Italy, the prevalence of people aged over 65 years is slightly higher than the national average. A similar trend can also be seen in the Piedmont Region [3]. This demographic evolution is expected to have an influence on morbidity, with an increase in the prevalence of chronic diseases and an impact on the National Health Service (NHS), which already faces significant challenges in treating chronic pathologies [4-7]. The growing complexity of chronic illnesses and their socio-economic implications emphasize the need to ensure continuity in care pathways and patient management. In this regard, a critical aspect is the accurate selection of the care setting and of the most suitable professionals, not only to ensure the efficiency of healthcare services but also to guarantee the overall quality of care and to improve the relationship between the healthcare service and those who receive medical treatments.
Haggerty et al. [8] have identified three forms of healthcare continuity: a) continuity of information, which involves the use of patient history to tailor treatments to specific needs; b) continuity of management, which involves adopting a consistent and appropriate approach to coping with disease in such a way as to meet evolving patient needs; c) relational continuity, which means fostering an uninterrupted therapeutic relationship between the patient and one or more healthcare providers. The actual achievement of these objectives is challenging because, in addition to considerable personal contact with patients, it would require a substantial revision of how healthcare services are delivered and the adoption of strategies for both hospital and community care [9-11]. In order to implement an effective governance project in this context, it is essential to adopt a systemic and integrated approach by involving the stakeholders of the healthcare system and by requiring coordinated collaboration among all parties involved [12]. The Italian healthcare organization, despite its good intentions, is still predominantly "hospital-centered". Diseases which require healthcare continuity are on the rise, while the current service organization struggles to efficiently manage early patient discharges.
To ensure economic efficiency and the overall quality of care, the accurate selection of the care setting and of professionals is fundamental, and must consider both professional expertise and access to technologies and services. Moreover, overcoming the traditional opposition between hospitals and community care facilities requires cultural, organizational and operational changes in order to promote a more integrated approach in all healthcare contexts.
However, in this scenario of demographic changes and healthcare challenges, opportunities arise from the Next Generation EU Program and the promotion of a "One Health" approach [13]. Indeed, within the framework of

Mission 6 Health in the National Recovery and Resilience Plan (PNRR), which is part of the next generation EU program, Component 1 (Proximity Networks, Facilities and Telemedicine for Territorial Healthcare) aims to establish proximity networks to enhance territorial healthcare, in accordance with a "One Health" approach. Planned initiatives already include various actions to create and/or enhance local healthcare facilities and establish new standards for territorial healthcare [14]. For example, new Community Houses will be built: places where citizens will have rapid and easy access to primary healthcare services or other basic clinical services (*e.g.* physiotherapy, dietology, radiology, blood tests). The planned initiatives also include Community Hospitals – facilities that play an intermediate role between home care and hospital admission – with the aim of avoiding unnecessary hospitalizations or facilitating safe discharge to places more suited to the patient's clinical condition.

To implement this strategy, it is necessary to establish a suitable institutional and organizational framework, the main goal being to integrate the National Health Service into a broader context of well-being, as per the European standards. In this regard, a promising strategy is to establish dedicated outpatient clinics. Indeed, adopting integrated organizational approaches among different care settings can significantly improve the appropriateness of care by directing hospital outpatient activities towards specialized functions and by fully leveraging the technological potential of hospital facilities [14]. This solution is essential to creating integrated care pathways between the community and the hospital, offers a variety of care settings and reduces hospital overcrowding.

To move beyond the dual hospital-community structure of care, it is necessary to effect cultural, organizational and operational changes. What has been done at San Giovanni Bosco Hospital, the hub of the *"Città di Torino"* Local Health Authority (ASL), is aimed at designing targeted pathways, in order to streamline hospital flows and ensure optimal patient management at the territorial level. A further aim is to enable hospital personnel to work within community houses and with healthcare professionals who operate in this setting, thus promoting greater cohesion between the hospital and community care.

Methods

This study was conducted at San Giovanni Bosco Hospital, in the *"Città di Torino"* Local Health Authority. Its main goal was to design and manage patient flows in an integrated manner, so as to improve the efficiency of the entire healthcare system by focusing on the hospital and the community.

Several healthcare pathways were created in order to reduce patient flows in the hospital: the establishment of outpatient clinics for the Continuity of Oncological Care, Cardio-oncology, Hematology (2 clinics), Endometriosis, managed by a hospital gynecologist, Clinical Psychology, Audio-Vestibology and Otorhinolaryngology (ENT).

To assess the impact of these healthcare pathways, we analyzed the access records of patients with a diagnosis of neoplasia and the number of examinations and diagnostic tests performed. These data were examined in terms of effectiveness in optimizing hospital flows and ensuring better patient care.

Results

The main goal was to design and manage patient flows in such a way as to optimize the overall efficiency of the healthcare system through the involvement of the hospital staff at a territorial level.

The healthcare pathways under study necessitated the establishment of several outpatient clinics:

a Continuity of Oncological Care clinic, managed by a hospital oncology specialist and a psycho-oncologist; a Cardio-oncology clinic, which focuses on monitoring cardiotoxicity induced by chemotherapy: patients requiring routine checks for this specific issue are managed in this outpatient context; two Hematology clinics: one is dedicated to chronic patients with a priority class of P or D, indicating that treatment is to be provided within 120 and 30 days, respectively, while the other is reserved for patients with a priority class of B or U, indicating treatment to be administered within 10 days and within 72 hours, respectively; an Endometriosis clinic managed by a hospital gynecologist; a Clinical Psychology clinic, which provides a service both for oncology patients already followed up and supported during hospitalization and for grieving caregivers; an Audio-Vestibology clinic for the care and follow-up of patients and for the surveillance of the most vulnerable subjects, with patients being referred to second-level hospital audiology when necessary; and an ENT clinic managed by hospital staff, for the follow-up of oncology patients.

The ENT Outpatient Clinic emerged as the most successful, in that a third of oncology patients were involved were redirected to a community care facility. Specifically, one third of the patients with an ENT oncological desease diagnosed in San Giovanni Bosco Hospital were examined in the community outpatient facilities, which had been established to improve patient flows and the efficiency of the healthcare system by deploying hospital staff in a community setting. Starting from June 9, 2021, 249 examinations involved patients diagnosed with neoplasia who underwent follow-up visits and related diagnostic tests, such as laryngoscopy, at the outpatient clinics of the North-West District of the Local Health Authority of the City of Turin. This initiative helped to significantly reduce the number of patient admissions to the hospital, thereby improving its overall organization, especially since this hub hospital has space limitations. The experience terminated on December 21, 2022, in order to allow refurbishment work in the community clinics to enhance their capacity

to accommodate a growing number of patients. In January 2024, the new outpatient clinic dedicated to oncology patients became available and is managed by the medical staff of San Giovanni Bosco Hospital.

Discussion

Ongoing demographic changes in Italy are profoundly reshaping the national healthcare system, which is upon to cope with a notable increase in the prevalence of chronic diseases. Consequently, the National Health Service is faced with an increasingly heavy burden. To alleviate this burden, greater efforts should be made to improve the healthcare system's ability to manage certain patient categories. Moreover, the recent COVID-19 pandemic acted as a catalyst, impacting on the organization of both hospital and territorial healthcare [15-18]. Indeed, it is well documented that hospital admissions and examinations, also for oncological patients, decreased, especially during the first pandemic wave [26-30]. Despite the gradual post-COVID improvements, many challenges persist, and the current healthcare scenario remains far below pre-pandemic levels.

Moreover, general underfunding of the National Health Service is contributing to its progressive deterioration, which makes it difficult to ensure essential services. Indeed, waiting lists are getting longer, while emergency rooms are increasingly crowded and there is often a delay in providing timely assistance. The increased admission rate during the post-pandemic period, which has resulted in an increased patient flow in hospital facilities, could be partially offset by focusing on territorial care [2, 19]. In San Giovanni Bosco Hospital, we have tried both to redirect the growing patient flow resulting from efforts to tackle the backlog of services not performed during the pandemic and to respond to new health needs. This has involved the use of facilities other than hospital ones, albeit with the deployment of hospital staff.

Managing complex patients within a continuum of care requires a transitional approach that includes a set of actions aimed at ensuring continuity of care when patients are transferred from one location to another, or moved through different levels of care within the same setting [20]. The Ministry of Health has strongly supported the need to identify organizational models for managing patients in chronic rehabilitative phases by using alternative healthcare settings and not just dedicated facilities [21]. In addition to demographic changes and the increase in the elderly population, there has been a clear transformation in healthcare demand. Local settings must therefore ensure sufficient care for all patients, especially those who are chronic, disabled or elderly, and must in turn seek to strengthen primary care systems [22, 23]. New, highly integrated services have therefore emerged, in order to avoid excessive hospital admissions and to take care of patients by providing the best support to meet their needs [9, 14].

In this scenario, particularly within San Giovanni Bosco Hospital, a more holistic approach to healthcare has been adopted, which overcomes the traditional hospital-community care dichotomy. Certain strategies can be implemented in order to reduce hospital overcrowding, shorten waiting times in specific subgroups, minimize the possibility of errors and improve the perceived quality of assistance [24, 25]. A key goal of hospital-territory integration is to provide specialized outpatient care, which must be organized within a perspective of unity and continuity.

The positive experience of the ENT clinic can serve as an example of successful management, as a third of oncology patients were effectively involved in a territorial care program. The implementation of dedicated clinics supported by hospital staff improved the appropriateness of care settings, reduced hospital overcrowding and ensured better patient care. However, building an integrated network within which the patient has reliable and stable references requires considerable effort and clear criteria regarding who should be taken care of, by whom, and in which facilities. Indeed, through the integration of hospital specialists into territorial healthcare, patients who do not necessarily need hospital treatment can receive appropriate care. Moreover, this approach ensures the professional quality of specialists outside hospital facilities, which will, in turn, promote greater cohesion between the hospital and the territory. The hospital physician who interacts with the territorial network and with professionals in the field will contribute to the much-needed pooling of skills and resources.

A possible limitation of this study is that the data concerned a specific hospital context and may not be generalizable to all healthcare settings.

Conclusions

The positive result obtained at the ENT outpatient clinic is likely to serve as the foundation for future expansions, and even more effective and systematic patients care is envisioned. This goal will be achieved through the introduction of a multidisciplinary team in outpatient activities, for instance through the integration of the upcoming Community House.

These results indicate that the creation of outpatient care pathways in the community care setting can improve the management of hospital resources, increase access to healthcare services and ensure more comprehensive care for oncology patients. Another important element is patients' perception that territorial facilities can provide the quality of care that is normally available in a hospital, and therefore that they do not need to go to the hospital. Furthermore, by working in territorial facilities, the hospital specialist can experience the territorial reality and collaborate with local professionals, such as the general practitioner (GP), and other non-medical healthcare personnel. In sum, this approach promotes greater cohesion between the hospital environment and the territory, and contributes to a more integrated and patient-centered healthcare system.

Acknowledgments

We would like to thank Prof. Giovanni Succo and Dr. Laura Ferrara for their support in this study.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MS, FB and MM: conceptualization. MS, FB and MM: methodology. MS, MGV, FB and MM: writing-original draft preparation. MS, MM, and MGV: writing-review and editing. MS, FB and MM: supervision. MS, MGV, FB and MM share last authorship: project administration. All authors have read and agreed to the published version of the manuscript.

References

[1] United States Census Bureau. An Aging World: 2008. Census.gov. Available at: https://www.census.gov/library/publications/2009/demo/p95-09-1.html (Accessed on: 20/01/2023).

[2] Rapporto annuale 2023 - La situazione del Paese. Available at: https://www.istat.it/it/archivio/286191 (2023) (Accessed on: 30/06/2023).

[3] Il Censimento permanente della popolazione in Piemonte Anno 2021. Available at: https://www.istat.it/it/files//2023/09/Piemonte_Focus-2021_Censimento-permanente.pdf (Accessed on: 30/06/2023).

[4] Eurostat. Statistics Explained: population structure and ageing. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing#The_share_of_elderly_people_continues_to_increase (Accessed on:25/10/2023.

[5] Statistics | Eurostat. Population structure indicators at national level. Available at: https://ec.europa.eu/eurostat/databrowser/view/DEMO_PJANIND__custom_964289/bookmark/map?lang=en&bookmarkId=1276db8f-938f-4f55-a801-e0151d01702f (Accessed on: 25/10/2023).

[6] Demography 2023 edition - Interactive publications - Eurostat. Available at: https://ec.europa.eu/eurostat/web/interactive-publications/demography-2023 (Accessed on: 25/10/2023).

[7] Istat Annuario Statistico Italiano 2022. Capitolo 4. Sanità e Salute. Available at: https://www.istat.it/storage/ASI/2022/capitoli/C04.pdf (Accessed on: 25/10/2023).

[8] Haggerty JL, Reid RJ, Freeman GK, Starfield BH, Adair CE, McKendry R. Continuity of care: a multidisciplinary review. BMJ 2003;327:1219-21. https://doi.org/10.1136/bmj.327.7425.1219.

[9] Coleman, E. A., Boult, C., & American Geriatrics Society Health Care Systems Committee. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc 2003;51:556-7. https://doi.org/10.1046/j.1532-5415.2003.51186.x.

[10] Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc 2004;52:675-84. https://doi.org/10.1111/j.1532-5415.2004.52202.x. Erratum in: J Am Geriatr Soc 2004;52:1228.

[11] Coleman EA, Smith JD, Frank JC, Min SJ, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the Care Transitions Intervention. J Am Geriatr Soc 2004;52:1817-25. https://doi.org/10.1111/j.1532-5415.2004.52504.x.

[12] Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22. https://doi.org/10.1016/S0140-6736(20)30925-9. Erratum in: Lancet 2020;396:1562.

[13] Gazzetta Ufficiale. Piano Nazionale di Ripresa e Resilienza. Decreto-Legge 24 febbraio 2023. Available at: https://www.gazzettaufficiale.it/eli/id/2023/02/24/23G00022/sg (Accessed on: 30/06/2023).

[14] Gazzetta Ufficiale. Decreto 23 maggio 2022, n. 77. Available at: https://www.gazzettaufficiale.it/eli/id/2022/06/22/22G00085/sg (Accessed on: 28/06/2023).

[15] Savioli G, Ceresa IF, Gri N, Bavestrello Piccini G, Longhitano Y, Zanza C, Piccioni A, Esposito C, Ricevuti G, Bressan MA. Emergency Department Overcrowding: understanding the factors to find corresponding solutions. J Pers Med 2022;12:279. https://doi.org/10.3390/jpm12020279.

[16] Ackroyd-Stolarz S, Guernsey JR, MacKinnon NJ, Kovacs G. The association between a prolonged stay in the emergency department and adverse events in older patients admitted to hospital: a retrospective cohort study. BMJ Qual Saf 2011;20:564-9. https://doi.org/10.1136/bmjqs.2009.034926.

[17] Pines JM, Pollack CV Jr, Diercks DB, Chang AM, Shofer FS, Hollander JE. The association between emergency department crowding and adverse cardiovascular outcomes in patients with chest pain. Acad Emerg Med 2009;16:617-25. https://doi.org/10.1111/j.1553-2712.2009.00456.x.

[18] Pines JM, Shofer FS, Isserman JA, Abbuhl SB, Mills AM. The effect of Emergency Department crowding on analgesia in patients with back pain in two hospitals. Acad Emerg Med 2010;17:276-83. https://doi.org/10.1111/j.1553-2712.2009.00676.x.

[19] Rapporto Osservasalute 2022. Stato di salute e qualità dell'assistenza nelle regioni italiane. https://osservatoriosullasalute.it/wp-content/uploads/2023/06/ro-2022-volume_completo.pdf.

[20] Boockvar K, Vladeck BC. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc 2004;52:855-6. https://doi.org/10.1111/j.1532-5415.2004.52230_15.x.

[21] Ministero della Salute-Commissione Consultiva. Piano per il miglioramento del sistema emergenza/urgenza 2005. Availabe at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_856_allegato.pdf (Accessed on: 28/06/2023).

[22] Shepperd S, Iliffe S, Doll HA, Clarke MJ, Kalra L, Wilson AD, Gonçalves-Bradley DC. Admission avoidance hospital at home. Cochrane Database Syst Rev 2016;9:CD007491. https://doi.org/10.1002/14651858.CD007491.pub2.

[23] Sorlini M, Perego L, Silva S, Marinoni G, Zucchi A, Barbaglio G, Azzi M. Il modello CReG (Chronic Related Group) di presa in carico territoriale della cronicità: esperienza pilota dell'ASL di Bergamo - fase progettuale. Ig Sanita Pubbl 2012;68:841-61.

[24] De Koning ER, Boogers MJ, Beeres SL, Kramer ID, Dannenberg WJ, Schalij MJ. Managing Hospital Capacity: Achievements and Lessons from the COVID-19 Pandemic. Prehosp Disaster Med 2022;37:600-8. https://doi.org/10.1017/S1049023X22001169.

[25] Kenny JF, Chang BC, Hemmert KC. Factors Affecting Emergency Department Crowding. Emerg Med Clin North Am 2020;38:573-87. https://doi.org/10.1016/j.emc.2020.04.001.

[26] Di Martino G, Cedrone F, Di Giovanni P, Romano F, Staniscia T. Impact of COVID-19 pandemic on oncological surgery activities: a retrospective study from a Southern Italian Region. Healthcare (Basel) 2022;10:2329. https://doi.org/10.3390/healthcare10112329.

[27] Van Dusen RA, Abernethy K, Chaudhary N, Paudyal V, Kurmi O. Association of the COVID-19 pandemic on stroke

admissions and treatment globally: a systematic review. BMJ Open 2023;13:e062734. https://doi.org/10.1136/bmjopen-2022-062734.

[28] Roth GA, Vaduganathan M, Mensah GA. Impact of the COVID-19 pandemic on cardiovascular health in 2020: JACC state-of-the-art review. J Am Coll Cardiol 2022;80:631-40. https://doi.org/10.1016/j.jacc.2022.06.008.

[29] de Lange M, Carvalho AS, Brito Fernandes Ó, Lingsma H, Klazinga N, Kringos D. The Impact of the COVID-19 Pandemic on Hospital Services for Patients with Cardiac Diseases: A Scoping Review. Int J Environ Res Public Health 2022;19:3172. https://doi.org/10.3390/ijerph19063172.

[30] Angelini M, Teglia F, Casolari G, Astolfi L, Boffetta P. Decrease of visits and hospital admissions for cancer patients during the COVID-19 pandemic. A systematic review and meta-analysis. Z Gesundh Wiss 2023 Mar 16:1-7. https://doi.org/10.1007/s10389-023-01857-w.

Received on December 5, 2023. Accepted on March 28, 2024.

Correspondence: Marco Scattaglia, Ospedale San Giovanni Bosco, Piazza dei Donatori di Sangue, 3, Torino, Italy. E-mail: marco.scattaglia@aslcittaditorino.it

How to cite this article: Scattaglia M, Morandi M, Varì MG, Bert F. Rethinking patient flows in a changing healthcare system: a unified approach. J Prev Med Hyg 2024;65:E251-E255. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3138

HEALTH CARE MANAGEMENT

Violence against healthcare workers during the phases of the COVID-19 Pandemic: a descriptive observational study from 2018 to 2023 in the metropolitan city of Genoa (North-Western Italy)

GLORIA SPATARI[1], ANNA MARIA LIBERA DE MITE[2], ELISA CANTOVA[2], SILVIA REGGIANI[2], MICHELA RE[2], MICHELANGELO MERCOGLIANO[3], MARIA DE MARTINI[2], NADIA CASANOVA[2], ALESSANDRO GALLO[2], MARTA CALTABELLOTTA[2], BRUNA REBAGLIATI[2]

[1] Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; [2] Asl3 Healthcare System of the Liguria Region, Genoa, Italy; [3] Department of Public Health, University "Federico II" of Naples, Naples, Italy

Keywords

Healthcare workers • Violence • COVID-19 • Pandemic • Aggression

Summary

Background. *Violence against healthcare workers is an escalating public health concern, affecting the quality of care, and causing significant psychological and physical effects on healthcare professionals. This study analysed the trend in aggressions in healthcare settings in the pre-pandemic, pandemic, and post-pandemic periods.*

Methods. *An observational descriptive study was conducted to analyse reports of violence against healthcare workers from January 2018 to June 2023 at a Local Health Authority "ASL3" in the Liguria region of Italy. The study considered variables such as the severity of aggression, professional category involved, and location of incident. Episodes of violence were classified according to severity by means of a colour-coded system. We used multinomial logistic regression to examine any associations between the pandemic phase and the various factors, while controlling for relevant variables.*

Results. *The number of reported aggressions rose from 48 in 2018 to 90 in 2022, with a partial count of 35 in the first half of 2023. The pandemic phase saw a rise in incidents classified as Green codes, which accounted for 58.3%, and a significant involvement of District Services. The post-pandemic phase showed a reversion to pre-pandemic levels but with an increase in Yellow codes (5.6%). Nurses were the most frequent victims, with figures ranging from 50.8% to 95.6% over the years. The Emergency Department and Psychiatric Services emerged as the most critical settings of aggressions, with incidents recorded in these areas constituting over half of the total number. However, an increase in violence was also recorded in district healthcare settings during the post-pandemic phase.*

Conclusions. *There is an urgent need for comprehensive strategies for the prevention of violence in healthcare settings. The increasing trend in violence, especially during the pandemic, necessitates integrated approaches that encompass training, psychological support, security policies, and a strong organizational culture to promote safety and respect. Protecting healthcare workers is crucial to their wellbeing and the quality of healthcare delivery.*

Introduction

Violence against healthcare workers has adverse effects on the quality of their work, causing psychological stress and sleep disturbances, and negatively impacting healthcare provider-patient relationships. Indeed, it significantly affects healthcare settings and the overall quality of care [1-5]. The European Observatory on Risks of the European Agency for Safety and Health at Work (EU-OSHA) has identified violence and harassment as emerging psychosocial risks in terms of safety and health, especially in the healthcare sector, where staff are often exposed to threats and aggressions. In EU member States, workplace violence often goes unrecognised [6]. However, systematic reviews indicate that 60-70% of healthcare workers encounter violence, either physical or psychological, with approximately one-third suffering physical violence [7, 8]. These data underscore the urgent need to address this issue.

Interestingly, the frequency and the reporting of episodes of violence in healthcare settings vary markedly from one country to another. Anglo countries, such as Australia, Canada, England, Ireland, New Zealand, Scotland, and the United States show higher reporting rates; this may be due to greater awareness, and lower tolerance of the phenomenon [7]. In Europe, by contrast, reporting rates are lower, which may reflect a different culture or lower awareness of workplace violence. In this regard, a systematic review conducted in Spain has confirmed that, despite an increasing trend in recent years, episodes of violence are rarely reported and recorded [1-5, 7, 9]. In the United States, violence against healthcare workers is particularly problematic in Emergency Departments, with about one-quarter of physicians experiencing physical violence, and 78% of emergency room physicians reporting some form of violence in the past year [10-13]. In Italy, according to the Ministry of Health's data, reports of violent acts have

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3143

dramatically increased in the last 15 years, suggesting that the phenomenon is growing. The occurrence of a single case of violence is sufficient to trigger an audit, as it indicates organizational deficiencies and insufficient awareness of the potential danger of violence within healthcare facilities [14].

A crucial aspect is the widespread underreporting of incidents [15]. According to previous literature, only a small fraction of incidents is reported to the authorities [16]. Underreporting may be due to the perception that the risk of violence is a normal part of healthcare work [17-22], to the lack of organizational support [10, 23-25], and to the fear of consequences of reporting. Some healthcare workers may also feel too ashamed or afraid of the judgment of others to report being victims of violence [18, 26-28]. A study conducted in Istanbul revealed that about 80% of nurses did not report episodes of violence and felt more supported by their colleagues than by the healthcare authorities [29]. Additionally, healthcare staff may be unaware of reporting policies and procedures [30, 31].

To effectively address these issues, an integrated approach is necessary; this must include awareness-raising, training, and the promotion of a culture of safety. Moreover, it is essential to ensure the availability of accessible and confidential reporting procedures nationwide. In response to these needs, in 2007, the Italian Ministry of Health drafted the document "Recommendation for Preventing Acts of Violence against Healthcare Workers" [32]. During the COVID-19 pandemic, healthcare professionals played a central role in safeguarding public health, especially in emergency situations. Paradoxically, this increased the risk of aggression and violence [33, 34].

This observational study investigated trends in violence against healthcare workers in a Local Health Authority in the Liguria region from 2018 to 2023, focusing on pandemic-related changes.

Materials and methods

Study design

We conducted an observational descriptive study on violent episodes against healthcare workers in a Local Health Authority in Liguria, Italy, from 2018 to 2023, and compared the data collected before, during and after the COVID-19 pandemic. The study used data that were completely anonymised and routinely collected by the healthcare organisation for administrative and reporting purposes. The research adhered to robust research practices, and was aligned with the principles of the Declaration of Helsinki.

Collection of reports

In Local Health Authority 3 (ASL3) - Liguria Region Healthcare System, a specific procedure for reporting and managing acts of aggression against healthcare workers has been implemented, as outlined in the resolution "Recommendations for Preventing Acts of Violence Against Healthcare Workers" ("Raccomandazioni per prevenire atti di violenza nei confronti degli operatori"; third revision published on December 24, 2019).

The reporting procedure involves filling in a form, which is available on the corporate intranet. In cases of violence, affected healthcare workers complete this form, and send it to several key individuals within the organization, including the Director/Manager of their own Operational Unit, the Director of the Department concerned, the Manager of the Prevention and Protection Service, and the secretariats of the various Departments involved, depending on the location of the incident.

Upon receiving the report, the Director/Manager of the Operational Unit where the incident occurred is responsible for organizing an internal audit. This audit involves all relevant personnel and the safety representative. It is aimed at analysing the incident and identifying preventive and corrective strategies. The Prevention and Protection Service, upon receiving the report, plans, and activates corrective actions, which may include meetings at the location of the incident. Furthermore, in the presence of a "sentinel event", the Service sends a formal communication to the Clinical Risk Management Department. The Clinical Risk Management Department, in response to a sentinel event, activates the procedures outlined in the Ministerial Recommendation "Reporting and Management of Sentinel Events" [14].

Study variables

The study analysed reports collected by ASL3 from January 1, 2018, to June 30, 2023. From these reports, we extracted data on the number of individuals assaulted in cases of aggression involving more than one healthcare worker in a single incident. The data collected from the reporting form included details such as the context of the event (location, date, time), the roles and qualifications of the healthcare workers involved, whether the aggressor was previously known to the service, and the types of aggression experienced. Roles and qualifications are listed as: Medical Doctors, Nurses, Health Care Assistants, and Other Health Staff, such as prevention technicians, pharmacists, psychologists, radiology technicians, social workers, security guards, and administrative staff.

Within the Local Health Authority's jurisdiction, there are 6 Health Districts, each with outpatient services and facilities. The area is served by 4 hospitals, which include a variety of wards; one of these hospitals has an emergency department. Psychiatric services are available in all 6 districts: in 2 of the hospitals, and in various care centres throughout the territory [35].

In Italy, COVID-19 was declared an emergency on January 31, 2020 [36], signalling the beginning of the pandemic phase; the state of emergency was revoked on March 31, 2022 [37]. To ensure a coherent analytical framework and facilitate a consistent annual comparative analysis, considering that access to healthcare services can vary with the change in seasons and annual period, we divided the study period into three phases; the first

phase (2018 and 2019) was defined as pre-pandemic, *i.e.* before the pandemic's extensive socio-economic and public health ramifications; the second phase (2020 and 2021) was defined as the pandemic phase, *i.e.* when stringent emergency measures were in force, notably social distancing and mobility restrictions; the third, or post-pandemic phase, encompassed the years 2022 and 2023, when restrictions were substantially relaxed and large-scale vaccination had significantly mitigated the pandemic's public health impact.

Classification of violent episodes

Violent episodes were classified according to severity by means of a colour-coded system: White code (for verbal aggression, possession of dangerous objects, without use), Green code (brandishing objects, personal insults or threats), Yellow code (non-violent physical contact), and Red code (actual physical violence), in addition to any other damage caused by the aggressor within the facility (Tab. I).

Tab. I. Colour-coded classification of aggression against healthcare workers.

Colour-coded categories	Description
White	Verbal aggression.
	Possession of dangerous objects, without use.
Green	Brandishing objects, personal insults, or threats.
Yellow	Non-violent physical contact.
Red	Actual physical violence.

Colour-coded classification of aggression against healthcare workers in accordance with "Recommendations for Preventing Acts of Violence Against Healthcare Workers" of Local Health Authority (ASL) 3 - Liguria Region Healthcare System

Statistical Methods

To analyse the data collected, we adopted a descriptive approach in order to provide a clear and detailed overview of violent episodes, and their characteristics. To investigate the relationship between the phase of the pandemic and profession, place, and colour code, we conducted a multinomial logistic regression analysis. We controlled for month of the year, time of day, and whether the aggressor was known to the healthcare staff. Additionally, we controlled for profession, place, and colour code, but only when these were not the specific outcome variable under investigation. Results are presented as regression coefficients (Coeff.), and 95% confidence intervals (95% CI). Analyses were performed by means of Stata 15.0 MP.

Results

The characteristics of aggressions are presented in Table II.

Description of incidents over the years

In 2018, 48 incidents of aggression were reported. These incidents were classified by severity codes: White codes (20.8%), Green codes (39.6%), Yellow codes (18.8%), and Red codes (20.8%). The majority of the personnel involved were Nurses (87.5%), followed by Medical Doctors (8.3%), Health Care Assistants (2.1%), and Other Healthcare Staff (2.1%). A significant portion of these incidents (58.3%) occurred in the Emergency Department, with others happening in Psychiatric Services (37.5%) and District Services (4.2%). Notably, in approximately 60.4% of cases, the aggressor was already known to the healthcare service.

In 2019, 107 incidents of aggression were recorded: White codes (22.4%), Green codes (38.3%), Yellow codes (17.8%), and Red codes (21.5%). The personnel involved varied, with 64.5% being Nurses, 18.7% Medical Doctors, 5.6% other health staff, and 11.2% Health Care Assistants. These incidents occurred in various healthcare settings, including the Emergency Department (18.7%), Psychiatric Services (50.5%), District Services (8.4%), and Hospital Wards (22.4%). In 76.6% of cases, the aggressor was known to the healthcare service.

In 2020, 63 incidents of aggression were registered: White codes (19.1%), Green codes (47.6%), Yellow codes (7.9%), and Red codes (25.4%). The majority of personnel affected were Nurses (50.8%), followed by Medical Doctors (34.9%), Health Care Assistants (12.7%), and Other Healthcare Staff (1.6%). Incidents occurred in various healthcare settings, including the Emergency Department (14.3%), Psychiatric Services (71.4%), District Services (12.7%), and Hospital Wards (1.6%). In 82.5% of cases, the aggressor was known to the healthcare service.

In 2021, 52 incidents of aggression were reported: White codes (9.6%), Green codes (71.2%), Yellow codes (5.8%), and Red codes (13.5%). The personnel involved were: Nurses (50.0%), Medical Doctors (30.8%), Health Care Assistants (9.6%), and Other Healthcare Staff (9.6%). The majority of these incidents occurred in District Services (38.5%), followed by Psychiatric Services (30.8%), the Emergency Department (11.5%), and Hospital Wards (19.2%). In 2021, 76.9% of aggressors was known to the healthcare service.

In 2022, there were 90 documented incidents of aggression: White codes (13.3%), Green codes (54.4%), Yellow codes (5.6%), and Red codes (26.7%). Nearly all the personnel involved were Nurses (95.6%), with a smaller percentage of Medical Doctors (4.4%). Incidents occurred in various healthcare settings: the Emergency Department (31.1%), Psychiatric Services (22.2%), District Services (24.4%), and Hospital Wards (22.2%). In 63.3% of cases, the aggressor was known to the healthcare service.

In the first half of 2023, there were reports of 36 incidents of aggression: White codes (36.1%), Green codes (47.2%), Yellow codes (5.6%), and Red codes (11.1%). The personnel involved were Nurses (58.3%), Medical Doctors (30.6%), Health Care Assistants

Tab. II. Characteristics of reported aggressions.

	Total	2018	2019	2020	2021	2022	2023	Pre-pandemic	Pandemic	Post-pandemic	χ^2 test
N	*396*	*48*	*107*	*63*	*52*	*90*	*36*	*155*	*115*	*126*	
Colour Code											
White	76	10	24	12	5	12	13	34	17	25	0.003
%	*19.2*	*20.8*	*22.4*	*19.1*	*9.6*	*13.3*	*36.1*	*21.9*	*14.8*	*19.8*	
Green	193	19	41	30	37	49	17	60	67	66	
%	*48.7*	*39.6*	*38.3*	*47.6*	*71.2*	*54.4*	*47.2*	*38.7*	*58.3*	*52.4*	
Yellow	43	9	19	5	3	5	2	28	8	7	
%	*10.9*	*18.8*	*17.8*	*7.9*	*5.8*	*5.6*	*5.6*	*18.1*	*7.0*	*5.6*	
Red	84	10	23	16	7	24	4	33	23	28	
%	*21.2*	*20.8*	*21.5*	*25.4*	*13.5*	*26.7*	*11.1*	*21.3*	*20.0*	*22.2*	
Professional											
Doctor	77	4	20	22	16	4	11	24	38	15	< 0.001
%	*19.4*	*8.3*	*18.7*	*34.9*	*30.8*	*4.4*	*30.6*	*15.5*	*33.0*	*11.9*	
Nurse	276	42	69	32	26	86	21	111	58	107	
%	*69.7*	*87.5*	*64.5*	*50.8*	*50.0*	*95.6*	*58.3*	*71.6*	*50.4*	*84.9*	
Care Assistant	28	1	12	8	5	0	2	13	13	2	
%	*7.1*	*2.1*	*11.2*	*12.7*	*9.6*	*0.0*	*5.6*	*8.4*	*11.3*	*1.6*	
Other Health Staff	15	1	6	1	5	0	2	7	6	2	
%	*3.8*	*2.1*	*5.6*	*1.6*	*9.6*	*0.0*	*5.6*	*4.5*	*5.2*	*1.6*	
Place											
District Service	71	2	9	8	20	22	10	11	28	32	< 0.001
%	*17.9*	*4.2*	*8.4*	*12.7*	*38.5*	*24.4*	*27.8*	*7.1*	*24.4*	*25.4*	
Hospital Ward	63	0	24	1	10	20	8	24	11	28	
%	*15.9*	*0.0*	*22.4*	*1.6*	*19.2*	*22.2*	*22.2*	*15.5*	*9.6*	*22.2*	
Emergency Department	101	28	20	9	6	28	10	48	15	38	
%	*25.5*	*58.3*	*18.7*	*14.3*	*11.5*	*31.1*	*27.8*	*31.0*	*13.0*	*30.2*	
Psychiatric Service	161	18	54	45	16	20	8	72	61	28	
%	*40.7*	*37.5*	*50.5*	*71.4*	*30.8*	*22.2*	*22.2*	*46.5*	*53.0*	*22.2*	
Aggressor Identity											
Unknown	115	19	25	11	12	33	15	44	23	48	0.008
%	*29.0*	*39.6*	*23.4*	*17.5*	*23.1*	*36.7*	*41.7*	*28.4*	*20.0*	*38.1*	
Known	281	29	82	52	40	57	21	111	92	78	
%	*71.0*	*60.4*	*76.6*	*82.5*	*76.9*	*63.3*	*58.3*	*71.6*	*80.0*	*61.9*	

(5.6%), and Other Healthcare Staff (5.6%). These incidents took place in various locations: District Services (27.8%), the Emergency Department (27.8%), Psychiatric Services (22.2%), and Hospital Wards (22.2%). In 58.3% of cases, the aggressor was known to the healthcare service.

Description of aggressions during the pandemic phases

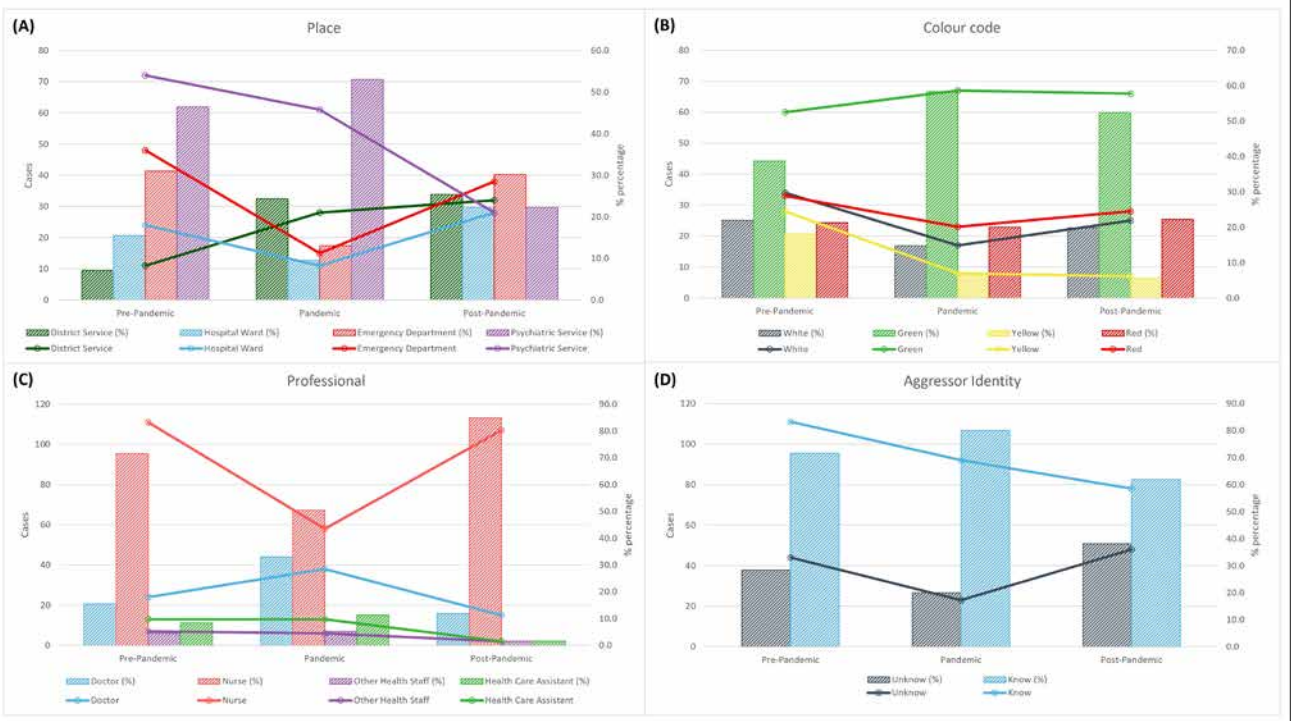
Trends in the characteristics of aggressions during the various phases of the pandemic are illustrated in Figure 1.

In the pre-pandemic phase, 155 incidents of aggression were reported; these were classified as White codes (21.9%), Green codes (38.7%), Yellow codes (18.1%), and Red codes (21.3%). Nurses were the most frequently involved professionals (71.6%), followed by Doctors (15.5%), Health Care Assistants (8.4%), and Other Healthcare Staff (4.5%). The majority of incidents occurred in Psychiatric Services (46.5%) and the Emergency Department (31.0%), with District Services (7.1%) and Hospital Wards (15.5%) accounting for the remainder. Known aggressors were involved in the majority of cases (71.6%).

During the pandemic phase, 115 incidents were recorded: White codes (14.8%), Green codes (58.3%), Yellow codes (7.0%), and Red codes (20.0%). Most victims were Nurses (50.4%) or Doctors (33.0%), though other health staff (5.2%), and Health Care Assistants (11.3%) were also involved. Psychiatric Services saw the majority of incidents (53.0%), followed by District Services (24.4%), the Emergency Department (13.0%), and Hospital Wards (9.6%). The proportion of known aggressors was the highest (80.0%).

In the post-pandemic phase, 126 incidents were

Fig. 1. Description of aggressions by pandemic phases.



A: Location of the aggression; B: Colour code of reported aggressions; C: Professional involved in the aggression; D: Aggressor known to the Healthcare Service. The Y-axis shows the absolute number of cases on the left, the percentage on the right; the X-axis presents the phase of the pandemic.

documented: White codes (19.8%), Green codes (52.4%), Yellow codes (5.6%), and Red codes (22.2%). Incidents involving Nurses (84.9%), Doctors (11.9%), Other Healthcare Staff (1.6%), and Health Care Assistants (1.6%) were recorded. Increases were observed in the Emergency Department (30.2%) and District Services (25.4%), with Hospital Wards (22.2%) also reported, while aggressions in Psychiatric Services decreased (22.2%). Known aggressors showed a decline from the pandemic phase (61.9%).

The χ^2 test revealed significant differences across the pandemic phases, in terms of the colour codes of the incidents, the professional groups involved and the locations of the aggression. Additionally, the ratio of known to unknown aggressors differed significantly, with the number of known aggressors increasing during the pandemic phase.

Statistical analyses

We observed that, during the pandemic phase, the probability of having a Green code was higher than that of having a White code (Coef. 0.836, p-value 0.029, 95% CI 0.084 to 1.59). Conversely, in the post-pandemic phase, the probability of having a Yellow code was lower than that of having a White code (Coef. -1.174, p-value 0.034, 95% CI -2.260 to -0.087) (Fig. 2).

Regarding professions, when comparing trends with those concerning assaults on doctors, nurses were less likely to be involved during the pandemic phase (Coef. -0.807, p-value 0.023, 95% CI -1.504 to -0.110). Moreover, Other Health Staff were less involved during the post-pandemic phase (Coef. -2.394, p-value 0.040, 95% CI -4.677 to -0.112) (Fig. 2).

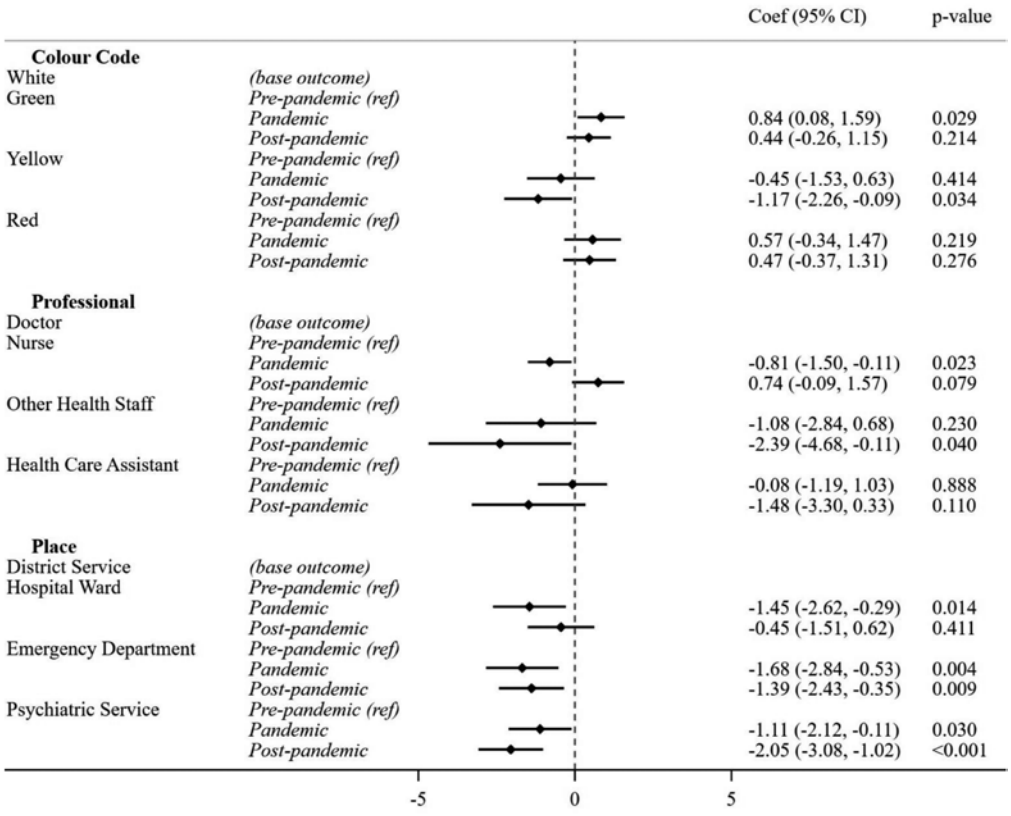
Regarding the place of aggression, the probability of aggression occurring in a Hospital Ward was lower than in District Services during the pandemic phase (Coef. -1.452, p-value 0.014, 95% CI -2.616 to -0.289). In the Emergency Department, a decrease was observed both during (Coef. -1.684, p-value 0.004, 95% CI -2.839 to -0.528) and after the pandemic (Coef. -1.387, p-value 0.009, 95% CI -2.426 to -0.347). Additionally, in Psychiatric Services, the probability was lower during (Coef. -1.113, p-value 0.030, 95% CI -2.117 to -0.110) and after the pandemic (Coef. -2.050, p-value < 0.001, 95% CI -3.081 to -1.019) (Fig. 2).

Multinomial logistic regression analysis was conducted to assess the association between the Pandemic Phase and Colour Code, Profession, or Place of aggression. This analysis was controlled for the month of the year, the time of day when the event occurred, aggressor identity, and for professional category, place, and colour code, if these were not the outcome. Results are presented as regression coefficients (Coef.) and 95% confidence intervals (95% CI).

Discussion

The data on reported aggressions against healthcare workers in Genoa's ASL3 from January 2018 to June

Fig. 2. Association of Pandemic Phase with Colour Code, Professional Category, and Place of Aggression.



2023 show a significant increase: from 48 in 2018 to 90 in 2022, with a partial count of 35 in the first half of 2023. This local pattern also reflects a global trend, where verbal violence is more prevalent than physical violence [38]. The classification of aggressions into colour-coded categories of severity provides further insight into the nature of the violence, underscoring the higher frequency of verbal incidents [34]. During the pandemic phase, Green codes increased, while in the post-pandemic phase, the types of aggressions reverted to a pattern similar to that observed in the pre-pandemic phase, but with a significant increase in Yellow codes.

The predominant incidence of aggressions against nursing staff – ranging from 50.8% to 95.6% in the years under review – highlights the particular vulnerability of these healthcare workers. This finding aligns with global trends and calls for specific attention to the safety of this professional category. Indeed, targeted prevention strategies are needed in order to ensure a safe working environment. This pattern, which has been observed in various settings, healthcare systems and countries [9, 25, 39-45], suggests that the greater exposure of Nurses to violence may be due to their closer contact with patients and their families. In our analysis, nurses consistently emerged as the group most frequently targeted throughout the study period. During the pandemic phase, however, we observed a marked decrease in both the absolute numbers, and the percentages of nurses involved in aggressive incidents. This was probably because of the reduced patient and family interactions due to pandemic-related restrictions [46]. In the post-pandemic phase, the frequency of aggressions involving healthcare workers returned to pre-pandemic levels, with nurses again constituting the majority of victims, albeit in a slightly higher proportion than during the pre-pandemic phase. Remarkably, the incidence of aggression towards physicians significantly increased during the pandemic but reverted to lower levels in the subsequent post-pandemic phase. It is also noteworthy that non-medical and non-nursing HCWs, including administrative, and support staff, consistently accounted for only a small fraction of cases of aggression, a trend that further declined over time.

Of particular interest are the data regarding the locations of aggression. The majority of violent episodes were recorded in the Emergency Department and Psychiatric Services, a trend consistent with the previous literature [8]. During the pandemic phase, however, District Services saw a significant increase in aggressive behaviour, while other healthcare settings, particularly emergency services, registered a decrease. This could be attributed to the reduced use of emergency services during the pandemic, and patients' preference to avoid the Emergency Department and the hospital setting whenever possible [47]. In the post-pandemic phase, the picture that emerged was significantly different from that seen during the pre-pandemic phase, in that the hospital setting and territorial services were more

frequently involved. Clearly, there is a need for specific preventive and safety measures in these areas, so as to reduce the risk of aggression, and improve staff safety. Future trends will also need to be monitored in order to understand how to adapt measures to counteract emerging phenomena in new healthcare settings, especially in light of the changes that will be implemented by the National Recovery and Resilience Plan [48].

The high percentage of aggressors already known to healthcare services, which increased from 60.4% to 76.9%, indicates the need for a proactive approach to managing relationships, and preventing conflictual situations. In this regard, the early identification of individuals at risk of committing violence can significantly contribute to prevention and staff protection [45]. These data are particularly interesting, as they show that aggressive behaviour is enacted even when the perpetrator is not protected by anonymity, and deliberately risks legal repercussions. The peak of known aggressors was recorded during the pandemic phase; this could have been due to entry screening, and greater control of patient flows [36, 46].

When analysing the phenomena associated with the various pandemic phases, we observed a greater involvement of nursing staff during the post-pandemic phase, along with an increase in Green and Red codes during the pandemic phase. The increased involvement of nurses during the post-pandemic phase aligns with previous literature [9, 25, 39-45], but further investigation is needed in order to explain this significant increase. Also interesting is the increase in Green and Red codes, compared with White codes, during the pandemic [33]. Despite the reduction in non-urgent services provided during the pandemic, the level of reporting remained largely unchanged, and the severity seemed to increase [47].

There are several areas that require further research. Indeed, it would be useful to explore regional or national differences in experiences of violence, and to assess the effectiveness of specific prevention and intervention strategies. Research should also investigate the long-term impact of violence on healthcare staff, including effects on staff turnover and the quality of care.

Strengths and limitations

The primary limitation of this study is its reliance on self-reported data on incidents of aggression, which may have resulted in underreporting. Indeed, voluntary reporting may be prone to errors and inaccuracies [49]. Secondly, although the study focused on the specific context of ASL3, the findings seem to be applicable to similar settings, given the substantial number of healthcare workers and patients involved and the diversity of facilities and services provided. Moreover, this study did not explore the extent of underreporting, nor did it examine the reasons behind the decision to report or not report incidents. Additionally, the study did not analyse the frequency of reports or estimate the overall prevalence of incidents of aggression. Lastly, regarding 2023, only data from the first semester were available, and we did not conduct analyses of prevalence or incidence; however, on comparing the first and second semesters of each year, the proportions of events were consistent. Despite this, the study is based on the most complete and credible official data available for the healthcare setting considered.

Policy

The systematic collection and analysis of incidents of aggression against healthcare workers are crucial to comprehending the risks faced by these people and highlight significant ethical and social concerns. Establishing a secure and respectful working environment for healthcare professionals is imperative and tackling the underlying causes of violence in healthcare settings, including societal, economic, and cultural factors, is a collective responsibility. Training staff to recognise, manage and de-escalate potentially violent situations is pivotal, and implementing specific training programmes can empower staff with effective conflict management skills, thereby mitigating the risk of escalation and augmenting overall safety. However, an efficacious approach to managing violence in healthcare settings demands a collaborative, interdisciplinary strategy that incorporates the expertise of psychologists, social workers, and other specialists. The present research underscores the need for healthcare policies that address violence against healthcare workers by integrating preventive strategies into policy planning and ensuring that sufficient resources are allocated for staff safety and welfare. The overarching aims are to raise collective awareness of this issue, and to enact effective strategies prevention, in order to guarantee a safe working environment for individuals who are dedicated to the care of others.

Conclusions

The data collected from January 2018 to June 2023 reveal an escalating trend of violence against healthcare workers, particularly in new healthcare settings, such as District Services, which have been enhanced due to the COVID-19 pandemic. While no significant difference emerged between the post-pandemic and the pre-pandemic phases, in terms of the type of aggression or personnel involved, the pandemic phase saw a shift in aggressions in terms of severity, healthcare settings, and staff involved.

This analysis underscores the urgent need for effective prevention policies and strategies to safeguard healthcare workers. Its findings offer a robust foundation for developing targeted interventions and emphasize the importance of an integrated approach that includes not just physical security but also organisational improvement and staff training. Ensuring that healthcare workers operate in a safe and protected environment is paramount in order to deliver high-quality healthcare and guarantee patient safety.

Acknowledgements

We thank the ASL3 Healthcare System of the Liguria Region for allowing us to use the data for this study.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The anonymised data presented in the study can be provided upon request and authorisation from the data-holding authority.

Authors' contributions

GS, SR, and BR: conceived and supervised the study, and devised its methodology. NC and AG: contributed to the acquisition of data. MM and GS: analysed the data. GS, MM, AMLDM, and EC: wrote the first draft of the manuscript. BR and GS: had final responsibility for the decision to submit for publication. All authors reviewed, and edited the manuscript, contributed to the article, and approved the submitted version.

References

[1] Ielapi N, Andreucci M, Bracale UM, Costa D, Bevacqua E, Giannotta N, Mellace S, Buffone G, Cerabona V, Arturi F, Provenzano M, Serra R. Workplace violence towards healthcare workers: an Italian cross-sectional survey. Nurs Rep 2021;11:758-64. https://doi.org/10.3390/nursrep11040072.

[2] Hamdan M, Abu Hamra A. Workplace violence towards workers in the emergency departments of Palestinian hospitals: a cross-sectional study. Hum Resour Health 2015;13:28. https://doi.org/10.1186/s12960-015-0018-2.

[3] Tucker JD, Cheng Y, Wong B, Gong N, Nie JB, Zhu W, McLaughlin MM, Xie R, Deng Y, Huang M, Wong WC, Lan P, Liu H, Miao W, Kleinman A; Patient-Physician Trust Project Team. Patient-physician mistrust and violence against physicians in Guangdong Province, China: a qualitative study. BMJ Open 2015;5:e008221. https://doi.org/10.1136/bmjopen-2015-008221.

[4] Sun T, Gao L, Li F, Shi Y, Xie F, Wang J, Wang S, Zhang S, Liu W, Duan X, Liu X, Zhang Z, Li L, Fan L. Workplace violence, psychological stress, sleep quality and subjective health in Chinese doctors: a large cross-sectional study. BMJ Open 2017;7:e017182. https://doi.org/10.1136/bmjopen-2017-017182.

[5] Davey K, Ravishankar V, Mehta N, Ahluwalia T, Blanchard J, Smith J, Douglass K. A qualitative study of workplace violence among healthcare providers in emergency departments in India. Int J Emerg Med 2020;13:33. https://doi.org/10.1186/s12245-020-00290-0.

[6] Workplace Violence and Harassment: a European Picture. [cited 2023 Dec 5]; Available at: https://osha.europa.eu/en/publications/workplace-violence-and-harassment-european-picture (Accessed on: 5/12/2023).

[7] Spector PE, Zhou ZE, Che XX. Nurse exposure to physical and nonphysical violence, bullying, and sexual harassment: a quantitative review. Int J Nurs Stud 2014;51:72-84. https://doi.org/10.1016/j.ijnurstu.2013.01.010.

[8] Liu J, Gan Y, Jiang H, Li L, Dwyer R, Lu K, Yan S, Sampson O, Xu H, Wang C, Zhu Y, Chang Y, Yang Y, Yang T, Chen Y, Song F, Lu Z. Prevalence of workplace violence against healthcare workers: a systematic review and meta-analysis. Occup Environ Med 2019;76:927-37. https://doi.org/10.1136/oemed-2019-105849.

[9] Serrano Vicente MI, Fernández Rodrigo MT, Satústegui Dordá PJ, Urcola Pardo F. Agresiones a profesionales del sector sanitario en España, revisión sistemática. Rev Esp Salud Pública 2019;93:e201910097.

[10] Kowalenko T, Gates D, Gillespie GL, Succop P, Mentzel TK. Prospective study of violence against ED workers. Am J Emerg Med 2013;31:197-205. https://doi.org/10.1016/j.ajem.2012.07.010.

[11] Kowalenko T, Cunningham R, Sachs CJ, Gore R, Barata IA, Gates D, Hargarten SW, Josephson EB, Kamat S, Kerr HD, McClain A. Workplace violence in emergency medicine: current knowledge and future directions. J Emerg Med 2012;43:523-31. https://doi.org/10.1016/j.jemermed.2012.02.056.

[12] Pompeii LA, Schoenfisch AL, Lipscomb HJ, Dement JM, Smith CD, Upadhyaya M. Physical assault, physical threat, and verbal abuse perpetrated against hospital workers by patients or visitors in six U.S. hospitals. Am J Ind Med 2015;58:1194-204. https://doi.org/10.1002/ajim.22489.

[13] Behnam M, Tillotson RD, Davis SM, Hobbs GR. Violence in the emergency department: a national survey of emergency medicine residents and attending physicians. J Emerg Med 2011;40:565-79. https://doi.org/10.1016/j.jemermed.2009.11.007.

[14] Monitoraggio eventi sentinella. Available at: https://www.salute.gov.it/portale/sicurezzaCure/dettaglioContenutiSicurezzaCure.jsp?lingua=italiano&id=238&area=qualita&menu=vuoto (Accessed on: 05/12/2023).

[15] Brunetti L, Bambi S. Le aggressioni nei confronti degli infermieri dei dipartimenti di emergenza: revisione della letteratura internazionale. Prof Inferm 2013;66:109-16. https://doi.org/10.7429/pi.2013.662109.

[16] Lyneham J. Violence in New South Wales emergency departments. Aust J Adv Nurs 2000;18:8-17.

[17] Civilotti C, Berlanda S, Iozzino L. Hospital-based healthcare workers victims of workplace violence in Italy: a scoping review. Int J Environ Res Public Health 2021;18:5860. https://doi.org/10.3390/ijerph18115860.

[18] Crilly J, Chaboyer W, Creedy D. Violence towards emergency department nurses by patients. Accid Emerg Nurs 2004;12:67-73. https://doi.org/10.1016/j.aaen.2003.11.003.

[19] Pich J, Hazelton M, Sundin D, Kable A. Patient-related violence at triage: A qualitative descriptive study. Int Emerg Nurs 2011;19:12-9. https://doi.org/10.1016/j.ienj.2009.11.007.

[20] Ayasreh IR, Hayajneh FA. Workplace violence against emergency nurses: a literature review. Crit Care Nurs Q 2021;44:187-202. https://doi.org/10.1097/CNQ.0000000000000353.

[21] Pich JV, Kable A, Hazelton M. Antecedents and precipitants of patient-related violence in the emergency department: Results from the Australian VENT Study (Violence in Emergency Nursing and Triage). Australas Emerg Nurs J 2017;20:107-13. https://doi.org/10.1016/j.aenj.2017.05.005.

[22] Hesketh KL, Duncan SM, Estabrooks CA, Reimer MA, Giovannetti P, Hyndman K, Acorn S. Workplace violence in Alberta and British Columbia hospitals. Health Policy 2003;63:311-21. https://doi.org/10.1016/s0168-8510(02)00142-2.

[23] Zafar W, Siddiqui E, Ejaz K, Shehzad MU, Khan UR, Jamali S, Razzak JA. Health care personnel and workplace violence in the emergency departments of a volatile metropolis: results from Karachi, Pakistan. J Emerg Med 2013;45:761-72. https://doi.org/10.1016/j.jemermed.2013.04.049.

[24] AbuAlRub RF, Al Khawaldeh AT. Workplace physical violence among hospital nurses and physicians in underserved areas in Jordan. J Clin Nurs 2014;23:1937-47. https://doi.org/10.1111/jocn.12473.

[25] Algwaiz WM, Alghanim SA. Violence exposure among health care professionals in Saudi public hospitals. A preliminary investigation. Saudi Med J 2012;33:76-82.

[26] Rose M. A survey of violence toward nursing staff in one large Irish Accident and Emergency Department. J Emerg Nurs 1997;23:214-9. https://doi.org/10.1016/s0099-1767(97)90010-6.

[27] Eslamian J, Fard SH, Tavakol K, Yazdani M. The effect of anger management by nursing staff on violence rate against them in the emergency unit. Iran J Nurs Midwifery Res 2010;15(Suppl 1):337-42.

[28] Luck L, Jackson D, Usher K. Innocent or culpable? Meanings that emergency department nurses ascribe to individual acts of violence. J Clin Nurs 2008;17:1071-8. https://doi.org/10.1111/j.1365-2702.2006.01870.x.

[29] Pinar R, Ucmak F. Verbal and physical violence in emergency departments: a survey of nurses in Istanbul, Turkey. J Clin Nurs 2011;20:510-7. https://doi.org/10.1111/j.1365-2702.2010.03520.x.

[30] Kitaneh M, Hamdan M. Workplace violence against physicians and nurses in Palestinian public hospitals: a cross-sectional study. BMC Health Serv Res 2012;12:469. https://doi.org/10.1186/1472-6963-12-469.

[31] Rafeea F, Al Ansari A, Abbas EM, Elmusharaf K, Abu Zeid MS. Violence toward health workers in Bahrain Defense Force Royal Medical Services' emergency department. Open Access Emerg Med 2017;9:113-21. https://doi.org/10.2147/OAEM.S147982.

[32] Ministero della Salute, Dipartimento della Qualità Direzione Generale della Programmazione Sanitaria, dei Livelli di Assistenza e dei Principi Etici di Sistema Ufficio, III Raccomandazione per prevenire gli atti di violenza a danno degli operatori sanitari. 2007. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_721_allegato.pdf (Accessed on: 23/03/2024).

[33] Zhang S, Zhao Z, Zhang H, Zhu Y, Xi Z, Xiang K. Workplace violence against healthcare workers during the COVID-19 pandemic: a systematic review and meta-analysis. Environ Sci Pollut Res Int 2023;30:74838-52. https://doi.org/10.1007/s11356-023-27317-2.

[34] Ministero della salute. Osservatorio Nazionale sulla Sicurezza degli Esercenti le Professioni Sanitarie e socio-sanitarie Relazione attività anno 2022. Available at: https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?lingua=italiano&id=3302 (Accessed on: 23/03/2024).

[35] Sistema Sanitario Regione Ligure. Asl3 - Azienda Sanitaria Ligure 3. Available at: https://www.asl3.liguria.it/ (Accessed on: 23/03/2024).

[36] Consiglio dei Ministri - Italy. Delibera del Consiglio dei Ministri 31 gennaio 2020. GU Serie Generale n. 26. 2020. Available at: https://www.gazzettaufficiale.it/eli/id/2020/02/01/20A00737/sg (Accessed on: 23/03/2024).

[37] Presidente della Repubblica - Italy. Decreto-Legge 24 marzo 2022, n. 24. GU Serie Generale n. 70. 2022. Available at: https://www.gazzettaufficiale.it/eli/id/2022/03/24/22G00034/sg (Accessed on: 23/03/2024).

[38] Rosenthal LJ, Byerly A, Taylor AD, Martinovich Z. Impact and Prevalence of Physical and Verbal Violence Toward Healthcare Workers. Psychosomatics 2018;59:584-90. https://doi.org/10.1016/j.psym.2018.04.007.

[39] Park M, Cho SH, Hong HJ. Prevalence and perpetrators of workplace violence by nursing unit and the relationship between violence and the perceived work environment. J Nurs Scholarsh 2015;47:87-95. https://doi.org/10.1111/jnu.12112.

[40] Abed M, Morris E, Sobers-Grannum N. Workplace violence against medical staff in healthcare facilities in Barbados. Occup Med (Lond) 2016;66:580-3. https://doi.org/10.1093/occmed/kqw073.

[41] Ferri P, Silvestri M, Artoni C, Di Lorenzo R. Workplace violence in different settings and among various health professionals in an Italian general hospital: a cross-sectional study. Psychol Res Behav Manag 2016;9:263-75. https://doi.org/10.2147/PRBM.S114870.

[42] Alsaleem SA, Alsabaani A, Alamri RS, Hadi RA, Alkhayri MH, Badawi KK, Badawi AG, Alshehri AA, Al-Bishi AM. Violence towards healthcare workers: A study conducted in Abha City, Saudi Arabia. J Family Community Med 2018;25:188-93. https://doi.org/10.4103/jfcm.JFCM_170_17.

[43] Honarvar B, Ghazanfari N, Raeisi Shahraki H, Rostami S, Lankarani KB. Violence against Nurses: A Neglected and Health-threatening Epidemic in the University Affiliated Public Hospitals in Shiraz, Iran. Int J Occup Environ Med 2019;10:111-23. https://doi.org/10.15171/ijoem.2019.1556.

[44] Demirci Ş, Uğurluoğlu Ö. An evaluation of verbal, physical, and sexual violence against healthcare workers in Ankara, Turkey. J Forensic Nurs 2020;16:E33-41. https://doi.org/10.1097/JFN.0000000000000286.

[45] Relazione sulle attività dell'Osservatorio Nazionale sulla sicurezza degli esercenti le professioni sanitarie e socio-sanitarie, anno 2022. Available at: https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?lingua=italiano&id=3302 (Accessed on: 23/03/2024).

[46] Decreto del Presidente del Consiglio dei Ministri, 1 marzo 2020. Available at: https://www.gazzettaufficiale.it/atto/stampa/serie_generale/originario (Accessed on: 10/12/2023).

[47] Mahmassani D, El Helou C, El Remlawi A, Mghames A, Mneimne O, Hitti E. Factors associated with emergency department avoidance during the COVID-19 pandemic and alternatives sought: a cross-sectional, telephone-based survey of frequent emergency department users in Beirut, Lebanon. BMJ Open 2023;13:e072117. https://doi.org/10.1136/bmjopen-2023-072117.

[48] Piano nazionale di ripresa e resilienza. Cos'è la Missione Salute. Available at: https://www.pnrr.salute.gov.it/portale/pnrrsalute/dettaglioContenutiPNRRSalute.jsp?lingua=italiano&id=5833&area=PNRR-Salute&menu=missionesalute (Accessed on: 10/12/2023).

[49] Veronesi G, Ferrario MM, Giusti EM, Borchini R, Cimmino L, Ghelli M, Banfi A, Luoni A, Persechino B, Di Tecco C, Ronchetti M, Gianfagna F, De Matteis S, Castelnuovo G, Iacoviello L. Systematic Violence Monitoring to Reduce Underreporting and to Better Inform Workplace Violence Prevention Among Health Care Workers: Before-and-After Prospective Study. JMIR Public Health Surveill 2023;9:e47377. https://doi.org/10.2196/47377.

Received on December 10, 2023. Accepted on May 9, 2024.

Correspondence: Gloria Spatari, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy. E-mail: drgloriaspatari@gmail.com

How to cite this article: Spatari G, De Mite AML, Cantova E, Reggiani S, Re M, Mercogliano M, De Martini M, Casanova N, Gallo A, Caltabellotta M, Rebagliati B. Violence against Healthcare Workers during the Phases of the COVID-19 Pandemic: a Descriptive Observational Study from 2018 to 2023 in the Metropolitan City of Genoa (North-Western Italy). J Prev Med Hyg 2024;65:E256-E264. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3143

Nursing

Motivational interview and teach back: effectiveness on the rate of hand hygiene compliance in ICU Nurses

ZEINAB ABBASI[1], MOHSEN MOLLAHADI[2], FERYAL KHAMSEH[3], ZOHREH VAFADAR[4,5]
[1] MSc of Critical Care Nursing, Student research committee, Baqiyatallah University of Medical Sciences, Tehran, Iran;
[2] Assistant Professor of Nursing, Exercise physiology research center, Life Style institute and Nursing Faculty, Baqiyatallah University of Medical Sciences, Tehran, Iran; [3] MSc in Nursing, Instructor, Behavioral Sciences Research Center, Life Style Institute, Faculty of Nursing, Baqiyatallah University of Medical Sciences, Tehran, Iran; [4] Associate Professor of Nursing, Nursing Faculty, Medical-Surgical Department, Baqiyatallah University of Medical Sciences, Tehran, Iran;
[5] Associate Professor of Nursing, Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

Keywords

Hand Hygiene • Motivational Interview • Teach back • Nurses • Intensive Care Unit

Summary

Introduction. *Hand hygiene in nurses is the most effective factor in controlling nosocomial infections. The objective of this study was to assess the effectiveness of motivational interviews and teach-back on the rate of hand hygiene compliance in Intensive Care Unit nurses.*

Methods. *A quasi-experimental study with pre-test and post-test design was performed. Three Intensive Care Units with 88 nurses were randomly divided into three study groups. The control group received only the usual hospital teaching in hand hygiene, the experimental groups 1 and 2, in addition to the usual teaching, they received motivational interview and teach back in five weekly sessions, respectively. The rate of hand hygiene compliance in nurses was measured by Hand Hygiene Practices Inventory.*

Results. *There was a statistically significant difference for the rate of hand hygiene compliance before and after the intervention in the study groups with $p < 0.001$. In comparison before and after, in experimental group 1, the rate of hand rub increased from 8% to 18.5% and the rate of hand wash from 1.5% to 22%; and in the experimental group 2, these values increased from 4% to 19.5% in hand rub and from 3.5% to 17% in hand wash, respectively. However, in the control group, the rate of hand hygiene compliance before and after the test did not show a statistically significant difference with $p > 0.05$.*

Conclusions. *Motivational interview and teach back methods were effective in promoting hand hygiene compliance in nurses and thus improve the control of nosocomial infections.*

Introduction

Nurses are at the forefront of patient care. In this regard, hand hygiene in nurses is the most effective factor in controlling nosocomial infections, reducing costs, complications and mortality rate [1-3]. There is some evidence that the rate of hand hygiene compliance in nurses is not satisfactory and 70% of health care workers do not routinely observe hand hygiene [4, 5]. A review of 61 studies showed that the hand hygiene rate, with an average of 59.6% in the Intensive Care Unit, was significantly lower than the desired international targets. It is also around 64.5% in high-income countries, compared to 9.1% in low-income countries. This rate is 43.4% for nurses, 32.6% for physicians and 53.8% for other medical staff [6]. Chang et al. found that nurses observed less hand hygiene before intensive care than after that. In other words, nurses protect themselves more than patients, and do not follow methods in providing care that reduce the rate of infection transmission to patients. These conditions increase the risk of nosocomial infections in patients [7]. Evidence in health centers in Iran is somewhat similar to the statistics of other countries; in a study, the rate of hand hygiene by physicians was reported by 32% and nurses by 48% [8]. Nouri et al. reported that the average hand hygiene rate of Iranian nurses was 40.5% [9]. Ziasheikholeslami reported that the average hand hygiene in Intensive Care Unit nurses was 44.5% [10]. Mohanty et al. in a study on 171 medical and nursing students and faculty members at several teaching hospitals in India showed that although 66.4% of the participants had sufficient knowledge of hand hygiene, only 32% observed hand hygiene in the situations required [11]. Evidence at the international rate shows that despite the improvement of employees' knowledge to observe hand hygiene, the rate of hand hygiene compliance is not optimal yet. In other words, the main challenge is not lack of awareness, but the lack of commitment and adherence to hand hygiene in the treatment staff [12]. The study of Neda Khairkhah showed that while education using film screening has increased awareness and belief change in nursing students, but has not changed the performance of hand hygiene in them [13]. Farias also showed that despite sufficient knowledge of nurses, they are not committed to hand hygiene in clinical situations. There is a need for interventions that turn nurses' knowledge into positive behavior [14]. Numerous studies in the investigation of

the causes of hand hygiene non-compliance showed that barriers such as lack of positive attitude, negligence and underestimation of hand hygiene, lack of motivation, internal commitment or professional commitment, poor understanding of the negative consequences of non-compliance with hand hygiene, high workload, disproportion of the number of nurses to the patient, the type of organizational culture, the facilities of each ward as well as common skin problems are effective in adhering to hand hygiene in nurses [15-17]. Some researchers divided the unfavorable situation in hand hygiene into several areas of knowledge, attitude, motivation and practice and believe that promoting hand hygiene in nurses is a complex and multifaceted behavior change process that requires the combination of educational and motivational interventions and change in systems structure [18]. Interventions in this area should lead to behavior change by increasing nurses' motivation and professional commitment along with a supportive and empathetic environment [3, 19]. So far, various educational interventions are implemented to improve nurses' adherence to the principles of hand hygiene, but the impact of these teachings on increasing nurses' adherence is still disputed, so that some report the effectiveness of teaching and some report its ineffectiveness [20]. One of the most common educational methods is the transfer of information by lecturing method, the results of scientific research indicate that in this method, 40 to 80% of information is forgotten almost immediately after hearing it, plus half of the information that nurses remember, is incorrect, so appropriate teaching methods should be selected that lead to behavior change [21]. Some researchers consider the use of motivational approaches in this area to be more effective and some others the use of educational approaches, and less study has compared the effect of two educational and motivational approaches in promoting hand hygiene [22]. Various researches show that behavior change depend on the analysis and removal of internal contradictions, doubts in individuals, and changing these conditions is not possible with advice and education, but appropriate motivational interventions should be used [17, 23]. In contrast, experts in the field of education believe that education leads to behavior change when it is properly understood and internalized and a person is able to self-assess and transfer their knowledge to others [24-26]. Two famous interventions are based on theories of behavioral change, motivational interview, and teach back [27-29]. Motivational interview is one of the most effective behavioral change approaches developed in 1983 by William Miller and Stephen Rolnick. And was quickly used in various areas of behavior change [29, 30]. Motivational interview helps to strengthen the intrinsic motivation to change behavior in individuals by discovering, identifying and resolving doubts and ambivalence. A significant advantage of motivational interview is its flexibility and applicability in different areas of behavior [30, 31]. Several studies have confirmed the effectiveness of motivational interviewing in changing behavior [32-34]. A study by Östlund et al. on the effectiveness of motivational interview on patients' lifestyle changes showed that nurses who use motivational interview in the patient education process had more positive effects on patients' lifestyle changes [35]. Teach back is a well-known educational and interactive intervention to acquire health-promoting behaviors that combines three aspects of learning, teaching and evaluation, in which a person while mastering his/her perceptual problems, has reached a degree of mastery in skills and performance that teaches behavior in practice to others [36]. Pawase et al. studied the effectiveness of teach back method on the knowledge and performance of students in schools regarding hand hygiene. Their results have shown the positive effects of this method on the improvement of students' knowledge and performance in hand hygiene techniques [37]. Considering the sensitivity of Intensive Care Units and the inevitable need to improve hand hygiene behavior in nurses with effective motivational and educational approaches, this study is designed and implemented to assess the effectiveness of motivational interviews and teach-back on the rate of hand hygiene compliance in Intensive Care Unit nurses.

Methods

A three-group quasi-experimental study with pre-test and post-test design was performed from May to September 2020 in a selected hospital in Tehran. Out of 9 Intensive Care Units of the hospital, 3 Intensive Care Units were randomly selected. Then the nurses working in selected ICUs were measured and statistically analyzed in terms of variables affecting the outcomes of the interventions such as age, gender, education level, work experience in ICU, marital status, and there was no statistically significant difference between all groups in terms of the mentioned variables with $p < 0.05$ (Tab. I). So the selected wards were randomly assigned to 3 study groups including: control group, experimental group 1 with motivational interview intervention and experimental group 2 with teach back intervention. The control group received only the usual hospital teaching in hand hygiene, but in the experimental groups 1 and 2, in addition to the usual teaching, they received motivational interview intervention and teach back in five weekly sessions, respectively. Inclusion criteria were having a bachelor's degree or higher in nursing and at least 1 year of experience in the Intensive Care Unit, and exclusion criteria included not attending more than 20% of sessions.

The study instrument consisted of two parts, the first part of the demographic information questionnaire including age, sex, degree of education, work experience and the second part, standard checklist (Hand Hygiene Practices Inventory (HHPI)) approved by the Ministry of Health and Medical Education to assess hand hygiene behaviors which is used equally for all medical centers across the country. According to the checklist, each nurse was examined in an open and direct observation with a time interval of 20 ± 10

Tab. I. Comparison of Demographic Variables among Nurses in the study groups.

Group →		Experimental 1 (Motivational Interview)	Experimental 2 (Teach back)	Control	Total	Statistic tests
Variable		Number (percent)	Number (percent)	Number (percent)	Number (percent)	
Gender	Male	19 (61.3%)	23 (79.3%)	19 (67.9%)	61 (69.3%)	Chi-square = 3.75 P Value = 0.440
	Female	12 (38.7%)	6 (20.7%)	9 (32.1%)	27 (29.5%)	
Marital status	Married	28 (90.3%)	29 (100%)	26 (92.9%)	83 (94.3%)	Chi-square = 2.78 P Value = 0.249
	Single	3 (9.7%)	0 (0%)	7 (7.1%)	5 (5.7%)	
Educational attainment*	BS	24 (77.4%)	20 (69%)	27 (96.4%)	71 (80.7%)	Chi-square = 7.53 P value = 0.110
	MS	6 (19.4%)	7 (24.1%)	1 (3.6%)	14 (15.9%)	
	PhD	1 (3.2%)	2 (6.9%)	0 (0%)	3 (3.4%)	
Employment history	< 7 years	16 (51.6%)	13 (44.8%)	19 (67.9%)	48 (54.5%)	Chi-square = 3.213 P Value = 0.217
	>7 years	15 (48.4%)	16 (55.2%)	9 (32.1%)	40 (45.5%)	
Age		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	ANOVA F = 1.88 P value = 0.159
		43.12 ± 8.99	41.68 ± 11.45	37.82 ± 11.86	40.96 ± 10.88	

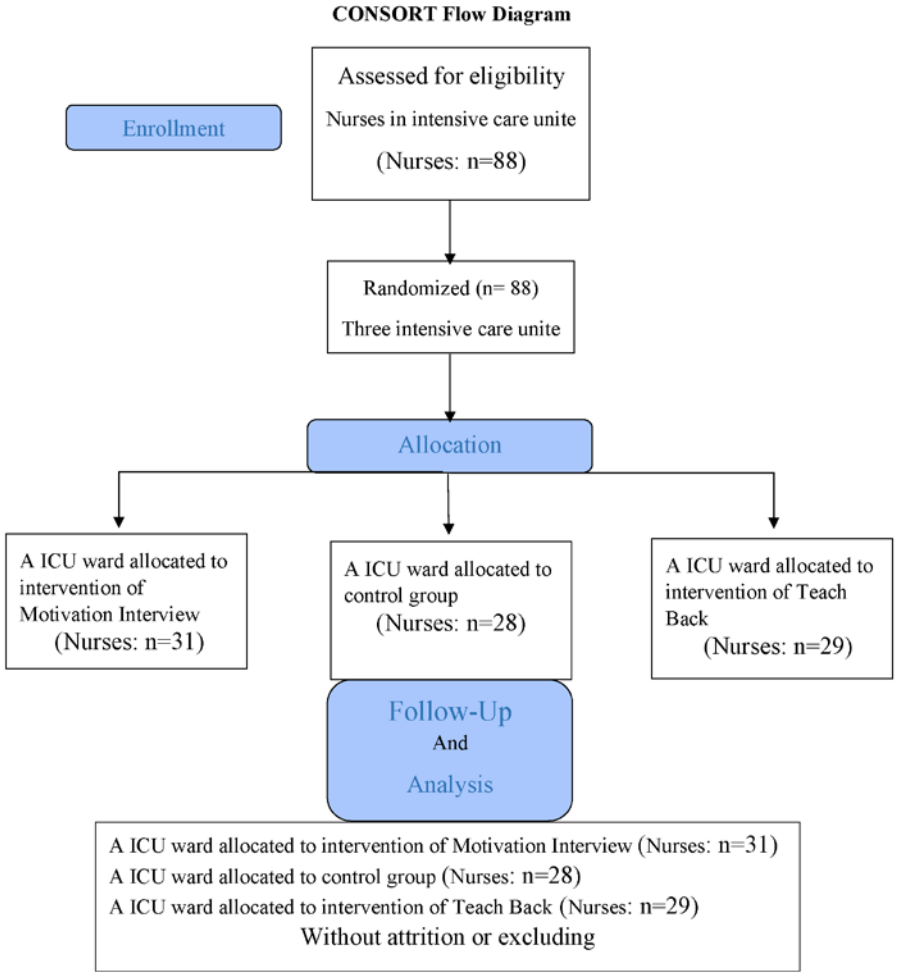
Educational attainment* including: BS (*Bachelor of Science*), MS (Master of Science), PhD (Doctor of Philosophy).

minutes in terms of hand hygiene compliance in 5 defined positions including: (before contact with the patient, before aseptic procedures, after contact with the patient's secretions, after physical contact with the patient and after contact with the patient's environment) and in terms of hand hygiene including three types of performance: hand washing with soap and water (Hand Wash), rubbing with an alcohol-based solution (Hand Rub) and hand hygiene non-compliance or acting in an incorrect way. All observations were performed equally by a trained and experienced nurse in measuring hand hygiene behaviors in the morning and evening work shifts. The presence of the observer in the study sections was informed by the nurses. Based on the above checklist, the rate of hand hygiene compliance in the nurses under study was presented with the number and percentage based on the type of action taken in each observed position. Pre-test was performed within two weeks before the intervention and post-test was performed 4 weeks (follow-up stage) after the intervention. Data were analyzed using SPSS 24 software. For the nominal variables, we conducted descriptive analysis by using frequencies and percentages as well as inferential analysis was carried out using the Chi-square test. The normally distributed continuous variables (*e.g.*, age) were analyzed by using mean (M) and standard deviations (±) also ANOVA test.

Method of intervention

The executive model of motivational interview sessions is based on the relevant literatures [38, 39] and the outline of teach back sessions is based on the model proposed by Bodenheimer and Anderson [36, 40]. and was performed after obtaining the experiences of previous researchers and expert approval (consisting of 6 people with specialties of PhD in Health Education, Nursing Faculty, Infection Control Supervisor). To perform the interventions, a nurse participated in a special teaching course and was trained and the interventions were performed by a qualified nurse (certified) and under the supervision of the research team. Sessions in both types of interventions included 5 sessions in 5 consecutive weeks, which were held in accordance with the conditions and needs of nurses in different shifts in the morning and evening. The content of motivational interview sessions is: Session 1: Familiarity and agreement between nurses and the interviewer, Session 2: Identifying emotions and its effect on behavior, Session 3: Determining healthy and unhealthy behaviors and the need to change behavior, Session 4: Explaining personal values and goals, Session 5: Discovering doubts and ambiguities and being ready to change and determine the perspective. The duration of the sessions is between 20 to 45 minutes and in each session, special worksheets are provided to the samples to record their feelings, attitudes, thoughts, ambiguities and doubts, personal and professional values. After completing the next session, the necessary feedback was given to the samples. 5 teach back sessions included 3 individual sessions and 2 group sessions and the duration of the sessions was between 20-30 minutes. In individual sessions, educational concepts were presented and incorrect perceptions were corrected by receiving frequent feedback from the nurse. In the group meetings, in addition to the exchange of concepts between the instructor and the nurses, among the members of the group, an exchange took place so that each nurse repeated the correct concept to his colleague and created an atmosphere of participation, collective acceptance, empathy, emotional support, self-evaluation and mutual evaluation.

Fig. 1. CONSORT Flow Diagram for the study.



After the interventions, 4 weeks of follow-up and continuous exchange of information between the instructor and the samples in a WhatsApp group for both experimental groups continued, and after 4 weeks of follow-up, the post-test phase was measured.

Results

All 88 nurses of the mentioned wards met the inclusion criteria and were fully present until the end of the intervention. The number of samples was 31 in the motivational interview group, 29 in the teach back group and 28 in the control group (Fig. 1). The age range of nurses participating in the study was between 25 and 61 years. There was no Statistically significant difference between the groups in terms of demographic variables such as age ($p = 0.159$), gender ($p = 0.440$), marital status ($p = 0.249$), educational attainment ($p = 0.110$), employment history ($p = 0.217$) (Tab. I).

In the pre-test stage, 200 positions in each study group were observed for hand hygiene compliance and in the post-test, 200 positions were observed, so a total of 600 positions were observed in the pre-test and 600 positions after the test. The rate of hand hygiene compliance in both stages of the assessment and in all three study groups was lower than the standard rate set by the Ministry of Health and Medical Sciences, *i.e.* 50%. In the pre-test stage, there was no statistically significant difference with $p = 0.158$ in all 3 groups in terms of hand hygiene. However, after the intervention, in the experimental group 1, the rate of hand hygiene compliance in the use of alcohol-based solution (hand rub) raised from 8% in the pre-test to 18.5% in the post-test and the rate of hand washing with soap and water (hand wash) increased from 1.5% to 22% and these values in experimental group 2, increased from 4% to 19.5% in hand rub and from 3.5% to 17% in hand wash, respectively. Chi-square test showed that the rate of hand rub and hand wash before and after the intervention in the experimental groups was statistically significant with $p < 0.001$. But in the control group, the rate of hand hygiene with two methods of hand rub and hand wash in the pre-intervention stage was 5.5% and 5%, respectively, which after the intervention was 1% and 2.5%, respectively. There was not a statistically significant difference in the rate of hand hygiene before and after the intervention in the control group (Tab. II).

Tab. II. Comparison of Nurses performance in the study groups in 200 position of hand hygiene compliance in each stage of measurement.

Group →		Experimental 1 (Motivational Interview)	Experimental 2 (Teach back)	Control	Chi-square test
Stage	Variable	Number (percent)	Number (percent)	Number (percent)	
Pre Test	Correct HW*	3 (1.5%)	7 (3.5%)	10 (5%)	Chi-square = 6.603 P value = 0.158
	Correct HR*	16 (8%)	8 (4%)	11 (5.5%)	
	Non/incorrect*	181 (90.5%)	185 (92.5%)	179 (89.5%)	
	Total	200 (100%)	200 (100%)	200 (100%)	
Post Test	Correct HW	44 (22%)	34 (17%)	5 (2.5%)	Chi-square = 85.512 P value < 0.001
	Correct HR	37 (18.5%)	39 (19.5%)	2 (1%)	
	Non/incorrect	119 (59.5%)	127 (63.5%)	193 (96.5%)	
	Total	200 (100%)	200 (100%)	200 (100%)	

Correct HW*: correct hand washing with soap and water (Hand Wash); Correct HR*: correct rubbing with an alcohol-based solution (Hand Rub); Non/ incorrect*: hand hygiene non-compliance or acting in an incorrect way.

Discussion

The present study was conducted with the aim of investigating the effectiveness of motivational interviews and teach-back on the rate of hand hygiene compliance in Intensive Care Unit nurses. The average age of the nurses participating in this study was 40.96 ± 10.88 years. The majority of them were male (69.3%), married (94.3%) with a bachelor's degree in nursing (80.7%) and (54.5%) had less than 7 years of work experience in the ICU. In the wards under our study, due to the need for greater physical strength and endurance as well as sufficient knowledge and skills, the majority of nurses are men with a bachelor's degree or higher. In a similar study, Salamati et al. showed the effectiveness of the motivational interviews following lecture teaching on hand hygiene behaviors in 128 nurses working in a pediatric hospital. The mean age of the nurses was 35.83 ± 7.184 years, also the majority of them were married (82.8%) and (76.6%) had a bachelor's degree or higher. But unlike our study, (90.6%) were female [41]. This could be due to the fact that the research environment was a pediatric hospital. However, despite the different gender distribution in both studies, the results were similar and consistent.

Results of this study showed that both motivational interview and teach back were effective in promoting health compliance, but motivational interview was more effective that teach back on hand hygiene in Intensive Care Unit nurses. Numerous studies examined the positive effects of motivational interview [42-44] or teach back [26, 37, 45, 46] on behavior change separately, but the comparative study of the effect of both in one study was very small. Despite the need to promote behaviors related to hand hygiene in health workers, less of these two methods are used.

So, we had to use similar studies in other fields for comparison. Zabolipour et al. in comparing the effect of two methods of motivational interview and teach back on adherence of patients with hypertension to the treatment regimen showed that both methods are effective in increasing patients' adherence to the treatment regimen but the rate of adherence to the treatment regimen in the motivational interview group was higher than the teach back group [47]. In their study, Najjar Nasab et al. showed the positive effect of motivational interviews on behavior change and lifestyle in women with eating disorders [48]. These findings indicate the facilitative effect of motivational interview on changing health-promoting behaviors.

In fact, no one is 100% unmotivated to change, but to motivate the individual to change requires internal conflicts to be resolved in an empathetic and supportive environment which is provided by a motivational interview. Real motivation is also enhanced by the successful experience that a person freely acquires in the right course of action [49]. It is noteworthy that although most studies emphasize the positive effect of motivational interview on behavior change, its persistence is still questionable. Dorstyn et al. investigated the effects of motivational interviewing on 987 patients with multiple sclerosis for their health care management. They found that motivational interview may improve rehabilitation care for these patients. However, evidence for persisting benefits to health outcomes and behavior is currently limited [50]. A meta-analysis study examining the effect of motivational interview on treatment adherence in 962 patients with chronic pain showed that the effect of motivational interview is limited and short-term and more studies are needed for long-term effect and change in patient self-management behavior [51]. In other words, the time and follow-up in an effective motivational interview, increases it. Numerous studies showed that most of the effects of motivational interview are mostly high in the first few months, but decrease over time, and this decrease is not due to a decrease in the effect of motivational

interview, but to the fact that behavior changes requires appropriate contexts and other co-treatments in addition to motivational interview [52, 53]. Therefore, combining different methods of behavior change, such as teach back, motivational interview and follow-up care can be effective in perpetuating behavior change.

Numerous studies emphasized the effectiveness of teach back in changing health-promoting behaviors and the need to use it in various therapies. However, in the field of behavior, hand hygiene received less attention [54, 55]. Some studies showed that, when more information is provided, less information is remembered and almost half of the information remembered is incorrect. The use of teach back method has a great effect on strengthening and consolidating educational content and their application [21]. In one project, using teach back, 300 members of a multidisciplinary team (including intensive care nurses, emergency, surgical nurses, nutritionists, respiratory care practitioners, and occupational and physical therapists) were shown that the teach back method was able to enhance the quality and safety of the care provided by the team members [56]. Despite the effectiveness of teach back, the lasting effects cannot be definitively stated. In their study, Rahmani et al. showed that teach back was effective on knowledge, practice, reducing readmission and quality of life in patients with chronic hepatitis in the short term after the intervention, but its effect was reduced in the long term [57]. Although both teach back and motivational interview methods improved the rate of hand hygiene compliance in nurses in the present study, but the persistence of its desired effects still needs further investigation. On the other hand, context factors and working conditions such as the high volume of tasks assigned, non-observance of the standard ratio of nurse to patient, lack of attention of officials to the proper performance of a nurse, weakness of incentive systems play a significant role in reducing nurses' motivation to maintain and adhere to the correct behavior and adherence to it; as well as failure in performing continuous visits in the field of measuring the rate of hand hygiene compliance, lack of nurses' knowledge about the prevalence of nosocomial infections in the workplace and inappropriate access to facilities required for hand hygiene, including (low quality of solutions with an alcohol base, unsuitable wash basin and poor quality soap for washing hands) can significantly reduce the effects of these educational methods. Therefore, in order to study the durability and greater effectiveness of these methods, in addition to solving the problems raised, long-term studies and foresight are needed. Lack of follow-up and lack of understanding of support can reduce the effectiveness of interventions over time. One of the limitations of the present study is the lack of long-term follow-up and measuring the duration of the effect of motivational interview variables and teach back on the rate of hand hygiene compliance in nurses and also the limitation of the research environment to Intensive Care Units. Another limitation of the study was that nurses' awareness of observing and measuring hand hygiene behaviors could have an effect on their performance and interfere with the results.

Conclusions

Findings showed that although both teach back and motivational interview methods are effective in promoting hand hygiene in nurses, the effect of motivational interview is more than teach back. Findings can help health policy makers in educational planning to improve nurses' health behavior. Utilizing motivational interviews and teach back in medical centers can be a step in improving the performance of nurses in the field of hand hygiene and reduce nosocomial infections, treatment costs and length of hospital stay and death of patients.

Acknowledgments

This study was conducted in collaboration with the School of Nursing and the Health Management Research Center of Baqiyatallah University of Medical Sciences in Tehran, Iran. The officials of the selected hospital and the nurses participating in the study are appreciated. We also express our gratitude towards Clinical Research Center of Baqiyatallah Educational and Medical Hospital. The authors would like to acknowledge the School of Nursing of Baqiyatallah University of Medical Sciences in Tehran for their financial support in this study.

Funding

This study was supported by Baqiyatallah University of Medical Sciences in Tehran, Iran.

Etical consideration

Include observance of honesty and trustworthiness for the collection of information, consideration of the principle of usefulness for samples and obtaining written informed consent and the right to withdraw at any stage, and anonymity and confidentiality of information. This research project is registered and approved by National Ethics System in Biomedical Research under the supervision of the Ministry of Health and Medical Education of Iran with ID: (IR.BMSU.BAQ.REC.1398.019).

Informed consent statement

Informed consent was obtained from all participants (nurses).

Conflict of interest statement

The authors are responsible for the content of this article and state that there is no conflict of interest.

Authors' contributions

ZA: contributed to design, implementation and data collection and writing of the manuscript. MM: contributed to the data collection, analysis and report the results. FK, MM: contributed to the conception, design, implementation of the study. ZV: contributed to the conception, design, implementation, data collection, analysis, and writing of the manuscript.

References

[1] Anwar MM, Elareed HR. Improvement of hand hygiene compliance among health care workers in intensive care units. J Prev Med Hyg 2019;60:E31-5. https://doi.org/10.15167/2421-4248/jpmh2019.60.1.918.

[2] Boyce JM. Current issues in hand hygiene. Am J Infect Control 2019;47S:A46-52. https://doi.org/10.1016/j.ajic.2019.03.024.

[3] Sands M, Aunger R. Process evaluation of an acute-care nurse-centred hand hygiene intervention in US hospitals. Eval Rev 2020;41:29 https://doi.org/10.1186/s40985-020-00141-6.

[4] Longtin Y, Sax H, Allegranzi B, Schneider F, Pittet D. Videos in clinical medicine. Hand hygiene. N Engl J Med 2011;364:e24. https://doi.org/10.1056/NEJMvcm0903599.

[5] Seferi A, Parginos K, Jean W, Calero C, Fogel J, Modeste S, Scott BA, Daly-Walsh M, Yap W, Kaur M, Brady T, Madaline T. Hand hygiene behavior change: a review and pilot study of an automated hand hygiene reminder system implementation in a public hospital. Antimicrob Steward Healthc Epidemiol 2023;3:e122. https://doi.org/10.1017/ash.2023.195.

[6] Lambe KA, Lydon S, Madden C, Vellinga A, Hehir A, Walsh M, O'Connor P. Hand hygiene compliance in the ICU: a systematic review. Crit Care Med 2019;47:1251-7. https://doi.org/10.1097/CCM.0000000000003868.

[7] Chang NC, Jones M, Reisinger HS, Schweizer ML, Chrischilles E, Chorazy M, Huskins WC, Herwaldt L. Hand hygiene and the sequence of patient care. Infect Control Hosp Epidemiol 2022;43:218-23. https://doi.org/10.1017/ice.2021.82.

[8] Najafi Ghezeljeh T, Abbas Nejhad Z, Rafii F. A literature review of hand hygiene in Iran. Iran Journal of Nursing (IJN) 2013;25:1-13.

[9] Nouri B, Hajizadeh M, Bahmanpour K, Sadafi M, Rezaei S, Valiee S. Hand hygiene adherence among Iranian nurses: a systematic review and meta-analysis. Nurs Pract Today 2021;8:11-24. https://doi.org/10.18502/npt.v8i1.4488.

[10] Ziasheikholeslami N, Razavian F, Vafaei K, Esmkhani S. Evaluation of the Level of Hand Hygiene in Intensive Care Unit personnel of Kamkar Education, Research and Treatment Center of Qom in 2014, Iran. Qom University of Medical Sciences Journal 2016;10:64-9.

[11] Mohanty A, Gupta PK, Gupta P, Kaistha N, Gupta P, Shankar R, Kumar P. Baseline assessment of hand hygiene knowledge perception: an observational study at a newly set up teaching hospital. J Family Med Prim Care 2020;9:2460-4. https://doi.org/10.4103/jfmpc.jfmpc_20_20.

[12] Santy-Tomlinson J. We need to talk about hand hygiene: a time to reflect on compliance. Int J Orthop Trauma Nurs 2020;39:100819. https://doi.org/10.1016/j.ijotn.2020.100819.

[13] Kobra P, Sima L, Fariborz R, Rasouli AS, Neda K. The comparison of the effectiveness of two education methods video and lecture on knowledge, belief and practice of hand hygiene in nursing students: clinical trial. Int J Med Res Health Sci 2016;5:240-8.

[14] De Farias MEL, da Silva Gonçalves J, de Jesus IS. Adesão à higiene das mãos antes e após intervenções educativas do dia mundial para higienização das mãos em um hospital universitário. Revista Eletrônica Acervo Saúde 2019;11:e1354-e. https://doi.org/10.25248/reas.e1354.2019.

[15] Martos-Cabrera MB, Mota-Romero E, Martos-García R, Gómez-Urquiza JL, Suleiman-Martos N, Albendín-García L, Cañadas-De la Fuente GA. Hand hygiene teaching strategies among nursing staff: a systematic review. Int J Environ Res Public Health 2019;16:3039. https://doi.org/10.3390/ijerph16173039.

[16] Zandiyeh M, Borzo SR. The level of hand hygiene compliance by operating room personnel of Educational Hospitals in Hamadan University of Medical Science. JHNM 2012;22:23-9.

[17] Sands M, Aunger R. Development of a behaviour change intervention using a theory-based approach, Behaviour Centred Design, to increase nurses' hand hygiene compliance in the US hospitals. Implement Sci Commun 2021;2:1-18. https://doi.org/10.1186/s43058-021-00124-x.

[18] Nour-Eldein H, Eldahshan NA. The effectiveness of hand hygiene education intervention for medical students in primary care settings, Ismailia city, Egypt. Middle East J Fam Med 2015;13:32-40. https://doi.org/10.5742/MEWFM.2015.92667.

[19] Ghaffari M, Rakhshanderou S, Safari-Moradabadi A, Barkati H. Exploring determinants of hand hygiene among hospital nurses: a qualitative study. BMC Nurs 2020;19:109. https://doi.org/10.1186/s12912-020-00505-y.

[20] Bikmoradi A, Mardani D, Soltanian A, Khatiban M. The impact of educational evidence-based hand washing program on knowledge, attitude, and adherence of intensive care units nurses. Avicenna J Nurs Midwifery Care 2013;21:5-13.

[21] Yen PH, Leasure AR. Use and effectiveness of the teach-back method in patient education and health outcomes. Fed Pract 2019;36:284-9.

[22] Graveto JM, Santos C, Costa PS, Fernandes E, Alarico S, Osório N, Albano H, Oliveira V. Hand hygiene management among nurses: collective health challenges. Rev Bras Enferm 2018;71(Suppl 1):562-7. https://doi.org/10.1590/0034-7167-2017-053.

[23] Naar S, Suarez M. Motivational interviewing with adolescents and young adults. Guilford Publications 2021.

[24] Choi S, Choi J. Effects of the teach-back method among cancer patients: a systematic review of the literature. Support Care Cancer 2021;29:7259-68. https://doi.org/10.1007/s00520-021-06445-w.

[25] Shersher V, Haines TP, Sturgiss L, Weller C, Williams C. Definitions and use of the teach-back method in healthcare consultations with patients: A systematic review and thematic synthesis. Patient Educ Couns 2021;104:118-29. https://doi.org/10.1016/j.pec.2020.07.026.

[26] Oh EG, Lee HJ, Yang YL, Lee S, Kim YM. Development of a discharge education program using the teach-back method for heart failure patients. BMC Nurs 2021;20:109. https://doi.org/10.1186/s12912-021-00622-2.

[27] Barikani A, Negarandeh R, Moin M, Fazlollahi MR. The impact of motivational interview on self-efficacy, beliefs about medicines and medication adherence among adolescents with asthma: a randomized controlled trial. J Pediatr Nurs 2021;60:116-22. https://doi.org/10.1016/j.pedn.2021.04.020.

[28] Eloi H. Implementing teach-back during patient discharge education. Nurs Forum 2021;56:766-71. https://doi.org/10.1111/nuf.12585.

[29] McKay D. Motivational interviewing: accelerating readiness to change. J Cogn Psychother 2021 Apr 8:JCPSY-D-21-00005. https://doi.org/10.1891/JCPSY-D-21-00005.

[30] Miller W.R, Rollnick S. Motivational interviewing: helping people change and grow. Guilford Publications 2023.

[31] Bischof G, Bischof A, Rumpf HJ. Motivational interviewing: an evidence-based approach for use in medical practice. Dtsch Arztebl Int 2021;118:109-15. https://doi.org/10.3238/arztebl.m2021.0014.

[32] Sokalski T, Hayden KA, Raffin Bouchal S, Singh P, King-Shier K. Motivational interviewing and self-care practices in adult patients with heart failure: a systematic review and narrative synthesis. J Cardiovasc Nurs 2020;35:107-15. https://doi.org/10.1097/JCN.0000000000000627.

[33] Suire KB, Kavookjian J, Wadsworth DD. Motivational interviewing for overweight children: a systematic review. Pediatrics 2020;146:e20200193. https://doi.org/10.1542/peds.2020-0193.

[34] Oveisi S, Stein LAR, Babaeepour E, Araban M. The impact of motivational interviewing on relapse to substance use among women in Iran: a randomized clinical trial. BMC Psychiatry 2020;20:157. https://doi.org/10.1186/s12888-020-02561-9.

[35] Östlund AS, Wadensten B, Kristofferzon ML, Häggström E. Motivational interviewing: experiences of primary care nurses trained in the method. Nurse Educ Pract 2015;15:111-8. https://doi.org/10.1016/j.nepr.2014.11.005.

[36] Anderson KM, Leister S, De Rego R. The 5Ts for Teach Back: An Operational Definition for Teach-Back Training. Health Lit Res Pract 2020;4:e94-e103. https://doi.org/10.3928/24748307-20200318-01.

[37] Pawase MA, Tomy S, Gaikwad VS, Naik P, Gunjal VR, Kadam SB. Effectiveness of teach back method on knowledge and practice regarding hand washing among students of selected school. International Journal of Nursing Education and Research 2023;11:137-42. https://doi.org/10.52711/2454-2660.2023.00030.

[38] Widder R. Learning to use motivational interviewing effectively: modules. J Contin Educ Nurs 2017;48:312-9. https://doi.org/10.3928/00220124-20170616-08.

[39] Miller WR, Rollnick S. Motivational interviewing: helping people change and grow. Guilford press 2012.

[40] Bodenheimer T. Teach-back: a simple technique to enhance patients' understanding. Fam Pract Manag 2018;25:20-2.

[41] Salamati P, Poursharifi H, Rahbarimanesh AA, Koochak HE, Najafi Z. Effectiveness of motivational interviewing in promoting hand hygiene of nursing personnel. Int J Prev Med 2013;4:441-7.

[42] Gönderen Çakmak HS, Kapucu S. The effect of educational follow-up with the motivational interview technique on self-efficacy and drug adherence in cancer patients using oral chemotherapy treatment: a randomized controlled trial. Semin Oncol Nurs 2021;37:151140. https://doi.org/10.1016/j.soncn.2021.151140.

[43] Huang X, Xu N, Wang Y, Sun Y, Guo A. The effects of motivational interviewing on hypertension management: a systematic review and meta-analysis. Patient Educ Couns 2023;112:107760. https://doi.org/10.1016/j.pec.2023.107760.

[44] Pas ET, Bradshaw CP. Introduction to the special issue on optimizing the implementation and effectiveness of preventive interventions through motivational interviewing. Prev Sci 2021;22:683-8. https://doi.org/10.1007/s11121-021-01278-9.

[45] Mohammadi F, Jahromi MS, Bijani M, Karimi S, Dehghan A. Investigating the effect of multimedia education in combination with teach-back method on quality of life and cardiac anxiety in patients with heart failure: a randomized clinical trial. BMC Cardiovasc Disord 2021;21:535. https://doi.org/10.1186/s12872-021-02357-z.

[46] Oh EG, Lee HJ, Yang YL, Kim YM. Effectiveness of discharge education with the teach-back method on 30-day readmission: a systematic review. J Patient Saf 2021;17:305-310. https://doi.org/10.1097/PTS.0000000000000596.

[47] Zabolypour S, Alishapour M, Behnammoghadam M, Abbasi Larki R, Zoladl M. A comparison of the effects of teach-back and motivational interviewing on the adherence to medical regimen in patients with hypertension. Patient Prefer Adherence 2020;14:401-10. https://doi.org/10.2147/PPA.S23171.

[48] Najjarnasab S, Dashbozorg Z. The effect of motivational interviewing on health promoting lifestyles and blood pressure of women with eating disorders. Health Psychology 2019;8:103-18. https://doi.org/10.30473/hpj.2019.40367.4005.

[49] Dehghani F S, Ghasemi H, Safari S, Ebrahimi AA, Etemadi O. The effectiveness of group motivational interviewing sessions on enhancing of addicted women's self-esteem and self efficacy. J Res Addict 2013;7:145-58.

[50] Dorstyn DS, Mathias JL, Bombardier CH, Osborn AJ. Motivational interviewing to promote health outcomes and behaviour change in multiple sclerosis: a systematic review. Clin Rehabil 2020;34:299-309. https://doi.org/10.1177/0269215519895790.

[51] Alperstein D, Sharpe L. The efficacy of motivational interviewing in adults with chronic pain: a meta-analysis and systematic review. J Pain 2016;17:393-403. https://doi.org/10.1016/j.jpain.2015.10.021.

[52] Vafadar Z, Reazei R, Navidian A. Effectiveness of motivational interviewing on the weight self-efficacy life style in overweight and obese teenager boys. International Journal of Behavioral Sciences 2014;8:185-93.

[53] Arkowitz H, Westra HA. Introduction to the special series on motivational interviewing and psychotherapy. J Clin Psychol 2009;65:1149-55. https://doi.org/10.1002/jclp.20640.

[54] Feinberg I, Hendry T, Tighe E, Ogrodnick M, Czarnonycz C. Teach-Back Training for Nursing Students: Knowledge and Beliefs After Training for Health Literate Communication. Nurs Educ Perspect 2021;42:177-8. https://doi.org/10.1097/01.NEP.0000000000000670.

[55] Masror Roudsari D, Feizi S, Maghsudlu M. Nurses' hemovigilance knowledge and performance after teach-back, concept map, and lecture: a quasi-experimental study. Heliyon 2021;7:e05982. https://doi.org/10.1016/j.heliyon.2021.e05982.

[56] Klingbeil C, Gibson C. The Teach Back Project: a system-wide evidence based practice implementation. J Pediatr Nurs 2018;42:81-5. https://doi.org/10.1016/j.pedn.2018.06.002.

[57] Rahmani A, Vahedian-Azimi A, Sirati-Nir M, Norouzadeh R, Rozdar H, Sahebkar A. The effect of the teach-back method on knowledge, performance, readmission, and quality of life in heart failure patients. Cardiol Res Pract 2020;2020:8897881. https://doi.org/10.1155/2020/8897881.

Received on January 25, 2022. Accepted on January 18, 2024.

Correspondence: Zohreh Vafadar, Associate Professor of Nursing. Nursing Faculty, Baqiyatallah University of Medical Sciences, Tehran, Iran. E-mail: zohrehvafadar@gmail.com

How to cite this article: Abbasi Z, Mollahadi M, Khamseh F, Vafadar Z. Motivational interview and teach back: effectiveness on the rate of hand hygiene compliance in ICU Nurses. J Prev Med Hyg 2024;65:E265-E272. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.2484

Nosocomial infection

Surveillance of surgical site infections in orthopedic prosthetic surgery: a tool for identifying risk factors and improving clinical practice

MARTINA PORRETTO[1,2], FLAVIO PARENTE[1,2], FILIPPO DEL PUENTE[3], ANDREA PARISINI[3], STEFANIA TIGANO[3], MAURO NELLI[1], CLAUDIO MAZZOLA[4], GUIDO DAMIANI[4], GIULIA ADRIANO[5], MARINA SARTINI[2,5], EMANUELE PONTALI[3], MARIA LUISA CRISTINA[2,5], SILVIA BONI[3]

[1] Health Directorate Galliera Hospital, Genoa, Italy; [2] Department of Health Sciences, University of Genoa, Genoa, Italy; [3] Department of Infectious Diseases, Galliera Hospital, Genoa, Italy; [4] S.C. Joint Orthopedics, Galliera Hospital, Genoa, Italy; [5] SSD UO Hospital Hygiene, Galliera Hospital, Genoa, Italy

Keywords

Surgical Site Infection • Knee and Hip prosthesis • Antimicrobial prophylaxis

Summary

Introduction. *Surgical site infections (SSIs) are among the most frequently encountered complications in prosthetic surgery, and are associated with increased hospitalization, costs and in-hospital mortality. There is no national system for the comprehensive monitoring of the incidence of SSIs.*

Methods. *All patients undergoing orthopedic prosthetic surgery from April 1 to June 30, 2023 were enrolled. Clinical evaluation of the surgical site was conducted at 30 days, and a follow-up telephone interview was carried out by means of a specially designed questionnaire at 90 days.*

Results. *A total of 59 patients were included. Surgery was performed on the knee in 71.19% and on the hip in 28.81%. The patients' mean BMI was 28.25 ± 2.97, and their mean ASA score was 2.67 ± 0.58. Six patients had diabetes mellitus. The incidence of SSIs was 5.08%; two infections occurred in knee prosthesis surgery and one in hip surgery. Analysis of the data revealed that diabetes was the main risk factor for the development of infection.*

Conclusions. *Although based on a small number of patients, these results are encouraging, especially considering that the patients had an average ASA score of more than 2 and a high BMI. However, to further reduce the risk of infection, improved hygiene measures have now been implemented in the operating room and the antibiotic prophylaxis protocol has been updated to take into account the potential for MRSA colonization.*

Introduction

Surgical site infections (SSIs) are among the most frequent complications arising from medical care. These infections result in a significant increase in hospitalization duration, costs and mortality [1].

Given their potentially devastating consequences [3], postoperative infections constitute highly serious events, both for the individual patient and for society [2]. The treatment of such infections often involves prolonged hospitalization, the use of targeted, sometimes prolonged, antibiotic treatments and, in many instances, additional surgical procedures. The implications of all this, in terms of the patient's prognosis and healthcare costs, are evident [3].

The infection rate after prosthetic knee surgery ranges from approximately 0.8 to 1.9%, while for total hip prostheses, infection rates are between 0.3 and 1.7% [4]. A different scenario emerges in the case of infections associated with osteosynthesis devices, with incidence rates varying from 1-2% for closed fractures to 30% or more for open fractures [4]. Moreover, mortality in elderly patients with prosthetic infections is estimated to be around 5-10% [4].

The contamination of joint prostheses results from an intricate interplay between bacterial elements, prostheses and host-related factors. Various bacteria adhere to prosthetic material in several ways, and adhesion is influenced by the type of material employed and the smoothness of its surface [3].

Bacterial infections may occur early through direct contamination of prostheses during surgical procedures and/or diffusion from surrounding areas, or later, through hematogenous spread from other foci (20-30%) [3]. Prostheses can be contaminated directly during surgery if pathogens are present in the operating room, on the patient's skin, or on medical staff. Hematogenous sources of infection include skin ulcerations, periodontal infections, and bacteremias from urological procedures. Late infections arise after the first year post-surgery and are often due to hematogenous infections from other foci or skin lesions. These latter infections are more difficult to diagnose, owing to their less evident clinical presentation [3].

Coagulase-negative Staphylococci (CoNS) are the microorganisms most frequently involved in prosthetic infections, with S. epidermidis and S. aureus being predominant in early infections and other bacterial species in late infections. Anaerobic bacteria are less frequently responsible for these infections, and fungal and mycobacterial infections are even less frequent [3].

Risk factors for the development of prosthetic infections can be categorized in three groups: 1) host-related

factors (including advanced age, uncontrolled diabetes, neoplasms, rheumatoid arthritis, sickle cell anemia and previous joint replacement procedures); 2) intraoperative factors (including the use of large prostheses, hematoma formation in the surgical wound and poorly aligned skin incisions); 3) postoperative factors (including the spread of infections from other sites or the presence of skin ulcers) [3].

The implementation of intervention programs reduces the risk of SSIs. Indeed, such programs continue to be a prominent focus in the surveillance of healthcare-associated infections in Europe. The ECDC initiated SSI surveillance in July 2008. In Italy, the National Surgical Site Infection Surveillance System (SNICh) utilizes voluntary participation by regional authorities and healthcare institutions in order to gather epidemiological data, which are then transmitted to the ECDC. The primary goal of SSI surveillance is to standardize data collection, thereby promoting comparability among participating operational units and institutions at the regional, national and international levels [1].

Methods

From April 1, 2023, to June 30, 2023, we enrolled patients in a prospective study on surgical site surveillance in prosthetic surgery. The surgical site was inspected on the 30th day after the procedure. As part of surgical site infection surveillance, a telephone interview was conducted after 90 days by means of a specially formulated questionnaire. The questionnaire was designed to take into account the epidemiological surveillance needs of the hospital's surgical setting, according to the items in Table I.

Statistical analysis

All characteristics were expressed as means with standard deviations, medians and ranges for continuous variables, and, for categorical variables, as absolute values and percentages. As the data did not display a normal distribution, every possible numerical transformation of the data was evaluated. As none of these transformations was able to reduce the effect of skewness, the data were analyzed by means of non-parametric tests. The Kruskal-Wallis test was used to compare means, while the Chi-square test was used to assess independence between variables. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed by means of Stata/SE 14.2 software (StataCorp LP, College Station, TX, USA).

Results

A total of 59 patients, with an average age of 74 ± 8 years (median 75, range 53-90), were enrolled in the study. Of these, 42 (71.19%) were women. The average BMI of the patients enrolled was 28.56 ± 4.52 (median 28.68, range 18.65-38.80).

Tab. I. Demographic and surveillance characteristics.

Age	
Gender	
Type of discharge	Alive or deceased in hospital
Type of surgery	Hip or knee
Date of surgery	
ASA classification	
BMI	
Comorbidity	Diabetes, COPD, hypertension
Cigarette smoking	
Antibiotics	Type of antibiotics, time of administration
Hair removal	Clipper or razor
Skin preparation	2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol antiseptic solution
Perioperative glucose monitoring	
Number of operators in the operating room	
Procedure duration	
Surgical site infection	Date and microorganism
MRSA Surveillance	Nasal swab

ASA: American Society of Anesthesiologists; BMI: body mass index; MRSA: methicillin-resistant staphylococcus aureus; COPD: Chronic obstructive pulmonary disease.

Concerning the types of prosthetic procedures, 42 patients (71.19%) underwent knee prosthesis surgery, which was performed by means of either traditional or robotic techniques, while 17 (28.81%) underwent hip prosthesis surgery (Tab. II). All hip prosthesis procedures were conducted by means of traditional surgical methods, whereas 52.38% of knee prosthesis procedures (22 patients) utilized robotic techniques, and 47.62% (20 patients) employed traditional surgical approaches. Patient classification according to the American Society of Anesthesiologists (ASA) revealed that 34 patients (57.63%) were classified as ASA 2, and 42.37% (25 patients) as ASA 3 (Tab. II). Regarding comorbidities, 10.17% (6 patients) had a history of diabetes. Only one patient had nasal colonization with MRSA, and was treated with mupirocin before surgery [5].

Surgical prophylaxis during the procedures involved the administration of cefazolin in 69.49% (41 patients), levofloxacin plus teicoplanin in 27.12% (16 patients), and teicoplanin alone in 3.39% (2 patients). The median number of operators present in the operating room was 6. The mean duration of the procedures was 98.29 ± 23.05 minutes, with a median of 94 (85-116) minutes, and the average length of hospital stay was 6.39 ± 3.23 days, with a median of 5 (4-8) days.

Only three patients (5.08%) developed an infection; specifically, two infections occurred in knee prosthesis procedures (4.76%) both after robotic surgery, and one after hip prosthesis surgery (5.9%)

The average age of patients who developed an SSI was 76.33 ± 5.03 years, with a mean BMI of 28.25 ± 2.97 and an ASA score of 2.67 ± 0.58. The mean duration of

Tab. II. Characteristics of patients and procedures.

		% (N°)
Type of surgery	Mako robotic arm-assisted	37.29% (22)
	Non-robotic	62.71% (37)
Type of prosthesis	Hip	28.81% (17)
	Knee	71.19% (42)
Diabetes	Yes	10.17% (6)
	No	89.83% (53)
N. operating room operators	5	28.81% (17)
	6	52.54% (31)
	7	10.17% (6)
	8	5.09% (3)
	9	3.39% (2)
Surgical prophylaxis	Cefazolin	69.49% (41)
	Levofloxacin plus teicoplanin	27.12% (16)
	Only teicoplanin	3.39% (2)
Trichotomy	No	5.08% (3)
	Yes	94.92% (56)
ASA score	2	57.63% (34)
	3	42.37% (25)

Tab. III. Patient- and procedure-related features.

	SSIs	No SSI	p
Age (years)	76.33 ± 5.03	74.12 ± 7.81	NS
BMI	28.25 ± 2.97	28.58 ± 4.61	NS
Procedure duration (min)	97.67 ± 11.24	98.32 ± 23.58	NS
Hospital stay (days)	10.33 ± 6.11	6.18 ± 2.95	NS
ASA score	2.67 ± 0.58	2.41 ± 0.50	NS
Number of operators in operating room	6.33 ± 0.58	6 ± 0.97	NS

NS: not significant.

procedures was 97.67 ± 11.24 minutes, and an average of 6.33 ± 0.58 operators were present in the operating room. The average length of hospital stay of those with SSI was 10.33 ± 6.11 days (Tab. III).

Regarding risk factors, only diabetes was found to be significantly associated with the risk of developing a Healthcare-Associated Infection (Tab. IV). Furthermore, analysis of the relationship between the number of operators in the operating room and the risk of developing an SSI revealed an odds ratio (OR) of 1.44 (95% CI 0.43-4.86) for each additional operator present; however, this association was not statistically significant.

Demographic characteristics and intrinsic and extrinsic risk factors were evaluated for each patient who developed an SSI.

Patient 1: a man 71-year-old underwent hip prosthesis surgery; the procedure lasted 95 minutes and a maximum of 7 operators were simultaneously present in the operating room. The patient's risk factors were: ASA 3, BMI 31.47 and impaired glucose tolerance. He was hospitalized for 9 days; 28 days post-surgery, he developed an early infection according to current definitions, caused by Methicillin-Resistant Staphylococcus epidermidis (MRSE).

Patient 2: a man 81-year-old underwent knee prosthesis surgery; the procedure lasted 88 minutes and a maximum of 6 operators were simultaneously present in the operating room. The patient's risk factors were: ASA 2, BMI 27.68 and diabetes. He was hospitalized for 5 days and developed an early infection without culture isolation 3 days post-surgery.

Patient 3: a man 77-year-old patient underwent knee prosthesis surgery; the procedure lasted 110 minutes and a maximum of 6 operators were simultaneously present in the operating room. The patient's risk factors were: ASA 3, BMI 25.6. He was hospitalized for 17 days and developed an MRSE infection 27 days post-surgery.

All three patients had received prophylactic cefazolin, with correct timing and dose.

Discussion

Post-surgical infections in orthopedic prosthetic surgery carry serious disabling sequelae for the patient. Moreover, their treatment often necessitates re-operation or prolonged antibiotic therapy, with a potential impact on the onset of microbial resistance, and increases hospitalization costs. For these reasons, surveillance programs have been introduced into clinical practice, at both local and national levels. Indeed, SSI surveillance improves the quality of care, as it reduces the risk of infection [6]. In the SENIC

Tab. IV. Patient- and procedure-related risk factors.

		No SSI	Yes SSI	p
Type of surgery	Mako robotic arm-assisted	90.91% (20)	9.09% (2)	NS
	Open	97.30% (36)	2.70% (1)	
Site of surgery	Hip	94.12% (16)	5.88% (1)	NS
	Knee	95.24% (40)	4.76% (2)	
Diabetes	Yes	66.67% (4)	33.33% (1)	< 0.001
	No	98.11% (52)	1.89% (2)	
Antibiotic prophylaxis	Cefazolin	92.68% (38)	7.32% (3)	NS
	Levofloxacin + teicoplanin	100% (16)	0	
	Only teicoplanin	100% (2)	0	
Trichotomy	No	100% (3)	0	NS
	Yes (hair removal cream)	94.64% (53)	5.36% (3)	

NS: not significant.

study, for instance, SSI surveillance programs, combined with a control and feedback program for surgeons, were found to be associated with a reduction in the incidence of SSIs [7]. Moreover, a systematic literature review suggested that participating in a surveillance program could improve patient outcomes by reducing SSIs; this may be due either to a "surveillance effect" or to the implementation of evidenced - based practice aimed at preventing SSIs [8].

The Surgical Site Infections Surveillance Service in the United Kingdom reported the chronological development of SSIs from surgery to infection over a maximum one-year monitoring period [9]. In the years 2010/2011 1,221 infections detected in 72,000 patients who had undergone hip and knee replacement procedures.

Of the 1,221 infections detected in 72,000 patients who had undergone hip and knee replacement procedures in 2010/11 on considering inpatient monitoring, readmissions and post-discharge follow-up, most infections (85%) were manifested within 30 days following surgery, with an average time to infection of 14 days [9]. Of these infections 42% were labeled as superficial, 43% as deep incisional, and 15% as organ/space infections, with occurrences of superficial incisional infections being documented only within 30 days post-surgery [9].

Data from an observational study conducted in California on 25 patients who experienced an infection after hip surgery between March 2001 and December 2002 showed that referrals owing to a diagnosis of infection after total hip arthroplasty significantly increased over five years ($p = 0.0083$), while rates of non-infection-related revisions remained steady ($p = 0.3910$) [10]. Deep infection, which is a severe complication, occurred in about 0.5 to 3% of primary total hip arthroplasties and in 4 to 6% of revisions [10].

SSI prevention includes a set of actions that are implemented during the preoperative, intraoperative and postoperative phases. In our case series, all patients underwent preoperative hair removal with depilatory cream, and in all the procedures observed, 2% chlorhexidine gluconate in 70% isopropyl alcohol [11] in single-dose dispensers was used as an antiseptic for skin preparation immediately before surgery (evidence 1A).

To date, no specific risk factors for the onset of SSIs in prosthetic surgery have been identified in the literature. Among the various risk factors described in the literature, with regard to the preoperative phase, we considered the ASA score, BMI, diabetes, immunosuppressive therapies, trichotomy (performed or not), nasal carriage of methicillin-resistant Staphylococcus aureus (MRSA), and blood glucose control. Concerning the intraoperative phase, we considered the administration of perioperative prophylaxis at appropriate times and in appropriate ways, the duration of surgery, and the number of operators present in the operating room. The only factor that proved to be significantly associated with SSIs was diabetes, the impact of which was greater than that of BMI or ASA score. This evidence is even more crucial in clinical practice, and emphasizes the need for intensive monitoring of blood glucose levels, both preoperatively and postoperatively, in order to keep blood glucose below 140 mg/dL. Monitoring should be consistently performed, even in non-diabetic patients. Unfortunately, however, monitoring is not consistently performed, even in diabetic patients

Conclusions

In our study, surveillance of surgical site infections enabled us to identify only one risk factor that significantly impacted the development of postoperative infections, namely the presence of diabetes. In the three patients who developed an infection, blood glucose levels were not intensively controlled in the perioperative period, and in only one case was blood glucose tested before the procedure; the value recorded was 184 mg/dL, which is well above the recommended cutoff. Once orthopedic surgeons had been informed of our findings, glycemia testing was routinely undertaken in both diabetic and non-diabetic patients. This adjustment to evidence-based practice was made possible only through active and prospective surveillance, which highlights the importance of such surveillance not only in numerical terms but also in terms of clinical impact. In the coming year, we plan to enroll further patients, in order to assess their outcomes and adherence to the newly implemented measure and to evaluate the impact of this measure on the incidence of infections.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the writing of the manuscript. Data collection: MP, SB. Statistical analysis: MS.

References

[1] Bandini L, D'Ancona F, Creti R, Ricchizzi E, Moro ML, Gagliotti C, Vecchi E, Fabbri E, Cavazzuti L, Tedeschi S. Protocollo Sorveglianza Nazionale delle Infezioni del sito chirurgico (SNICh2) e indicatori di prevenzione negli Ospedali. (versione 1.0 - 12 ottobre 2022). Documento tecnico 0050406-15/12/2022-DGPRE-DGPRE-P.

[2] Romanini E, Tucci G, Zanoli G, Ascione T, Balato G, Baldini A, Borre S, Capanna R, Da Rin De Lorenzo F, Drago L, Falez F, Fantoni M, Galluccio P, Maccauro G, Macri E, Marsella L.T, Meani E, Molendini L.O, Momoli A, Mongardi M, Mugnaini M, Nocco L, Pellegrini A.V, Piccioli A, Riccio G, Romano C, Salomone C, Sandrone C, Schiavone Panni A, Sciortino R, Sessa G, Tarantino U, Tartaglia R, Venditti M, Zagra L, Pavan L. Linee Guida SIOT: prevenzione delle infezioni in chirurgia ortopedica - SISTEMA NAZIONALE LINEE GUIDA DELL'ISTITUTO SUPERIORE DI SANITÀ- Società Italiana di Ortopedia e Traumatologia. 21 maggio 2021. Available at: https://siot.it/wp-content/uploads/2021/06/LG-366-SIOT-Prevenzio-

ne-delle-infezioni-in-chirurgia-ortopedica.pdf (Accessed on 06/12/2023).

[3] Lazzarini L, de Lalla F. Treatment and prevention of prosthetic joint infections. Trends Med 2003;3:75-82. Pharma Project Group srl.

[4] AMCLI ETS. Percorso Diagnostico Le infezioni di protesi articolari e mezzi di osteosintesi. - Rif. 2023-14, rev. 2023. Available at: https://www.amcli.it/wp-content/uploads/2023/05/14_PD-protesi_def16mag2023-tabelle-def.pdf (Accessed on: 06/12/2023).

[5] Borchardt RA, Tzizik D. Update on surgical site infections: The new CDC guidelines. JAAPA 2018;31:524. https://doi.org/10.1097/01.JAA.0000531052.82007.42.

[6] Marchi M, Pan A, Gagliotti C, Morsillo F, Parenti M, Resi D, Moro ML; Sorveglianza Nazionale Infezioni in Chirurgia (SNICh) Study Group. The Italian national surgical site infection surveillance programme and its positive impact, 2009 to 2011. Euro Surveill 2014;19:20815. https://doi.org/10.2807/1560-7917.es2014.19.21.20815.

[7] Hughes JM. Study on the efficacy of nosocomial infection control (SENIC Project): results and implications for the future. Chemotherapy 1988;34:553-61. https://doi.org/10.1159/000238624.

[8] Abbas M, Tartari E, Allegranzi B, Pittet D, Harbarth S. The Effect of participating in a Surgical Site Infection (SSI) Surveillance Network on the time trend of SSI rates: a systematic review. Infect Control Hosp Epidemiol 2017;38:1364-6. https://doi.org/10.1017/ice.2017.186.

[9] Lamagni T. Epidemiology and burden of prosthetic joint infections. J Antimicrob Chemother 2014;69(Suppl 1):i5-10. https://doi.org/10.1093/jac/dku247.

[10] Bozic KJ, Ries MD. The impact of infection after total hip arthroplasty on hospital and surgeon resource utilization. J Bone Joint Surg Am 2005;87:1746-51. https://doi.org/10.2106/JBJS.D.02937.

[11] Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med 2010;362:18-26. https://doi.org/10.1056/NEJMoa0810988.

Received on December 8, 2023. Accepted on January 18, 2024.

Correspondence: Martina Porretto, Health Directorate Galliera Hospital, Genoa, Italy, Department of Health Sciences, University of Genoa, Genoa, Italy. E-mail: martina.porretto@gmail.com

How to cite this article: Porretto M, Parente F, Del Puente F, Parisini A, Tigano S, Nelli M, Mazzola C, Damiani G, Adriano [G], Sartini M, Pontali E, Cristina Ml, Boni S. Surveillance of surgical site infections in orthopedic prosthetic surgery: a tool for identifying risk factors and improving clinical practice. J Prev Med Hyg 2024;65:E273-E277. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3141

E-HEALTH

Development of a User-friendly Health Promotion Website to Spread Evidence-based Information in Italy

ELISA FURIA[1]; CAROLA MINET[1], LUCIA VALCHI[1], MARTA CROCETTI[1], BIANCA RONCAN[1], ELVIRA MASSARO[1], CARLO-SIMONE TROMBETTA[1], DONATELLA PANATTO[1,2]
[1] Department of Health Sciences, University of Genoa, Genoa, Italy;
[2] Interuniversity Centre for Research on Influenza and other Transmissible Infections (CIRI-IT), Genoa, Italy

Keywords

Health communication • Website • Health literacy • Digital platform • Health promotion

Summary

Introduction. *Appropriate communication models and strategies are crucial in order to strengthen preventive and health promotion interventions via digital platforms. Today, 52.23% of the Italian population use the Internet as a source of health-related information. The aim of the "Insegna Salute" project was to create a website that would enable people to satisfy their knowledge health needs and increase their awareness in the field of prevention.*
Methods. *To develop the website, a qualitative literature research was carried out to collect an overview of effective online health communication strategies and tools before, during and after the COVID-19 pandemic. Further, we implemented the website insegnasalute.it according to the one-to-many (screen-to-face) communication model. The second part of the research focused on identifying tools to ensure the constant update of the platform. Finally, we proceeded with the creation of the visual identity.*
Results. *The research resulted in 28 sources regarding health communication, vaccine hesitancy, online health information seeking, visual identity, current digital and social trends and mis/disinformation. Many publications reported that healthcare professionals (HCPs) are the main providers of evidence-based information and the most effective agents against misinformation. Furthermore, most of the articles advocated the use of digital technologies, such as social media and websites, along with proactive and targeted communication strategies.*
Conclusions. *Vaccination hesitancy and other health prevention issues require accurate tools to build trust-based relationships between users and healthcare professionals. In line with the preventive guidelines issued by the Italian Ministry of Health, new tools, such as "Insegna Salute", integrate health knowledge with communication strategies. In the wake of the COVID-19 pandemic, preventive measures are essential to protect the population from misinformation spread and the probability of getting ill.*

Introduction

Information and Communication Technologies (ICT) are a set of technologies that provide access to information via telecommunications and enable users to create and exchange contents. The advent of ICT in the 1990s and their subsequent worldwide diffusion have influenced human life, improving the quality of services and activities and reducing their costs. Their widespread applications have brought changes to the functioning of the public, private and non-profit sectors, including that of public health organizations [1].
According to the DIGITAL 2023 report, approximately 64.4% of the world's population has access to the Internet; 91% of online users access the web from smartphones, while 65.6% also connect from laptop or desktop computers. Users aged from 16 to 64 years access the Internet for the following main reasons: to find information, to stay in touch with friends and family, to keep up to date with news and events, to watch videos, TV programmes and movies, and to find out how to do things [2].
In Italy, 86.1% of the population access the Internet; 94% of users between 16 and 64 years of age do so from smartphones, and 77.3% also from laptops or desktops. Their main reasons are: to find information, to keep up to date with news and events, to find out how to do things, to find new ideas or inspiration, to gather information on places and to organise vacations and travel [3]. Moreover, 52.23% of Italians seek health-related information online [4]. However, 52.4% of adults (> 18) are concerned about online misinformation [3, 5]. Since the early 2000s, online health information has proliferated, and attitudes toward physicians and health organizations have changed. As individuals now feel more empowered and actively involved in taking decisions regarding health issues, many turn to the Internet as their primary source of health-related information before seeking medical attention [6]. However, the quality of online health information can vary enormously, ranging from professionally reviewed and evidenced-based information to personal opinions and conspiracy theories [7, 8]. Moreover, individuals do not always have the skills to understand whether online information is reliable or not. This can lead to unnecessary distress and can increase the tendency to self-diagnose and self-treat. By contrast, if online health information is used with awareness, it can also have a positive impact, as improving the patient-physician relationship [9, 6, 10].

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3148

Since 2020, following the COVID-19 pandemic, an era of unprecedented "infodemic" has emerged. Indeed, the World Health Organization (WHO) has identified the "uncontrolled spread of false information", including misinformation on vaccines, as one of its pressing health concerns for the coming decade [11, 12]. In this regard, studies carried out in Italy have reported that people who access the available evidence-based information and institutional websites display greater acceptance of vaccination. By contrast, individuals who use social media or the Internet as their first source of information are more likely to be vaccine hesitant, owing to the frequent incorrectness of such sources [13, 14]. Indeed, in navigating the web, e-health literacy skills have become crucial, as they can mitigate the effects of false information on vaccination. Providing health literacy skills and implementing certified online evidence-based sources are therefore essential to fight the "infodemic" phenomenon [15, 16, 10].

Historically and consistently, healthcare professionals (HCP), healthcare organizations and academic institutions have played a leading role in driving vaccination acceptance. Furthermore, HCP-led messaging via social media platforms has been proven to be beneficial during recent public health crises and vaccination campaigns. Pro-active strategies that focus on effectively and safely engaging HCPs via social media foster collaboration between medical and public health communities, thereby spreading accurate information and correcting misinformation online. These initiatives offer promising approaches to improve vaccination coverage and prevent health problems [16, 17, 12].

To be successful, communication strategies aimed at countering misinformation must be targeted to specific subgroups, as enhanced specificity in interventions can efficiently mitigate the spread of the infodemic [8]. For instance, large-scale research indicates that approximately half of online health-related search sessions do not concern the individual's own health, but rather that of another person. Searches are more likely to occur when there is a significant emotional connection between the individuals involved, particularly in intrafamily relationships such as parent-child relationships. The results of these studies indicate that parents worldwide frequently rely on the Internet to seek information regarding their child's health-related symptoms and guide their decisions [18]. According to a recent survey, 60% of parents in Italy stated that they would use the Internet to search for information on vaccines [19].

Meta-analyses indicate that fact-checking or debunking can serve as effective methods of rectifying misinformation [20]. Developing platform-based interventions that verify the source and quality of information is a potentially effective approach to tackle widespread misinformation. Public organisations are among the main stakeholders involved in implementing these interventions [20].

A valid example of a successful preventive platform is the Italian VaccinarSì project. Created in 2013 by the Italian Society of Hygiene and Preventive Medicine (SItI), this vaccine communication website was designed to fight vaccination hesitancy. Following the success of the national website, several Italian Regions began to develop their own regional versions [19].

In this setting, the project "Insegna Salute" was developed by the Department of Health Sciences of the University of Genoa (Italy), with the aim of creating a website to share all the health promotion and preventive actions targeting the population, such as informative health and vaccination campaigns. The website provides a source of evidence-based information that allows users to satisfy their knowledge health needs and raise awareness in the field of prevention, by combating misinformation and teaching the skills needed to recognise reliable sources.

Materials and methods

To develop the website, previous studies on the implementation of online awareness-raising projects on health topics were sought via the main search engines: PubMed, Scopus and Google Scholar. The topics of interest and analysis mainly concerned health communication, vaccine hesitancy, communication models and strategies, website design and the target populations of the projects.

The methodology adopted for the research was qualitative, with the intention of collecting information regarding the online seeking behaviour of the population from a socio-communicative point of view. During the harvesting process, the research group paid special attention on effective communication interventions and strategies applied in contexts comparable to "Insegna Salute". The primary literature search did not include any geographical criteria, whereas the secondary search was restricted to Italian contents. Overall, the investigation was limited to data published since 2015, in order to obtain a perspective before, during, and after the COVID-19 pandemic.

Each source collected was verified and applied coherently with the specific case, in order to determine the most effective approach to the development of the website and its content.

Regarding websites designed for information and educational purposes, the one-to-many (screen-to-face) communication model is the most widely used. Therefore, this tool will be used and combined with other specific targeted communication strategies to achieve the goal stated above.

The second part of the research process concerned the identification of tools that would allow the platform to be constantly updated over time. Tools such as Google analytics and questionnaires are implemented in order to verify its effectiveness, by analysing the number of visitors and their satisfaction with the platform and to ascertain individuals' online health information seeking tendencies.

Another crucial step in the "Insegna Salute" project was the creation of the visual identity, which started by

Tab. I. Summary of the medical papers selected in the present article.

Authors	Publication year	Main Theme/Topic	Main conclusions	Methods of evaluation
Yifeng Hu [5]	2015	Online health communication	Technologies can be implemented as tools to improve health communication.	Systematic review
Tan SS et al. [6]	2017	Patient-Physician Relationship Online health communication	Internet health information seeking can improve the patient-physician relationship.	Systematic review
Getman R et al. [9]	2018	Vaccine Hesitancy Online health information	A crowd-based mode of authority, that provides understandable information about vaccines, may be more effective at distributing pro vaccine messages.	Media Analisys
Kubb C et al. [18]	2020	Online health information Parents online behaviour	More studies are needed to understand parental online search behaviours and support parents in their medical decision making.	Systematic review
Islam MS et al. [7]	2021	COVID-19 Online health communication Vaccine Hesitancy	Tracking COVID-19 vaccine misinformation in real-time and engaging with social media to disseminate correct information could help safeguard the public against misinformation.	Online content analysis
Garett R et al. [12]	2021	Vaccine hesitancy Online health information	Public health experts, the medical community and vaccine advocates should correct misinformation online. In addition to social media engagement, new digital tools and applications may be useful in this effort.	Systematic review
Hernandez RG et al. [16]	2021	COVID-19 Online health information Vaccine Hesitancy	Strategies focused on efficiently and safely engaging HCPs on social media and sustaining efforts across vaccine implementation stages will help prevent misinformation.	Algorithms and online content analisys
Viswanath K et al. [17]	2021	COVID-19 Online health information Vaccine Hesitancy	Implementing a pro-active communication campaign strategy must ensure that people are willing to vaccine and that vaccination is uniform across different population groups.	Online survey
Bordin P et al. [19]	2021	Health information website Vaccination	Findings can help website developers to update future strategies to increase the platform popularity and optimize visitors' engagement.	Google Analytics
Zhang J et al. [20]	2021	Online health information Vaccination	Fact checking using evidence-based sources can minimize misinformation.	Online survey experiment
Arghittu A et al. [28]	2021	Health information website Vaccination	Initiatives, such as health information website must be implemented to fight vaccine hesitancy.	Google Analytics
Arghittu A et al. [14]	2021	COVID-19 Online health communication Vaccination	Cooperation between the media and scientific professional can constitute an effective network in debunking disinformation and providing evidence-based sources.	Google Analytics
Kim S et al. [8]	2022	COVID-19 Online health information	The existence of groups with unique characteristics allows targeting of misinformation mitigation strategies.	Online Survey
Wu P et al. [10]	2022	Online health information	E-satisfaction should be further enhanced by information seeking as online healthcare practices evolve and change.	Online Survey
Dib F et al. [11]	2022	COVID-19 Online health information eHealth literacy	e-Health and media literacies should be viewed as fundamental skills that allow citizens to recognize online mis/disinformation and ensure informed decision about vaccination.	Systematic Review
Pierri F et al. [15]	2022	COVID-19 Online health information Vaccine Hesitancy	Results support a need for interventions that address misbeliefs, allowing individuals to make better-informed health decisions.	Online misinformation analysis
Covolo L et al. [22]	2022	Online health information	The result obtained for the survey suggest the need to improve health literacy in the general population. Healthcare professionals need to equip themselves with framework to respond effectively to their patients' needs.	Online Survey
Tagini S et al. [25]	2022	COVID-19 Online health information Vaccine Hesitancy	Vaccine-related communications should be clear and understandable to prevent the spreading of misunderstandings and fake information, that may foster people's insecurities and distrust. Efficacious vaccine-related communications may be crucial to inform policymakers and public authorities in the case of possible future infectious outbreaks.	Online Survey

▶

Tab. I (*follows*). Summary of the medical papers selected in the present article.

Authors	Publication year	Main Theme/Topic	Main conclusions	Methods of evaluation
Arghittu A et al. [1]	2023	COVID-19 Online health information	It is urgent to strengthen and innovate the network of territorial social-health services and to devise new integration strategies, promoting the active participation of citizenship.	Systematic Review
Bianchi FP et al. [13]	2023	COVID-19 Vaccination hesitancy Online health information	Achieving high vaccination coverages requires a multifactorial approach that demands major social, scientific, and health efforts. The success of vaccination campaigns in this population depends on the capillarity and consistency of the implemented interventions.	Systematic Reviews and Meta-Analyses (PRISMA)
Bianchi FP et al. [27]	2023	Online health information	A multifactorial approach is needed so that institutions can regain the trust of the population and thus better manage the feelings of online users and use mass media and social media as health promotion tools, to fight the issue of VH and understand the role of social and traditional media.	Systematic Reviews and Meta-Analyses (PRISMA)
Ferrara M et al. [26]	2023	Vaccine Hesitancy	It is necessary to strengthen the trust of the population through the implementation of health communication and public education strategies. Scientific literacy must continue to support families and individuals in discerning evidence from opinions.	Systematic review
Zhang Q et al. [24]	2023	Parents online behaviour	Operators need to create a user-friendly platform and improve information quality. Physicians and related organizations can raise awareness and assist patients in developing the skills to appropriately comprehend and utilize information online.	Online survey
D'Andrea et al. [23]	2023	Online health information	An important result of the study is that online health information seekers consider the family doctor a point of reference both for obtaining information and for discussing the information found online. The respondents mainly rely on official sources for health information research. Educational strategies should be activated at the school level to train students to become more aware of the risk associated with online health information.	Online survey

defining the goals of the project and determining how these could best be represented through a composition of elements and colours. This process involved several professionals: physicians, communication specialists, public health experts and medical graphics designers. Indeed, the visual identity is the manifestation of the product and is intended to evoke certain feelings in the viewer. It also makes the entity recognisable by giving more depth to the entire project structure [21].

Results

As a result of the literature research, 28 sources were selected. Of these, 24 were medical journals papers, 1 was a visual identity online article, 2 were digital and social scenario reports and 1 was a Eurostat database [1-28].

Out of the 24 medical papers (Tab I), 5 were published between 2015 and 2020 and dealt with the pre-COVID-19 online dissemination of health information and vaccination hesitancy. The rest (19) were defined as post-COVID-19 (2021-2023) papers: 9's main topics were health communication problems during the pandemic, while the other 10 covered topics such as primary care and strategies for fighting online misinformation. The main evaluation methods and tools used in the articles were: systematic reviews, analyses of media and online content, online surveys and Google analytics. Furthermore, 11 of the total were Italian and provided more specific knowledge about the setting for our website.

Of the latter, 2 papers reported that participants relied less frequently on online health information than expected. The first one, stated that 36.5% of the study participants believed that online information did not improve their health knowledge, and 40.8% that online information did not influence their health [22]. Moreover, in the second one, 37% of the participants reported that they rarely turned to websites for health information and 46% stated that they had little trust in information obtained from websites [23].

Finally, multiple team-work sessions led to the creation of the visual identity, which symbolises a pencil and a tree (Fig. 1). The aim was to represent the goals of the website: to educate and inform the population over a lifelong perspective. The colours most often used in education and awareness-raising settings of health

Fig. 1. Visual identity of the health promotion and prevention project "Insegna Salute".

prevention are orange and green. Indeed, green is often associated with trust, while warm colours such as orange convey positivity. Figure 1 shows the visual identity of the "Insegna Salute" project.

Discussion

Many publications cited HCPs as the main agents for the dissemination of evidence-based information and those who could most effectively fight mis/disinformation (see Tab. I). Furthermore, as previously said in the "Results" section, most articles advocated the use of digital technologies, such as social media and websites, combined with the implementation of active and targeted communication strategies.

During the literature search, no sources were found to refute the use of digital platforms for the dissemination of health information. Most of the articles collected supported the fact that online media were found to be crucial in the last few years in the processes of educating the population on health.

Today, it is essential to adopt these combinations in order to enhance initiatives for health prevention and promotion, thereby supporting the goals of the "life-course" approach, which is aimed at maintaining well-being throughout life. Therefore, the *insegnasalute.it* website adopts the "one-to-many" (screen-to-face) communication model, which is used in mass communication and is aimed at educating and informing the population. The model involves one sender, who transmits to several receivers through a one-way communication channel, such as television or radio. Its application can also be targeted via devices that allow network access (screen-to-face), such as computers, smartphones and tablets. Thus, the interaction features of these tools can be linked to a more authoritative and informative communication, addressing the scientific knowledge of topics.

As the website has a user-centred design, it features a dynamic and user-friendly interface. The aim is to let individuals navigate the website easily and find the information they are looking for [24]. Another key feature is the use of clear and understandable language and terminology [25, 26]. Users are also able to learn the meanings of various scientific terms, thanks to a dedicated page called "Glossario". Moreover, in order to help people to distinguish between correct from false information and to increase their level of health literacy, a dedicated section shows them how to use online health information in a safer and more conscious way. Sections are dedicated to preventive health topics, the Department's projects, news from the Italian Ministry of Health and from the medical-scientific field.

Over the last few years, the concept of the superstar scientist has been debunked, as it is not effective in promoting health information. Instead, what is required is the widespread availability of institutional channels managed by teams of specialists in medicine, health, communication and psychology [27]. Our work team will make sure that the information reported will be transparent, objective and based on reliable scientific sources, which will be available for more specific consultation.

As specified above, the goal is not only to inform people, but also to understand and meet their needs. Google Analytics, questionnaires and surveys therefore provide data on users' health literacy, needs and online health-seeking behaviour, thus enabling the *insegnasalute.it* website to be constantly updated and its effectiveness enhanced. In addition, a newsletter will keep users informed about articles published on the website and news of interest [14, 28]. It is, however, important to remember that the pattern of visits to the website will be unpredictable and might be related to news facts or other events [19].

Conclusions

According to several studies, the features most required of a digital platform are performance expectancy, effort expectancy, social influence, perceived risk, and eHealth literacy. The new technology must therefore be easy to use and effective, satisfy users and attract new ones, respect privacy guidelines and provide accurate and comprehensible health information [27].

Vaccination hesitancy and other health prevention issues can only be addressed through the use of proper and accurate tools that allow a trust-based relationship to be built.

The creation of a dedicated digital platform enables on-site interventions to have continuity, through the constantly updated information provided and the communications sent to newsletter subscribers. In accordance with the 2020-25 National Prevention Plan guidelines provided by the Italian Ministry of

Health, modern tools are used in combination with health knowledge and new communication strategies. Indeed, in the wake of dangerous global events such as the COVID-19 pandemic, preventive measures have become essential in order to protect the population from the spread of communicable diseases.

Funding sources

This research did not receive any funding from agencies in the public, commercial, or non-profit sectors.

Informed consent statement

Not applicable.

Conflict of interest statement

The authors have no conflict of interest.

Authors' contributions

EF and DP: designed the study and coordinated the research; EF: wrote the manuscript; LV, CM and DP: critically reviewed the draft paper and made important contributions; LV, CM, CST, BR, MC and EM: drafted and developed the content of the website; EF, LV, BR and MC: participated in the development of the visual identity; all authors have read and approved the final manuscript.

References

[1] Arghittu A, Castiglia P, Dettori M. Family medicine and primary healthcare: the past, present and future. Healthcare 2023;11:2128. https://doi.org/10.3390/healthcare11152128.

[2] We Are Social Italy. DIGITAL 2023 - I DATI GLOBALI - We Are Social Italy; Available at: https://wearesocial.com/it/blog/2023/01/digital-2023-i-dati-globali (Accessed on: 19/10/2023).

[3] We Are Social Italy. DIGITAL 2023 - I dati Italiani - We Are Social Italy; Available from: https://wearesocial.com/it/blog/2023/02/digital-2023-i-dati-italiani/ (Accessed on: 19/10/2023).

[4] Eurostat | European Commission. Accessed on 08/11/2023 https://ec.europa.eu/eurostat/databrowser/view/tin00101__custom_8377861/default/table?lang=en.

[5] Yifeng Hu. Health communication research in the digital age: A systematic review. Journal of Communication in Healthcare 2015;4:260-88. https://doi.org/10.1080/17538068.2015.1107308.

[6] Tan SS, Goonawardene N. Internet health information seeking and the patient-physician relationship: a systematic review. J Med Internet Res 2017;19:e9. https://doi.org/10.2196/jmir.5729.

[7] Islam MS, Kamal AM, Kabir A, et al. COVID-19 vaccine rumors and conspiracy theories: the need for cognitive inoculation against misinformation to improve vaccine adherence. PLoS One 2021;16:e0251605. https://doi.org/10.1371/journal.pone.0251605.

[8] Kim S, Capasso A, Ali SH, et al. What predicts people's belief in COVID-19 misinformation? A retrospective study using a nationwide online survey among adults residing in the United States. BMC Public Health 2022;22:2114. https://doi.org/10.1186/s12889-022-14431-y.

[9] Getman R, Helmi M, Roberts H, et al. Vaccine hesitancy and online information: the influence of digital networks. Health Educ Behav 2018;45:599-606. https://doi.org/10.1177/1090198117739673.

[10] Wu P, Zhang R. Exploring the effects of health information seeking on e-satisfaction in online health communities: an empirical investigation. BMC Med Inform Decis Mak 2022;22:332. https://doi.org/10.1186/s12911-022-02079-y.

[11] Dib F, Mayaud P, Chauvin P, Launay O. Online mis/disinformation and vaccine hesitancy in the era of COVID-19: Why we need an eHealth literacy revolution. Hum Vaccin Immunother 2022;18:1-3. https://doi.org/10.1080/21645515.2021.1874218.

[12] Garett R, Young SD. Online misinformation and vaccine hesitancy. Transl Behav Med 2021;11:2194-9. https://doi.org/10.1093/tbm/ibab128.

[13] Bianchi FP, Stefanizzi P, Cuscianna E, et al. COVID-19 vaccination hesitancy among Italian parents: a systematic review and meta-analysis. Hum Vaccin Immunother 2023;19:2171185. https://doi.org/10.1080/21645515.2023.2171185.

[14] Arghittu A, Dettori M, Dempsey E, et al. Health Communication in COVID-19 Era: experiences from the Italian VaccinarSì Network Websites. Int J Environ Res Public Health 2021;18:5642. https://doi.org/10.3390/ijerph18115642.

[15] Pierri F, Perry BL, DeVerna MR, et al. Online misinformation is linked to early COVID-19 vaccination hesitancy and refusal. Sci Rep 2022;12:5966. https://doi.org/10.1038/s41598-022-10070-w.

[16] Hernandez RG, Hagen L, Walker K, et al. The COVID-19 vaccine social media infodemic: healthcare providers' missed dose in addressing misinformation and vaccine hesitancy. Hum Vaccin Immunother 2021;17:2962-4. https://doi.org/10.1080/21645515.2021.1912551.

[17] Viswanath K, Bekalu M, Dhawan D, et al. Individual and social determinants of COVID-19 vaccine uptake. BMC Public Health 2021;21:818. https://doi.org/10.1186/s12889-021-10862-1.

[18] Kubb C, Foran HM. Online Health Information Seeking by Parents for Their Children: Systematic Review and Agenda for Further Research. J Med Internet Res 2020;22:e19985. https://doi.org/10.2196/19985.

[19] Bordin P, Melot B, Tralli V, et al. Six years of activity of the Italian vaccine portal "VaccinarSì": a web traffic evaluation using Google Analytics. Ann Ig 2021;33:109-22. https://doi.org/10.7416/ai.2021.2417.

[20] Zhang J, Featherstone JD, Calabrese C, Wojcieszak M. Effects of fact-checking social media vaccine misinformation on attitudes toward vaccines. Prev Med 2021;145:106408. https://doi.org/ 10.1016/j.ypmed.2020.106408.

[21] Oppelt, J. What Is a Visual Identity and Why Does It Play a Crucial Role in Branding? The Branding Journal 2023. https://www.thebrandingjournal.com/2023/05/visual-identity (Accessed on: 13/11/2023).

[22] Covolo L, Guana M, Bonaccorsi G, et al. Exploring the Online Health Information-Seeking Behavior in a Sample of Italian Women: The "SEI Donna" Study. Int J Environ Res Public Health 2022;19:4745. https://doi.org/10.3390/ijerph19084745.

[23] D'Andrea A, Grifoni P, Ferri F. Online Health Information Seeking: An Italian Case Study for Analyzing Citizens' Behavior and Perception. Int J Environ Res Public Health 2023;20:1076. https://doi.org/10.3390/ijerph20021076.

[24] Zhang Q, Zhang R, Lu X, Zhang X. What drives the adoption of online health communities? An empirical study from patient-

centric perspective. BMC Health Serv Res 2023;23:524. https://doi.org/10.1186/s12913-023-09469-6.

[25] Tagini S, Brugnera A, Ferrucci R, et al. Behind the scenes of COVID-19 vaccine hesitancy: psychological predictors in an Italian community sample. Vaccines 2022;10:1158. https://doi.org/10.3390/vaccines10071158.

[26] Ferrara M, Bertozzi G, Volonnino G, et al. Learning from the past to improve the future-vaccine hesitancy determinants in the Italian population: a systematic review. Vaccines 2023;11:630. https://doi.org/10.3390/vaccines11030630.

[27] Bianchi FP, Tafuri S. Spreading of misinformation on mass media and digital platforms regarding vaccines. A systematic scoping review on stakeholders, policymakers, and sentiments/behavior of Italian consumers. Hum Vaccin Immunother 2023;19:2259398. https://doi.org/10.1080/21645515.2023.2259398.

[28] Arghittu A, Deiana G, Dettori M, et al. Web-based analysis on the role of digital media in health communication: the experience of VaccinarSinSardegna Website. Acta Biomed 2021;92:e2021456. https://doi.org/10.23750/abm.v92iS6.12072.

Received on December 14, 2023. Accepted on May 9, 2024.

Correspondence: Elisa Furia, Department of Health Science, University of Genoa, Via Pastore 1, 16132, GE, Italy. E-mail: elisafuria1999@gmail.com

How to cite this article: Furia E, Minet C, Valchi L, Crocetti M, Roncan B, Massaro E, Trombetta CS, Panatto D. Development of a User-friendly Health Promotion Website to Spread Evidence-based Information in Italy. J Prev Med Hyg 2024;65:E278-E284. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3148

e-Health

Perspectives on AI use in medicine: views of the Italian Society of Artificial Intelligence in Medicine

FRANCESCO ANDREA CAUSIO[1,2], LUIGI DE ANGELIS[1,3], GIACOMO DIEDENHOFEN[1,4], ANGELO TALIO[1,5], FRANCESCO BAGLIVO[1,3], Workshop Participants[1]

[1] Italian Society for Artificial Intelligence in Medicine (SIIAM - Società Italiana Intelligenza Artificiale in Medicina), Rome, Italy; [2] Section of Hygiene, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy; [3] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [4] Department of Public Health and Infectious Diseases, Sapienza University, Rome, Italy; [5] Department of Biomedical Sciences, Humanitas University, Milan, Italy

Keywords

Artificial Intelligence • Machine Learning • Large Language Models • Workshop

Summary

The first annual meeting of the Italian Society for Artificial Intelligence in Medicine (Società Italiana Intelligenza Artificiale in Medicina, SIIAM) on December 7, 2023, marked a significant milestone in integrating artificial intelligence (AI) into Italy's healthcare framework. This paper reports on the collaborative workshop conducted during this event, highlighting the collective efforts of 51 professionals from diverse fields including medicine, engineering, data science, and law. The interdisciplinary background of the participants played a crucial role in generating ideas for innovative AI solutions tailored to healthcare challenges. Central to the discussions were several AI applications aimed at improving patient care and streamlining healthcare processes. Notably, the use of Large Language Models (LLMs) in remote monitoring of chronic patients emerged as an area of focus. These models promise enhanced patient monitoring through detailed symptom checking and anomaly detection, thereby facilitating timely medical interventions. Another significant proposal involved employing LLMs to improve empathy in medical communication, addressing the challenges posed by cultural diversity and high-stress levels among healthcare professionals. Additionally, the development of Machine Learning algorithms for standardizing treatment in pediatric emergency departments was discussed, along with the need for educational initiatives to enhance AI adoption in rural healthcare settings. The workshop also explored using LLMs for efficient data extraction and analysis in scientific literature, interpreting healthcare norms, and streamlining hospital discharge records. This paper provides a comprehensive overview of the ideas and solutions proposed at the workshop, reflecting the participants' forward-thinking vision and the potential of AI to revolutionize healthcare.

Introduction

The Italian Society for Artificial Intelligence in Medicine (Società Italiana Intelligenza Artificiale in Medicina - SIIAM) conducted its First Annual Meeting on December 7, 2023, a pivotal step in its mission of integrating artificial intelligence (AI) into Italy's healthcare landscape. This event gathered a multidisciplinary cohort of 51 professionals (36 males and 15 females), comprising 36 physicians and 15 non-physicians, encompassing mathematicians, veterinarians, engineers, statisticians, lawyers, and data scientists. The diversity of this group is not merely a demographic characteristic but a critical asset for fostering innovation in healthcare through interdisciplinary collaboration on healthcare advancements [1].

Research indicates that the blend of diverse professional backgrounds catalyzes innovative thinking in healthcare. Additionally, the cognitive diversity of interdisciplinary teams, such as the one assembled at the SIIAM meeting, is crucial for fostering innovation through debate and knowledge exchange and enhancing group performance, particularly in innovative settings [2, 3].

During the conference, a key highlight was the collaborative workshop moderated by the organizers, wherein attendees were organized into diverse groups to brainstorm ideas centered on the integration of AI within Italy's healthcare framework. In this paper, we report the insights that emerged from this workshop, reflecting the participants' collective creativity and forward-thinking vision.

SIIAM collaborative workshop

The collaborative workshop was designed to foster individual and group discussion about introducing AI solutions in healthcare. Participants spent the first time slot thinking individually about a particular issue they identified within the Italian healthcare system that they thought could be addressed with AI-based solutions. Next, they had a time slot to discuss their thoughts with the person next to them. After this, they were joined into groups of four to five people to discuss their proposals. Each group chose a representative to present their ideas in a plenary session. Each group representative presented one or more proposals, based on group consensus. In this phase, a lively Q&A session with questions from the

moderators and the audience helped explore and refine the proposals.

Remote Patient Monitoring Using LLMs

The clinical applications of AI emerged as the topic that the proposals most frequently centered on. One emerging theme was the remote monitoring of patients, particularly chronic patients with several comorbidities. While some mHealth solutions already exist, Large Language Models (LLMs) show great potential for timely, detailed symptom checking and patient remote monitoring. This application of LLMs enables the development of anomaly detection and alert systems, which can identify deviations from a patient's usual health patterns and prompt timely interventions [4]. Participants highlighted how future solutions tackling remote monitoring of patients, including LLMs, will benefit from the implementation of the national telemedicine platform [5, 6].

Remote patient monitoring, while offering numerous benefits, faces several challenges. These include issues related to the implementation of national platforms, concerns about data privacy laws, costs associated with monitoring devices, the phenomenon of alert fatigue, and the necessity for real-world testing and validation.

Empathy in medical communication

Another proposal underlined the importance of empathy in medical communication [7, 8]. Communication between patients and healthcare professionals, either nurses or physicians, may be marred by misunderstandings or miscommunications, and empathy is an important element of a successful clinical communication strategy [9]. Factors that may negatively impact communication and the successful use of an empathic approach include high workload and burnout prevalence among healthcare workers, which is characterized by emotional exhaustion, depersonalization, and reduced personal accomplishment [10]. In addition, patients with different cultural and social backgrounds could have different communication styles. One group suggested using LLMs to collect data to enact better communication strategies tailored to individual patients' needs [11]. Whereas some tests already address this issue and attempt to gather data to identify specific communication styles best tailored to a patient's needs, they are flawed by the impossibility of collecting non-structured data. The nature of communication itself, however, suggests that there may be a need for a tool capable of analyzing conversations and extracting data flexibly [12]. Participants proposed conducting a prospective study where healthcare practitioners have a conversation with patients and record it, then fine-tune an LLM to analyze it and provide a report on possible strategies and improvements. Data standardization is, however, critical: such a qualitative data source must be handled with care to train an LLM.

The use of LLMs in medical communication is promising, but not without limitations. Challenges include establishing a reliable ground truth for communication, a high risk of biases, significant privacy concerns, and insufficient audio capability alone to capture emotional nuances. Moreover, while analyzing facial expressions could enhance understanding, it remains a contentious issue due to privacy and ethical considerations [13].

Standardizing Pediatric Emergency Care

One group suggested creating a Machine Learning (ML) algorithm to address the issue of inconsistent treatment approaches in pediatric emergency departments [14, 15]. The proposed steps were: a comprehensive review of existing literature, searching for existing solutions tackling problems in the realm of pediatric emergencies, consultation with clinical experts in the field to identify previously unaddressed solutions or to explore feedback from their side (*e.g.*, adopting Delphi surveys as an instrument for expert opinion collection), and the execution of targeted clinical studies to evaluate and refine the algorithm [16]. This algorithm should be designed to standardize patient care by incorporating a set of defined clinical parameters and systematically extracting data from patients' clinical files and other pertinent diagnostic information (*e.g.*, lung imaging, given the high burden of respiratory disease among pediatric patients in emergency departments) [17].

Developing an AI algorithm to standardize treatment in pediatric emergency departments is complex. Limitations include the scarcity of pediatric-specific emergency data, the need for a multimodal AI model due to the diverse nature of pediatric emergencies, and the challenge of achieving expert consensus, which is crucial for training an effective AI clinical model. These challenges highlight the necessity for a gold standard in data and methodology given the difficulties in data collection and expert agreement in these settings [18].

Bridging the technological divide

A critical challenge that emerged is the scarcity of infrastructure necessary for leveraging AI and optimizing data availability in hospitals situated in remote or low-income areas. Such limitations are particularly pronounced outside of metropolitan areas and university hospitals. To mitigate this issue, SIIAM should promote educational and informational projects to elevate awareness of the benefits of AI's application in healthcare in underserved regions. These initiatives are crucial for bridging the technological divide and ensuring that advancements in AI and data analytics translate into tangible health benefits across diverse geographical landscapes.

Moreover, addressing the technological and digital divide within the elderly population is imperative. Italy is the "oldest" country globally, with approximately 23% of its population over the age of 65. This demographic not only requires the majority of healthcare resources but also faces significant challenges in accessing and utilizing digital technologies. The elderly are often less familiar with digital tools and platforms, which hinders their ability to benefit from AI-driven healthcare solutions. Therefore, targeted efforts must be made to include elderly individuals in educational initiatives,

ensuring they understand and can access AI technologies. While education and awareness about AI's potential in healthcare are important, they alone cannot bridge the technological divide in remote or low-income areas and among the elderly. Significant investment in digital infrastructure is crucial for the practical implementation of AI solutions in these regions and for this demographic [19].

By combining educational efforts with substantial infrastructure investments, we can ensure that AI-driven healthcare improvements are inclusive and equitable, thereby addressing the diverse needs of Italy's aging population alongside other underserved communities.

Efficient data extraction and analysis

Researchers participating in the workshop reported on the issue of data extraction and quality analysis in scientific literature and suggested leveraging LLMs to address this [20]. These tools could navigate vast arrays of academic texts, identify pertinent data, and thoroughly assess the research findings. By deploying LLMs, researchers have the potential to streamline the process of manual literature reviews, facilitating more efficient extraction of relevant information and providing a rigorous analysis of the data's integrity and relevance. For example, tools like ChatGPT and similar models can quickly summarize key points from extensive research papers or support title-abstract screening phase in systematic reviews.

While LLMs offer transformative potential in data extraction and quality analysis in scientific literature, they place significant limitations. Researchers must validate each step performed by AI to ensure the accuracy and reliability of the results, Moreover, the over-reliance on automated systems can lead to the risk of deskilling researchers. Additionally, creating trustworthy systems that are readily accepted by healthcare professionals remains challenging, and there is a risk of misinformation, and biases being introduced into the research process [21].

Interpreting healthcare norms and communications

Introducing new norms in healthcare practice often yields diverse impacts, shaped by policy directives from various levels of governance, including local, regional, national, and international bodies [22]. Similarly, directives from hospital management play a pivotal role at a more localized level. Interpreting these norms and directives poses significant challenges, particularly in assessing their interplay with existing norms and recalling pertinent past communications. Workshop participants bringing up these problems underlined the potential of LLMs in this context. They can be effectively employed for assessing the impact of new norms, examining their interactions with pre-existing ones, and keeping abreast of relevant changes and updates [23]. These applications are valuable not only for individuals tasked with drafting these norms and communications but also for those who interpret and implement them. The utilization of LLMs in this capacity is anticipated to yield substantial benefits. By alleviating the burden associated with interpreting complex norms and translating them into plain language, these tools can aid healthcare professionals in adapting their practices to new or updated standards and guidelines. Additionally, they offer the potential to identify and address any blind spots in the norms before their implementation, enhancing the overall efficacy and applicability of healthcare policies and directives. While LLMs show promise in interpreting healthcare norms and directives, their use is not without challenges. These include the risk of generating inaccurate or misleading content (known as 'hallucinations') and the potential for deskilling professionals to over-reliance on automated interpretation. Additionally, interpreting laws involves a degree of subjectivity that may be difficult for LLMs to navigate.

Streamlining hospital discharge records

The task of compiling hospital discharge records (Scheda di Dimissione Ospedaliera, SDO) often presents a significant administrative burden for physicians. This process involves identifying the appropriate diagnosis-related group (DRG) for conditions and interventions and managing administrative details, which is complex and time-consuming. This situation often leads to heterogeneity in SDOs across different practitioners and healthcare facilities, potentially resulting in inconsistencies in patient information, variations in care quality, and challenges in maintaining comprehensive patient histories [24]. Data from discharge records in Italy flow into a unified national SDO database and are, at least theoretically, among the most highly standardized healthcare datasets available nationally, as they are relevant both to clinical and public health research and are how hospital services within the Italian national healthcare service are paid. The use of AI solutions to improve the standardization of data entry and create a semi-automatic process to complete SDO entries could significantly lighten the administrative burden on physicians while ensuring higher data quality. Additionally, physicians are tasked with preparing hospital discharge letters (HDLs) often resulting in unstructured texts that are pieced together through the repetitive copying and pasting from previous reports, which can compromise the quality of these documents. Despite these challenges, discharge records are indispensable for ensuring continuity of care, as they enable primary care and specialist doctors outside the hospital to manage patient care post-discharge effectively. A viable solution to mitigate these issues involves leveraging electronic healthcare records to populate HDLs automatically.

Subsequently, LLMs can draft discharge letters, which the physicians would review and finalize. This approach not only streamlines the administrative process but also enhances the consistency and quality of patient care documentation, ultimately reducing the workload on healthcare professionals and ensuring a more standardized approach to patient discharge procedures. The communication style in the discharge letter could be tailored to the individual patient’s communication style,

Tab. I. Summary of the key AI solutions that emerged during SIIAM's First Annual Meeting collaborative workshop: Advancing Healthcare Through Diverse AI Applications.

Advancing Italian healthcare: Artificial Intelligence solutions from SIIAM's interdisciplinary workshop	
Remote Patient Monitoring Using LLMs	The potential of LLMs in the remote monitoring of chronic patients was a major focus. LLMs can facilitate detailed symptom checking and anomaly detection, thereby enabling timely interventions
Empathy in Medical Communication	Enhancing Empathy in patient-healthcare professional communication through LLMs. This approach involves using LLMs to analyze conversation data, thereby enabling the development of patient-tailored communication strategies
Standardizing Pediatric Emergency Care	The development of an ML algorithm to standardize treatment approaches and pain management in pediatric emergency departments, incorporating clinical parameters and patient history data
Bridging the Technological Divide	Emphasizing the need for educational and informational projects to promote AI adoption in healthcare, particularly in rural and underserved regions
Efficient Data Extraction and Analysis	Leveraging LLMs for efficient and rigorous extraction and analysis of data from scientific literature, thus enhancing the research process and supporting healthcare professionals in keeping themselves up-to-date
Interpreting Healthcare Norms and Communications	Utilizing LLMs to assess the impact of new healthcare norms and directives, ensuring their effective integration and implementation in practice
Streamlining Hospital Discharge Records	Proposing using electronic healthcare records and LLMs to automate and standardize the process of preparing Hospital Discharge Records (SDO), thereby reducing the administrative burden on physicians and improving the quality of patient care documentation

integrating this solution with the one previously proposed. While leveraging electronic healthcare records with LLMs for drafting discharge letters streamlines the process, it faces limitations. These include potential legal issues related to giving LLMs access to sensitive health records and the legal ramifications of using LLM-compiled discharge letters in a medical context [25].

Conclusions

This paper has presented a comprehensive overview of the innovative ideas and solutions discussed during the SIIAM First Annual Meeting collaborative workshop. The confluence of diverse professional backgrounds significantly contributed to the creativity and feasibility of the proposed solutions. The key outcomes of this workshop focused on integrating artificial intelligence (AI) into Italy's healthcare system, are summarized in Table I.

These initiatives underscore SIIAM's commitment to spearheading the integration of AI into healthcare, recognizing the immense potential of AI to revolutionize patient care, improve healthcare outcomes, and streamline administrative processes while remaining mindful of the potential risks and limitations that may arise. The collaborative efforts of interdisciplinary teams, as demonstrated at the SIIAM meeting, are pivotal in realizing these advancements with an unwavering commitment to patient safety, clinical efficacy, and healthcare quality. At the moment, the Italian healthcare system is characterized by time-consuming manual processes, limited data utilization, and slower patient care response times. With the integration of AI, the future of healthcare in Italy promises to be more efficient, empathetic, and patient-centered, setting a benchmark for global healthcare innovation.

Acknowledgments

FAC, LDA, GD, AT, FB: have contributed equally to this work and share first authorship.

SIIAM Workshop participants:

Belpiede Alessandro, Bonaldi Filippo, Cappellini Luca Alessandro, Carmisciano Luca, Cerri Ambrogio, Chiaretti Antonio, Cosma Claudia, De Vita Vittorio, Di Pumpo Marcello, Di Sarno Lorenzo, Donadei Chiara, Gentili Nicola, Grieco Vittorio, Marchi Guido, Mercier Mattia, Mercogliano Michelangelo, Padovan Martina, Peruzzi Valerio, Pinciroli Tiziana, Spatari Gloria, Traglia Francesco.

Conflict of Interest statement

The authors declare no conflict of interest.

Funding

The SIIAM First Annual Meeting received non-conditional funding from SleepActa, Formula Medicine S.r.l., and Eight Twenty S.r.l. The provided funds were unrestricted, allowing for complete autonomy in the research process and the publication of findings without any influence or intervention from the funders.

Author's contributions

LDA, FB, GD, AT, FAC: conceived the paper, performed the literature search, drafted the manuscript, and contributed equally to the manuscript. The SIIAM workshop participants provided expert insights and

contributed to the manuscript revision. All authors contributed to the article and approved the submitted version.

References

[1] Moen A, Chronaki C, Petelos E, Voulgaraki D, Turk E, Névéol A. Diversity in health informatics: mentoring and leadership. Stud Health Technol Inform 2021;281:1031-5. https://doi.org/10.3233/SHTI210341.

[2] Mitchell R, Boyle B, O'Brien R, Malik A, Tian K, Parker V, Giles M, Joyce P, Chiang V. Balancing cognitive diversity and mutual understanding in multidisciplinary teams. Health Care Manage Rev 2017;42:42-52. https://doi.org/10.1097/HMR.0000000000000088.

[3] Roberge MÉ, van Dick R. Recognizing the benefits of diversity: When and how does diversity increase group performance? Human Resource Management Review 2010;20:295-308. https://doi.org/10.1016/j.hrmr.2009.09.002.

[4] Chi WN, Reamer C, Gordon R, Sarswat N, Gupta C, White Van-Gompel E, Dayiantis J, Morton-Jost M, Ravichandran U, Larimer K, Victorson D, Erwin J, Halasyamani L, Solomonides A, Padman R, Shah NS. Continuous remote patient monitoring: evaluation of the heart failure cascade soft launch. Appl Clin Inform. 2021;12:1161-73. https://doi.org/10.1055/s-0041-1740480.

[5] Cascini F, Gentili A, Melnyk A, Beccia F, Causio FA, Solimene V, Battilomo S, Paone S, Borghini A, Bartolo M, Chiarolla E, Ricciardi W. A new digital model for the Italian Integrated Home Care: strengths, barriers, and future implications. Front Public Health 2023;11:1292442. https://doi.org/10.3389/fpubh.2023.1292442.

[6] Mohammed KI, Zaidan AA, Zaidan BB, Albahri OS, Alsalem MA, Albahri AS, Hadi A, Hashim M. Real-time remote-health monitoring systems: a review on patients prioritisation for multiple-chronic diseases, taxonomy analysis, concerns and solution procedure. J Med Syst 2019;43:223. https://doi.org/10.1007/s10916-019-1362-x.

[7] Montemayor C, Halpern J, Fairweather A. In principle obstacles for empathic AI: why we can't replace human empathy in healthcare. AI Soc 2022;37:1353-9. https://doi.org/10.1007/s00146-021-01230-z.

[8] Kerasidou A. Artificial intelligence and the ongoing need for empathy, compassion and trust in healthcare. Bull World Health Organ 2020;98:245-50. https://doi.org/10.2471/BLT.19.237198.

[9] Sauerbrei A, Kerasidou A, Lucivero F, Hallowell N. The impact of artificial intelligence on the person-centred, doctor-patient relationship: some problems and solutions. BMC Med Inform Decis Mak 2023;23:73. https://doi.org/10.1186/s12911-023-02162-y.

[10] West CP, Dyrbye LN, Shanafelt TD. Physician burnout: contributors, consequences and solutions. J Intern Med. 2018;283:516-29. https://doi.org/10.1111/joim.12752 Epub 2018 Mar 24.

[11] Ayers JW, Poliak A, Dredze M, Leas EC, Zhu Z, Kelley JB, Faix DJ, Goodman AM, Longhurst CA, Hogarth M, Smith DM. Comparing physician and artificial intelligence chatbot responses to patient questions posted to a Public Social Media Forum. JAMA Intern Med 2023;183:589-56. https://doi.org/10.1001/jamainternmed.2023.1838.

[12] Zhan C, Miller MR. Administrative data based patient safety research: a critical review. Qual Saf Health Care 2003;12:ii58-63. https://doi.org/10.1136/qhc.12.suppl_2.ii58.

[13] Liévin V, Hother CE, Motzfeldt AG, Winther O. Can large language models reason about medical questions? Patterns (N Y) 2024;5:100943. https://doi.org/10.1016/j.patter.2024.100943.

[14] Alzahrani SA, Alzahrani AA, Al-Shamrani A. Artificial intelligence in paediatric emergencies: a narrative review. Am J Pediatr 2022;8:51-5. https://doi.org/10.11648/j.ajp.20220802.11.

[15] Singh D, Nagaraj S, Mashouri P, et al. Assessment of machine learning-based medical directives to expedite care in pediatric emergency medicine. JAMA Netw Open 2022;5:E222599. https://doi.org/10.1001/jamanetworkopen.2022.2599.

[16] Leegon J, Jones I, Lanaghan K, Aronsky D. Predicting hospital admission in a pediatric Emergency Department using an Artificial Neural Network. AMIA Annu Symp Proc 2006:1004.

[17] Ramgopal S, Sanchez-Pinto LN, Horvat CM, Carroll MS, Luo Y, Florin TA. Artificial intelligence-based clinical decision support in pediatrics. Pediatr Res 2023;93:334-341. https://doi.org/10.1038/s41390-022-02226-1.

[18] Rafay MF, Pontigon AM, Chiang J, Adams M, Jarvis DA, Silver F, Macgregor D, Deveber GA. Delay to diagnosis in acute pediatric arterial ischemic stroke. Stroke 2009;40:58-64. https://doi.org/10.1161/STROKEAHA.108.519066.

[19] Hosny A, Aerts HJWL. Artificial intelligence for global health. Science 2019;366:955-6. https://doi.org/10.1126/science.aay5189.

[20] Kumar Y, Koul A, Singla R, Ijaz MF. Artificial intelligence in disease diagnosis: a systematic literature review, synthesizing framework and future research agenda. J Ambient Intell Humaniz Comput 2023;14:8459-86. https://doi.org/10.1007/s12652-021-03612-z.

[21] De Angelis L, Baglivo F, Arzilli G, Privitera GP, Ferragina P, Tozzi AE, Rizzo C. ChatGPT and the rise of large language models: the new AI-driven infodemic threat in public health. Front Public Health 2023;11:1166120. https://doi.org/10.3389/fpubh.2023.1166120.

[22] Greenstein S. Preserving the rule of law in the era of artificial intelligence (AI). Artif Intell Law 2022;30:291-323. https://doi.org/10.1007/s10506-021-09294-4.

[23] Surden H. The ethics of artificial intelligence in law: basic questions, 2019. https://papers.ssrn.com/abstract=3441303.

[24] Using health care audit to improve quality of clinical records: the preliminary experience of an Italian Cancer Institute Annali dell'Istituto Superiore di Sanità. Available at: https://annali.iss.it/index.php/anna/article/view/339 (Accessed on: 19 April 2024).

[25] Weis JM, Levy PC. Copy, paste, and cloned notes in electronic health records: prevalence, benefits, risks, and best practice recommendations. Chest 2014;145:632-8. https://doi.org/10.1378/chest.13-0886.

Received on April 19, 2024. Accepted on May 31, 2024.

Correspondence: Luigi De Angelis, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, via San Zeno 35, 56123, Pisa, Italy. E-mail: l.deangelis2@studenti.unipi.it

How to cite this article: Causio Fa, De Angelis L, Diedenhofen G, Talio A, Baglivo F; Workshop Participants. Perspectives on AI use in medicine: views of the Italian Society of Artificial Intelligence in Medicine. J Prev Med Hyg 2024;65:E285-E289. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3261

History of medicine and ethics

The modernity of Achille Sclavo's (1861-1930) message for Italian schools 100 years after the publication of his book "*The Propagation of Hygiene*"

DAVIDE ORSINI[1], MARIA LUISA CRISTINA[2], MASOUD BEHZADIFAR[3], MARIANO MARTINI[2,4,5]
[1] University Museum System of Siena, History of Medicine, University of Siena, Siena, Italy;
[2] Department of Health Sciences, University of Genoa, Italy; [3] Social Determinants of Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran; [4] UNESCO Chair "Anthropology of Health - Biosphere and Healing System", University of Genoa, Italy; [5] Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy

Keywords

Achille Sclavo • History of hygiene • Public health • Healthy childhood • Educational message

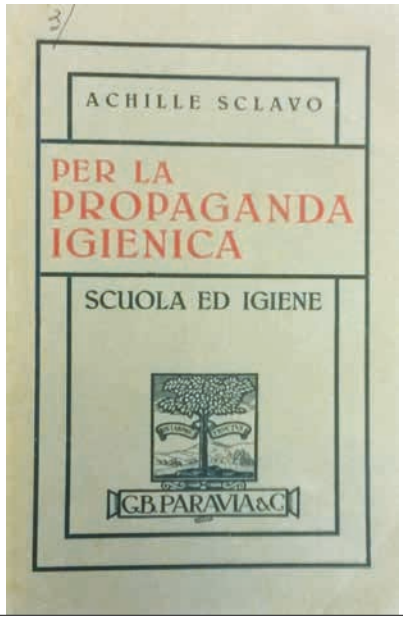
Summary

A hundred years ago, Achille Sclavo (1861-1930) published his book entitled "Per la Propaganda igienica. Scuola e Igiene" (The Propagation of Hygiene. Schools and Hygiene) which he dedicated "To elementary teachers, from whom Italy expects the most effective propaganda in favor of hygiene".
The words of the dedication were profoundly felt by Sclavo and reveal a precise choice by the great hygienist. Sclavo was then at an advanced age and had devoted his whole life to studying hygiene and disseminating its basic concepts, to promote a healthier life for all.
Nowadays, Sclavo's book "The Propagation of Hygiene. Schools and Hygiene" still remains an important statement to the commitment of the great hygienist to spreading a culture of hygiene, and public health in Italy. This was a commitment that Sclavo clearly felt throughout his life, as a teacher, as a scholar, as the entrepreneur who founded the Serotherapy and Vaccinogenic Institute in 1904, and mainly as a policymaker who spoke to all citizens, especially young people.

Sclavo's involvement in public health campaigns and the dissemination of the concepts of hygiene

A hundred years ago, Achille Sclavo (1861-1930) [1] published his book "*Per la Propaganda igienica. Scuola e Igiene*" (*The Propagation of Hygiene. Schools and Hygiene*) which he devoted "To elementary teachers, from whom Italy expects the most effective propaganda in favor of hygiene" [2] (Fig. 1).
Sclavo focused on many of his many studies and his professional life on hygiene, public health and spreading its essential, simple, and fundamental thoughts, in order to promote a healthier life for all [3].
Born in a small village in Piedmont, Achille Sclavo (1861-1930) graduated in medicine at the University of Turin on 19 July 1886. During the next year (1887) he was called by his mentor Luigi Pagliani (1847-1932) to the General Directorate of Health (Direzione Generale di Sanità), as a member of the work-group founded by prime Minister Crispi to reorganize national healthcare policy [3].
In this period, fortified by the outcomes of Louis Pasteur's studies and findings into the techniques of attenuating the virulence of germs, and the following implications for the preparation of new vaccines (live attenuated vaccines), Sclavo carried out rigorous experiments and researches on the biology of *Bacillus Anthracis* [1].
At the beginning of the 1890s, following his promotion to Director of the Bacteriology Laboratory and his appointment as a teacher at the Upper School of Hygiene (Scuola Superiore di Igiene), Sclavo started original studies on anti-diphtheria and anti-anthrax sera. In particular he carried out serious and remarkable

Fig. 1. The book cover of Achille Sclavo, "Per la Propaganda igienica. Scuola e Igiene", published on 1924 (Gruppo Anziani Sclavo - Siena).



https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3312

experiments on the biology of "Bacillus Anthracis" and as a result, he was able to discover a new method of achieving immunity to anthrax, in both animals and humans, by using serum achieved from infected sheep [1].
He continued and developed this scientific inquiry and advanced activity when, in the academic year 1896-1897, he was appointed to teach Hygiene at the University of Siena. A year later, in 1898, he became Extraordinary Professor of Hygiene and Director of the Laboratory of Hygiene.
Sclavo was therefore able to develop great experience in the fields of Hygiene and Public Health through his collaboration with Luigi Pagliani himself, Pietro Canalis (1856-1939) and Alfonso di Vestea (1854-1938) [3].
Achille Sclavo belonged to the second generation of Italian hygienists.
As Professor of Hygiene at the University of Siena, Sclavo made a great effort in the national health campaigns against cholera, smallpox, typhus and malaria [1].
Between 1893 and 1911 he was closely involved in the government's public health campaigns and in the fight against the serious diseases present in various parts of Italy, where the state of health of citizens was severely impaired by poverty, misery and, above all, ignorance.
On behalf of the government, in 1893 he took care of Cholera in Alessandria (Piedmont region in northern Italy) e in Campobasso (Molise region in southern Italy) in 1893; in 1910 in Sardinia to organize the new guidelines and criteria for the anti-malarial campaign with Alessandro Lustig (1857-1937) an Austrian-Italian pathologist who worked on a number of infectious diseases and their management and Michele Alivia (members together with Sclavo of the Commission of the Ministry of the Interior) [3].
He went to the region Puglia between 1910 and 1911 to fight cholera and prejudice, superstitions and ignorance of the population about the approach to infectious diseases; he also took care of water supply in the different affected areas. He also went to Palermo and his province in 1911 to eradicate smallpox and cholera. In 1904, he founded the Sclavo Institute of Serotherapy and Vaccinology[3].
His tireless commitment to improving the well-being of citizens enabled him to "recognize the sad conditions and needs of the population and, above all, to realize how necessary it was for people to try to achieve a sufficient level of education, including education in the concepts of hygiene, correct nutrition *etc.* […]". In particular, epidemics of cholera and smallpox involved him personally in public interventions for prevention and safety. Indeed, he drew up the necessary prophylactic measures and came to the realization that many improper behaviors depended on people's ignorance and prejudice. He also observed that these behaviors could easily be modified when, through careful and constant persuasion, the population was induced to follow a few simple, well-illustrated rules of hygiene [4].
He therefore determined to raise public awareness, firmly convinced that, alongside the work of scientists and doctors, a true "inner revolution" [5] should be fomented among the people, a revolution that would favor the progress of public health and generate a healthy respect for human life in its psycho-physical entirety. Indeed, according to Sclavo, it was necessary "to win over the soul of the whole people to the cause of hygiene" [6] - an important and indispensable reflection that would be followed in the years to come.
Despite being professor of Public Health at the University of Siena since 1898, to achieve this fundamental objective, Sclavo determined to address his message to the widest possible audience: soldiers, priests, medical officers, those in charge of public services, ordinary people. Thus, it was that his simple and clear "conversations", held in "common language" that was accessible to all, attracted an ever-increasing number of attentive listeners, beyond all expectations" [7].
He taught theoretical and practical courses to nurses and Red Cross soldiers on the prevention and prophylaxis of infectious diseases and nutrition. Among the collaborators and colleagues who cooperated with Sclavo to these projects the authors of this manuscript remember his pupil Giovanni Petragnani (1893-1969).
Sclavo wanted to present a new profile of the doctor-hygienist, characterized - in addition to specialist skill - by a profound knowledge of the social and health situation of the time, by great humanitarianism and by the extraordinary fervor of a lay apostolate.
In this respect, it should be pointed out that at the beginning of the 20th century, Sclavo was one of the founders, and the first president, of the Italian Association for Public Health [1].
He soon became convinced that full "hygiene awareness" could only be achieved through a slow learning process, and that this would be difficult to implement in the domestic environment, owing to the ignorance and prejudices of parents. It was therefore necessary to act through the school, on teachers and, above all, on the young, who were not burdened by the erroneous beliefs of their elders and were receptive to change. From this perspective, Sclavo believed that the teaching of hygiene had to free itself of its purely theoretical character and take on a more practical and applicative form.

"*The Propagation of Hygiene*": the school at the center of Achille Sclavo's educational message

Prof. Sclavo began by writing new manuscripts dealing with the difficult situation of schools of the time. In his publication "*Igiene ed edilizia scolastica*" (School buildings and hygiene) (1914) (Fig. 2), he specifically denounced the disconcerting reality of school buildings and proposed solutions to the most widespread health problems. He often expressed his dismay at the various governments' neglect of school problems, promptly denouncing the serious structural and moral shortcomings of the school system: "That schools in many places contribute to damaging children's health

Figs. 2, 3. Two publications by Achille Sclavo on hygiene problems in schools and physical education.

emerges from many facts, which have also been exposed in several well-known reports" [2].

In the same years, Sclavo wrote papers on proper nutrition, outdoor education and the benefits of physical activity for the healthy development of young people: "*Per l'educazione fisica*" (Physical Education) (1914) (Fig. 3); "*Diamo aria ai nostri polmoni*" (The Air We Breathe) (1915), his manifesto in favor of sunlight and pure air in the fight against tuberculosis; "*Sull'alimentazione umana – 5 lezioni tenute in Firenze alle infermiere della Croce Rossa italiana*" (On Human Nutrition - 5 lessons for nurses of the Italian Red Cross held in Florence) (1917); "*Per l'igiene sociale*" (On Social Hygiene) (1918).

Regarding these issues, and particularly the fight against tuberculosis and the importance of healthy and climatically salubrious environments, we should also remember the great work of the Genoese Prof. Edoardo Maragliano [8].

Through his teaching, his creation of facilities for the treatment of tuberculosis and sanatoriums [9] and his extensive propaganda to improve the living conditions of the population and promote prevention, Maragliano did so much [10].

He and Sclavo were both important scholars of that time; they respected each other and sometimes conducted similar studies. Their commitment to public health, epidemiology, hygiene, and infectious diseases was undoubtedly a common denominator of their research.

While continuing his university teaching, in his mature years Sclavo also devoted himself to a form of popular teaching. What he had observed during his life led him to regard youth as the most promising field in which to sow the precepts of hygiene, as "in its ability to adapt, youth is wax; in retaining the impressions received, it is bronze" [4]. He therefore promoted so-called "ascending education", whereby young people became the messengers of good practices among adults, parents and relatives, who often ended up recognizing their usefulness.

This was the underlying concept of his book "*The Propagation of Hygiene. Schools and Hygiene*", which constitutes a basic reference for a full understanding of the ideas of Sclavo as an educator.

The aim of this publication was to disseminate the basic concepts of hygiene and medical sciences in a simple and accessible way: a veritable model of scientific communication which starkly reveals the ingenuity of the scientist, the acuity of the politician and the simplicity of the common man. Through this original work he intended to provide Italian children and young people with an awareness of hygiene and an education. To do so, he abandoned traditional, uniform and standardized teaching methods, which ended up stifling children's interest and natural spontaneity, and explored new pathways.

"He had the most eminent qualities of the teacher: clarity and effectiveness; and above all he knew how to instill into his listeners the ardor and conviction that animated him, the enthusiasm with which his soul was pervaded, the faith in success that he regarded as indispensable" [11].

"First of all, the child must be provided with a healthy and well-governed school, where he must especially acquire those habits of cleanliness and hygiene which will protect him from many diseases. Furthermore, his brain must be trained in the most appropriate way, without fuss and with a judicious choice of what must penetrate it, in order to create knowledge, beliefs and desires. The school has to educate the child to live in society [...] As these tasks are very closely inter-related, it will be advantageous for the Hygienist to collaborate actively and cordially with the School Teacher, the one helping the other" [2].

The new School that Sclavo envisaged had new and broader educational purposes, including the development of a critical and reflective attitude in the pupils. And in this new vision of the school the teacher had a central role in bringing out students' individual talents, promoting diversified activities and responding to the natural curiosity of children by tracing a pathway to knowledge through dialogue.

For Sclavo, Dialogue was fundamental: it was the very pivot around which his educational idea revolved. According to his innovative vision, the teacher should not give lessons, but talk with the pupils in order to get them to think about scientific concepts. This is why, in the book "*The Propagation of Hygiene*", the word "lesson" is never mentioned, while constant reference is made to the term "conversation". This was a deliberate choice by Sclavo, and well represents his rejection of a spoon-feeding approach to education and his adherence to an "educational model based on the construction of knowledge" [12].

The first chapters of the book contain interesting indications on how to set up and prepare an "outdoor school". Indeed, Sclavo notes that "in the Garden of an Outdoor School nature provides the teacher with precious material to help him to impart the most useful knowledge, through observation and experiment and in an enjoyable way" [2].

The most innovative intuition of the outdoor school was the subversion of traditional teaching methods: "Almost everywhere, the ordinary school lends itself poorly to objective teaching. As Dewey rightly observes, the current school environment is specially designed to transmit ideas through words; it is not suitable for an education that arises from the judicious use of the various sense organs" [2].

John Dewey (1859-1952), the American pedagogist to whom Sclavo refers, claimed that, in the context of education, the notion of experience was of value. For Dewey, knowledge was nothing other than the most complex and effective way of solving life's problems.

In this perspective, Sclavo encouraged teachers to propose to their students six topics of conversation - reported in the book - regarding the concept of cleanliness.

These were followed by a series of interventions on physical education, rules for protecting oneself from cholera and tuberculosis, and a section on solidarity, because "the interests of hygiene are closely intertwined with those of solidarity" [2].

Sclavo's commitment to healthy childhood

Using simple language and copious examples, Sclavo focused above all on tuberculosis, "one of the most severe diseases that afflict humanity" [2]. In his book "*The Propagation of Hygiene. Schools and Hygiene*", he concisely summarized the useful information "that most needs to be disseminated among the public through schools" [2]. He explained the cause and the forms of tuberculosis, swept away false beliefs, such as that tuberculosis was hereditary, or that it only affected the elderly. In addition, he provided a series of important precepts of hygiene, such as avoiding spitting, as tuberculosis bacilli can be found in saliva, and covering one's mouth with a handkerchief when sneezing.

He also pointed out that tuberculosis bacilli that can infect humans are often found in cow's milk and therefore recommended boiling milk before drinking it [13]. "Crockery, cutlery and glasses used by a tuberculosis patient in the family should be disinfected by boiling them in water and ash for a quarter of an hour", he explained. The patient's clothes and bed linen should be exposed to the sun often and for a long time, as "direct sunlight kills Koch's bacilli". And "Tuberculosis patients should refrain from kissing other people, especially children, and it is very important that the tuberculosis patient sleeps alone in a separate room" [13].

These were issues that Sclavo addressed and disseminated to his students and the population right from the beginning of his career.

He also dealt specifically with children's health. Indeed, in the opening speech of his first university course in Siena, he argued that childcare should be among the first issues in any health program aimed at reducing infant mortality [14]. In the following years, he underlined the importance of focusing on childhood, both in order to improve children's health, and therefore to reduce mortality in the first years of life, and as a primary objective of education aimed at promoting knowledge of hygiene in the population.

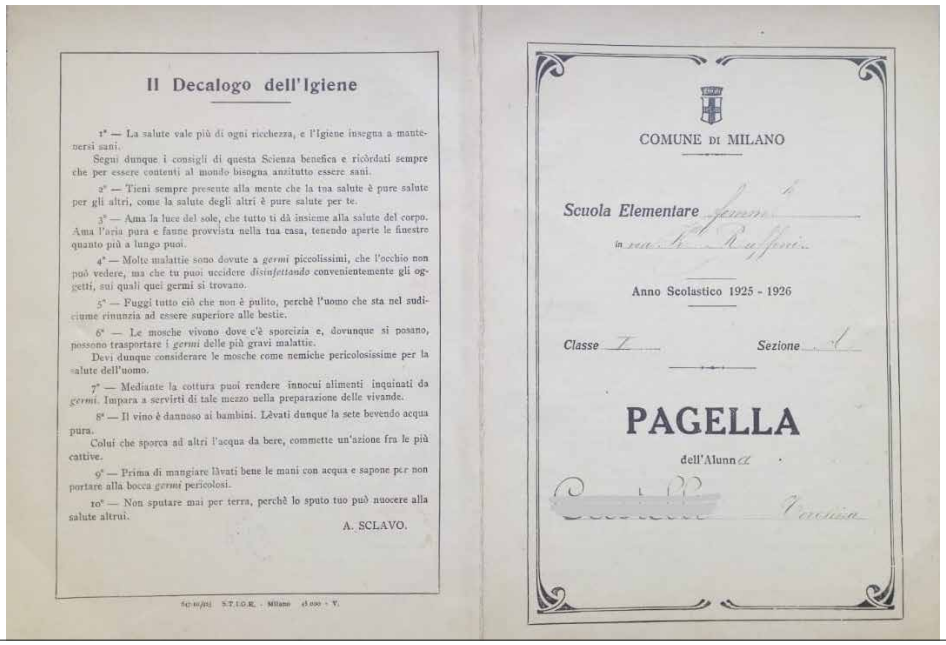
He later became involved in designing and constructing school facilities that complied with the principles of hygiene, such as the nursery and the outdoor school on the terraces of the Medici Fortress [15] (Fig. 4).

His aim was to create healthy environments where the precepts of hygiene could be integrated with physical education, thereby supporting the fight against tuberculosis [16, 17].

Sclavo concluded this section of the volume with a recommendation to all children and young people:

Fig. 4. Children and teachers in the open-air school created by Achille Sclavo in the Fortress of Siena (Archivio Sistema Museale Universitario Senese, University of Siena).

Fig. 5. School report card for the year 1925-1926, showing Achille Sclavo's Decalogue of Hygiene on the back. [Private Collection].



Il Decalogo dell'Igiene

1° — La salute vale più di ogni ricchezza, e l'Igiene insegna a mantenersi sani.
Segui dunque i consigli di questa Scienza benefica e ricòrdati sempre che per essere contenti al mondo bisogna anzitutto essere sani.

2° — Tieni sempre presente alla mente che la tua salute è pure salute per gli altri, come la salute degli altri è pure salute per te.

3° — Ama la luce del sole, che tutto ti dà insieme alla salute del corpo. Ama l'aria pura e fanne provvista nella tua casa, tenendo aperte le finestre quanto più a lungo puoi.

4° — Molte malattie sono dovute a *germi* piccolissimi, che l'occhio non può vedere, ma che tu puoi uccidere *disinfettando* convenientemente gli oggetti, sui quali quei germi si trovano.

5° — Fuggi tutto ciò che non è pulito, perchè l'uomo che sta nel sudiciume rinunzia ad essere superiore alle bestie.

6° — Le mosche vivono dove c'è sporcizia e, dovunque si posano, possono trasportare i *germi* delle più gravi malattie.
Devi dunque considerare le mosche come nemiche pericolosissime per la salute dell'uomo.

7° — Mediante la cottura puoi rendere innocui alimenti inquinati da *germi*. Impara a servirti di tale mezzo nella preparazione delle vivande.

8° — Il vino è dannoso ai bambini. Lèvati dunque la sete bevendo acqua pura.
Colui che sporca ad altri l'acqua da bere, commette un'azione fra le più cattive.

9° — Prima di mangiare lèvati bene le mani con acqua e sapone per non portare alla bocca *germi* pericolosi.

10° — Non sputare mai per terra, perchè lo sputo tuo può nuocere alla salute altrui.

A. SCLAVO.

S.T.I.G.M. - Milano

COMUNE DI MILANO

Scuola Elementare

Anno Scolastico 1925 - 1926

Classe I Sezione A

PAGELLA

dell'Alunn

"To strengthen the human organism, to extinguish tuberculosis infection before it appears, and to recover from the disease, you must live according to the rules of hygiene. This means, among other things, spending a long time outdoors; keeping the house clean and changing the air often by opening the windows; eating adequately and sufficiently; keeping the body perfectly clean and doing appropriate physical exercise" [2].
These prescriptions are also repeated in the *Decalogue of Hygiene*, which closes the book. Among them, the following invitation to children and young people is significant and certainly reflects Sclavo's thoughts on the fight against scrofula and tuberculosis: "Love the sunlight, which gives you everything, not just a healthy body. Love pure air and stock up on it in your home by keeping the windows open whenever you can" [2].
Achille Sclavo's *Decalogue of Hygiene* was widely distributed to the school boards, and from them to the schools; to the Episcopal Curias, which then circulated it among the parish clubs; to the Provincial Offices for Italian Youth and to the Industrial Associations, which in turn distributed it in the seaside and mountain youth colonies.
The distribution of these simple precepts of hygiene was so widespread that in the mid-1920s they were even printed on the back of school report cards (Fig. 5).

Conclusions

Today, Sclavo's book "*The Propagation of Hygiene. Schools and Hygiene*" still remains the highest testimony to the commitment of the great Sienese hygienist to spreading a culture of hygiene in Italy. This was a commitment that Sclavo keenly felt throughout his life, as a teacher, as a scholar, as the entrepreneur who founded the Sclavo Serotherapy and Vaccinogenic Institute [18] in 1904, and especially as a politician who spoke simply to all citizens, particularly young people.
And it was precisely to his young students that Achille Sclavo had made this heartfelt appeal since 1908:
"Young people, I remind you that Hygiene uses every means to achieve its purposes, so that you can all carry the weapons of Hygiene in your hands, in order to defend the greatest of rights, the right to life. I wish you well in the continuation of your studies, and, as a fisherman with a passion for helping the Science I profess, I take heart from the hope that today I have successfully cast my nets into the wholesome sea of your honest consciences" [19].

Funding

This research received no external funding.

Informed consent statement

Not applicable.

Data availability statement

Not applicable.

Conflicts of interest statement

The authors declare that the research was conducted in

the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contribution

DO: conceived the study; DO and MM: designed the study. DO and MM: drafted the manuscript; DO, MM, MLC: performed a search of the literature. MB and MLC: critically revised the manuscript, DO and MM: conceptualization and methodology. MLC and MB: investigation and data curation. MM and DO: original draft preparation. MLC: review. MM: Editing. All authors have read and approved the latest version of the paper for publication.

References

[1] Martini M, Orsini D. Achille Sclavo (1861-1930): A great 19th and 20th-century pioneer in the history of hygiene and public health. J Med Biogr 2024;32:247-8. https://doi.org/10.1177/09677720221130736.

[2] Sclavo A. Per la propaganda igienica. Scuola e Igiene. Torino: G.B. Paravia & C. 1924.

[3] Martini M, Orsini D. Achille Sclavo (1861-1930) and His Innovative Contributions to Italian Preventive Medicine and Healthcare Policy. Adv Exp Med Biol 2022;1369:107-16. https://doi.org/10.1007/5584_2021_673.

[4] Mazzetti G. La vita e l'opera di Achille Sclavo. Siena: Tipografia La Poligrafica 1949, p. 15.

[5] Sclavo A. Discorso di inaugurazione pronunciato il giorno 29 settembre 1929 al 7° Congresso nazionale dell'Associazione fascista per l'Igiene tenutosi in Siena. Siena: Arti Grafiche Lazzeri 1929, p. 5.

[6] Sclavo A. Per un più valido impulso all'Igiene nazionale. 2° Congresso Nazionale dell'Associazione Italiana per l'Igiene tenutosi in Venezia (24-29 giugno 1923). Siena: Stab. Tip. San Bernardino 1923, p. 20.

[7] Sclavo A. Discorsi di inaugurazioni pronunciati a Cagliari e a Sassari dal Prof. Achille Sclavo Presidente dell'Associazione Italiana per l'Igiene. 3° Congresso Nazionale d'Igiene tenutosi in Sardegna. Siena: StaB Arti Grafiche Lazzeri 1925, p. 9.

[8] Martini M, Barberis I, Bragazzi NL, Paluan F. The Fight Against Tuberculosis in the Mid-nineteenth Century: The Pivotal Contribution of Edoardo Maragliano (1849-1940). Adv Exp Med Biol 2018;1057:95-100. https://doi.org/10.1007/5584_2017_125.

[9] Martini M, Gazzaniga V, Behzadifar M, Bragazzi NL, Barberis I. The history of tuberculosis: The social role of sanatoria for the treatment of tuberculosis in Italy between the end of the 19 th century and the middle of the 20th. J Prev Med Hyg 2018 15;59:E323-7. https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1103.

[10] Martini M, Paluan F. Edoardo Maragliano (1849-1940): The unfortunate fate of a real pioneer in the fight against tuberculosis. Tuberculosis (Edinb) 2017:106:123. https://doi.org/10.1016/j.tube.2017.07.007.

[11] Commemorazione di Pietro Rossi. In: "Achille Sclavo" n. 1148-I, Archivio dell'Università di Siena.

[12] Bufalino G. La cura igienica nel pensiero e nell'opera educativa di Achille Sclavo. Medicina & Storia 2010;X:86.

[13] Martini M, Riccardi N, Maragliano E, Brigo F. "Edoardo Maragliano (1849-1940) and the immunogenicity of the tubercle bacillus: the pathway of a great italian physician". J Prev Med Hyg 2021;62:E552-4. https://doi.org/10.15167/2421-4248/jpmh2021.62.2.2095.

[14] Sclavo A. L'Igiene ed i mezzi per attuarla. Prelezione al Corso d'Igiene del dottor Achille Sclavo professore incaricato dell'insegnamento d'Igiene nell'Università di Siena. Torino: Stabilimento Fratelli Pozzo 1897.

[15] Orsini D. The struggle against infant scrofula in Siena between the nineteenth and twentieth centuries. Adv Exp Med Biol 2020;1282:139-46. https://doi.org/10.1007/5584_2019_468.

[16] Orsini D. Tuberculosis in Siena: evolution of the disease and its treatment, from the unification of Italy to the 1930s. J Prev Med Hygiene 2020;61:E19–23. https://doi.org/10.15167/2421-4248/jpmh2020.61.1s1.1346.

[17] Martini M, Besozzi G, Barberis I. The never-ending story of the fight against tuberculosis: from Koch's bacillus to global control programs. J Prev Med Hyg 2018;59:E241-7. https://doi.org/10.15167/2421-4248/jpmh2018.59.3.1051.

[18] Orsini D, Martini M. The history of vaccinology and hygiene through Achille Sclavo and the cultural patrimony conserved in the archives and museums: the key role of medical museology. J Prev Med Hyg 2022;63:E476-81. https://doi.org/10.15167/2421-4248/jpmh2022.63.3.2622.

[19] Università degli Studi di Siena. Annuario Accademico 1908-1909. Siena: Tip. e Lit. Sordomuti di L. Lazzeri 1909.

Received on June 17, 2024. Accepted on July 4, 2024.

Correspondence: Mariano Martini, University of Genoa - Department of Health Sciences, Largo R. Benzi 10 – Pad 3, 16123 Genoa - Italy.

How to cite this article: Orsini D, Cristina ML, Behzadifar M, Martini M. The modernity of Achille Sclavo's (1861-1930) message for Italian schools 100 years after the publication of his book "*The Propagation of Hygiene*". J Prev Med Hyg 2024;65:E290-E295. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3312

OPEN ACCESS J PREV MED HYG 2024; 65: E296-E302

History of medicine and ethics

The fight against smallpox during the Savoy kingdom in Genoa between 1815 and 1859

MARIANO MARTINI[1,2,3], LUCIA VALCHI[1,3], DAVIDE ORSINI[4], ARONNE PICCARDO[5]
[1] Department of Health Sciences, University of Genoa, Italy; [2] UNESCO Chair "Anthropology of Health - Biosphere and Healing System", University of Genoa, Italy; [3] Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy; [4] University Museum System of Siena, History of Medicine, University of Siena, Siena, Italy; [5] Independent Scholar, Genoa, Italy

Key words

The fight against smallpox • Genoa during Savoy Kingdom • 1815-1859 • Public health • Hygiene regulations • History of vaccination • Vaccine hesitancy

Summary

Introduction. *The article aims to outline the features of the efforts for smallpox eradication within the pre-unitary context of the Kingdom of Sardinia, characterized by a long tradition in medical-health prevention. This tradition is partly inherited from the health magistracies of the Italian states during the ancient regime and partly adopted from policies initially outlined by Napoleon and later by other European states. In addition to prevention activities, authorities also engage in a vigorous information and awareness campaign aimed at eliminating common prejudices and doubts about vaccination among the population.*
Methods. *In analyzing the authorities' achievements in combating smallpox, this study examines the two epidemic waves (1829-30 and 1852-54), along with the legislative developments before, during, and after these periods. It also compares these regulatory changes with those in other European contexts.*
Discussion. *The epidemiological situation turned out to be more complex to manage than the authorities had anticipated, as evidenced by the increasing controls imposed. Scientific and political communities, both in the Kingdom of Sardinia and in other European nations, found themselves divided on the legitimacy of proposing restrictive measures by the state. Some advocated for restricted access to public places and imposed mandatory vaccination for vulnerable individuals.*
Conclusions. *The comparison with smallpox resulted in a gradual improvement in of health security levels, although vaccination coverage did not reach the desired targets. Several factors contributed to this failure, including the limited expertise and reluctance of medical personnel, who were burdened with much of the operation's costs. Additionally, particularly in rural areas, there was widespread mistrust among the population towards doctors. Despite these challenges, the fight against smallpox enabled authorities to develop population control tools in the name of public health protection. However, it was not until 1888 that mandatory vaccination was introduced.*

Introduction

In the late early modern period and the onset of the modern age, smallpox significantly impacted Europe. Though Europeans were familiar with the disease from ancient records, it reemerged around 1500, becoming endemic by the second half of the 18th century and persisting until the 20th century. During this time, smallpox alternated with the plague, which gradually disappeared [1].
In Europe, the most crucial contribution to variolation/inoculation was made by a woman called Mary Wortely Montagu (1689-1762) (Fig. 1) whose husband Edward Wortley Montagu, was the British ambassador to the Ottoman Empire in Costantinople between 1716 and 1718 [2].
Lady Montagu was a spirited and independent woman who explored the city and learned about local customs. To preserve her anonymity, she wore a veil and, during this time, she learned about the practice of inoculation [3]. In a letter dated April 1, 1717, she provided a fascinating description of inoculation was performed, as she had seen it [4].
The inoculation procedure consisted of an immunological

Fig. 1. Mary Wortely Montagu in Turkish dress (Public Domain. Wikipedia commons).

https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3335

practice recorded by the medical community in the early 1720s, was rooted in Eastern traditions. Upon recognizing its origins, the medical community sought to establish a scientific basis for it to address the doubts it raised [5].

Credit for raising awareness of this method goes to Lady Mary Wortley Montagu. Her efforts were challenging due to the prejudices surrounding the practice's Eastern and Islamic origins, which were considered pagan at the time. Initially, the Church opposed the practice but eventually changed its stance [6].

Variolization consisted of inoculating a healthy patient with infected material or scabs taken from patients who had presented a mild form of smallpox. Inoculation was carried out using various methods; in Europe the practice adopted involved making an incision in the epidermis followed by grafting.

The problems related to this practice, which strongly hindered its widespread diffusion (unlike the Jennerian vaccine)[2], were due to multiple factors, with the primary one being the inherent risk of the practice. Patients who underwent this form of inoculation could contract a very severe and occasionally lethal form of smallpox [7].

The Cremonese doctor Valeriano Brera stated that «... smallpox inoculation produced one death for every sixty inoculated individuals ...» [8] another concern associated with this practice was the risk that the inoculated patients themselves could become sources of contagion for others, causing outbreaks. In some instances, the outcomes of the inoculation were uncertain due to the absence of the typical scar at the inoculation site.

Other types of immunization practices were present since ancient times among various populations, including the Chinese, Persians, or Indians. These practices involved methods such as «placing healthy and infected individuals in contact, or transmitting pus-stained clothing from sick individuals to non-immune individuals» [9] or «among the Chinese, according to the testimony of the Jesuit François Xavier d'Entrecolles (1726), crushed smallpox scabs were inhaled by individuals to be immunized, placed on cotton or on the cocoon of a silkworm» [9]. Nevertheless, variolation was the most commonly used method

Despite efforts to raise awareness of prevention methods, such practices remained rare due to the aforementioned reasons. Ultimately, the Church played a significant role, by invoking theological arguments against them, claiming that injecting "corrupted material" into individuals was contrary to the will of God. This narrative quickly resonated across different social layers in Italy and Europe reinforcing prejudices associated with the Eastern origin of variolation, associating racial stereotypes with the practice [9].

Things started to change towards the end of the 18th century, thanks to the discovery made by Edward Jenner (Fig 2).

The revolutionary significance of this discovery was understood from the very beginning, leading to the first powerful vaccination campaign between 1798 and 1814 [5]. By the early months of 1801, vaccination was being implemented on a large scale in the English army and in Napoleon's France. Napoleon himself promoted the practice, expanding it to the entire empire, which also included parts of Italy [10].

Fig. 2. Edward Jenner (1749-1823) (Public Domain. Wikipedia commons).

Vaccination campaigns in the Kingdome of Sardinia

Under the French rule, the territories of the Kingdom of Sardinia were subjected to French healthcare policies. In the effort to promote vaccination in Piedmont, Michele Francesco Buniva (1761-1834), an Italian naturalist and physician, played a central role. He became a professor of medical institutions in 1789 and later took up the chair of pathology at the University of Turin in 1799. Despite Bunvia was dismissed from the university in 1814 due to his liberal ideas, he was credited with introducing smallpox vaccination in Piedmont [11]. He was a leading advocate for a comprehensive healthcare reform that led to the creation of a superior health council aimed at overcoming the outdated forms of health governance implemented during the ancient regime [5]. While Italian cities such as Milan, Turin, Genoa, Venice, and Florence had been pioneers in healthcare prevention in the previous centuries, the leadership in healthcare innovation shifted to various northern European nations, between the 1700s and 1800s [13].

Buniva's vision was to set aside and beyond the outdated policing approach implemented in the past [14]. Despite their previous effectiveness, these methods were becoming increasingly inadequate for managing the complexities of 19th-century urban environments. The superior health council was intended to act as an intermediary between the scientific community of physicians and academics and that of civil society. Its role was to implement a policy of intense surveillance and control over food, workplaces, and the pathogenic forms related to these areas in order to protect public health [5].

With the end of the Napoleonic era, the territories of

the Republic of Genoa were annexed to the Kingdom of Sardinia. Following the restoration of the monarchy in 1815, vaccination efforts were abruptly halted. The group of physicians who worked in the superior health council, an institution established during the Napoleonic administration, including Buniva himself, were dismissed, as part of a political purge intended to eliminate those considered disloyal to the House of Savoy due to their collaboration with the French administration.

However, Vittorio Emanuele I of Savoy's decision proved to be short-sighted, in fact already starting from 1819, a Superior Vaccine Board was created in Turin, to which the provincial boards of Nice, Genoa, and Chambery [5] were to report. This sudden change was driven by new challenges emerging in the field of healthcare. It was, in fact, a recovery of the administrative structures created during the French rule.

As director-general of the Superior Vaccine Board, Giuseppe Audiberti was chosen and appointed for his expertise in the field, acquired through study trips abroad, particularly in Paris and London. His loyalty during the political turmoil of his exile earned him the admiration of King Vittorio Emanuele, who subsequently elevated him to the rank of count following Napoleon's downfall [15]. He was chosen because due to his role as the vice-president of the Academy of Sciences and for his clore relationship with the king during exile. To support him on the board, two other important physicians were appointed: Tommaso Domenico Griva, a student of Michele Buniva who became Audiberti's secretary in 1819 [5] and Lorenzo Martini [16] (1785-1844), a physician, physiologist, pedagogue, and future rector of the University of Turin, who served as vice-conservator in the Superior Board.

The board operated throughout the Kingdom from 1819 until 1859. Despite implementing smallpox containment and vaccination strategies similar to those of other European states, these efforts were insufficient to prevent repeated smallpox epidemics in the Kingdom of Sardinia, especially in the province of Genoa, during 1829-30 and 1852-54 [17]. The second epidemic lasted longer due to the simultaneous outbreak of cholera [18], which diverted many resources previously allocated to fight smallpox due to its greater perceived threat. Following the directives of the central Savoyard administration, the provincial board of Genoa moved following two different levels: a) preventive and b) extraordinary.

a. Among the preventive measures, numerous reports and inquiries were consucted with vaccinating physicians concerning vaccine administration and population's health status. Constant censuses were taken of vaccinating physicians and facilities dedicated to treating the sick. Vaccination, along with isolation, were recognized as the only effective methods for treating this disease. Preventive efforts particularly focused on the vaccine: its procurement, storage, population information-awareness campaigns, and administration.
b. Among the extraordinary measures, the board promptly issued the regulations under the royal patents concerning smallpox vaccination. Some articles extracted from the regulation of royal patents issued on July 1st, 1819 [18], include:

– Article 8: "All students who have not received a successful vaccination or have not contracted true smallpox shall not be admitted to schools" [19].
– Article 9: The mandatory nature of vaccination was extended to: "All those currently receiving or who will in the future receive free aid from charitable or benevolent congregations must provide proof within three months that all individuals in their family under the age of 20 have been vaccinated or have had smallpox" [19].

Vaccination thus became mandatory for all students to access public facilities with non-compliance resulting in exclusion. This mandate particularly targeted the youngest and the poorest segments of the population, requiring families receiving subsidies to vaccinate all members under 20 years of age, otherwise they had to face suspension of their aid.

To encourage young people who did not attend school, and thus were not subject to mandatory vaccination to still undergo the treatment, the service was made free of charge [10].

The provincial board, adhering to a utilitarian approach that differs significantly from our modern concept of public health welfare, decided to restrict assistance and free home care to only those poor families willing to have their child/children vaccinated. These families had make their children available to doctors who would use the child to vaccinate others. Mothers who accepted this agreement were provided with various forms of compensation.

In a letter to the president of the provincial health council in Genoa, D. Prasca, a regional health councilor in Genoa, highlighted the discord among the various administrators regarding the amount of rewards that would be distributed to the mothers of the children used for vaccination [19].

The practice of giving rewards was not necessarily an invention of the Savoyard administration; it already existed under the French administration. For instance, symbolic rewards such as a package of confectionery and a gratuity of three lire each were given, or in another case, a "complete outfit" including a hat and a pair of shoes [5].

-Regarding health patents, the regulation issued in 1819 established a rigorous standardization in their form and the data reported to avoid possible falsifications, which had occurred in the past [21].

During the vaccination campaign, authorities paid special attention to vulnerable individuals. Articles 6 and 7 of the instructions for vaccine propagation, dated January 1st, 1820, specified that if individuals presented themselves and officials deemed it prudent not to vaccinate them due to health reasons, their vaccination would be postponed until their health improved. In cases where deferred patients required a patent to access public facilities, a temporary certificate for three months was

issued, explaining the reason for not being vaccinated. At the end of the validity period, individuals had to return to the designated vaccination site and if they were deferred again, the procedure was repeated [19]. Patients could be deemed ineligible for vaccination due to high fever, poor health from other illnesses, or advanced age. Meanwhile, a powerful information and awareness campaign was financed, involing even Count Audiberti, the general director of vaccinations.
When compulsory vaccination for all schoolchildren was decreed, his speech was published in the official gazette, where he discussed about the recent vaccine as a new tool to combat smallpox. While such posters were not new, raising awareness among the population remained crucial due to the low number of visits to vaccinating physicians.

European contex

The issue of mandatory vaccination [22] and the forced recruitment of doctors who were in favor of spreading the serum but opposed to its imposition sparked heated debate across European nations [23] leading to various policies on this matter:

- Indeed, some nations, such as the Kingdom of the Netherlands, implemented mandatory vaccination for children under 6 months of age as early as 1818;
- During the same period, the Kingdom of Sardinia lacked a dedicated entity for vaccination [5] campaigns. Administrators loyal to the king, even during the Napoleonic period, chose to dissolve previous health bodies at the start of the restoration process due to political rivalries, without paying attention to public health protection. In contrast, other nations, such as England, took significant measured be enacting the *Vaccination Acts* of 1840, 1841, and 1854 to enforce universal and free smallpox vaccination, though this obligation was eventually abolished in 1898;
- Much stricter measures were adopted by the Kingdom of the Two Sicilies, which ordered "deportation of families who refused vaccination to locations at least six miles away from their homes, allowing their return only after they agreed to vaccinate their children" [8].

The strategy of the Kingdom of Sardinia was decidedly softer, opting for annual vaccination campaigns and inspections by inspectors in schools. However, the efforts made did not prevent smallpox from triggering an epidemic that spread in the province between 1829 and 1830 [24].
Following this, the authorities decided to tighten the regulations. The vaccination campaigns became more widespread, occurring annually even in peripheral areas. At the same time, there was increased scrutiny of doctors' actions, as many were found to issue false certificates in exchange for cash or other benefits, thus aiding those who did not want to be vaccinated and receiving gratification for each self-certified vaccination they performed. However, this was mainly the case for non-contracted physicians, who were hired and compensated based on their performance during emergencies or staff shortages. These doctors were rewarded for each self-certified vaccination they performed. Despite these challenges, the healthcare system overall remained resilient, and the state of emergency was quickly brought under control. Certainly, this was likely due to well-distributed healthcare facilities across the territory [12] and to the (though not yet sufficient) vaccination coverage.

Fig. 3. Lorenzo Martini (1785-1844) (Public Domain. Wikipedia commons).

The vaccination from 1830 and the role of Lorenzo Martini

Starting from 1830, Lorenzo Martini's [19] (Fig. 3) outreach activities became more intense. He educated both the civilian population and medical personnel through posters that conveyed his speeches.
It should be noted that these individuals often lacked adequate training on the subject, and even when they did have training, they viewed vaccination a task beneath their status [8]. Consequentially, they were not readily available to assist the authorities.
The posters aimed at both physicians and the general population addressed a range of topics related to vaccination. They covered methods for administering and controlling the inoculation process, the expected outcomes of vaccination (including how well-informed mothers and wet nurses could also conduct these controls independently, according to Martini), the proper preservation of vaccine pus, criteria for selecting patients for arm-to-arm vaccination, distinguishing chickenpox from smallpox, and other relevant subjects.
Lorenzo Martini followed a very particular course of study: his studies and research increased also towards medical-physiological and medico-legal studies, but he was not only a great physician because he extended his knowledge in the humanities field.
He devoted his time and developed his studies on thinkers' philosophers of the Greek classical period. Furthermore, in 1840 he managed to write a text on the history of philosophy entitled *"Storia della filosofia"*

(History of Philosophy), edited in three 3 volumes [Ed. Pirotta, Milano 1840]; *"Della sapienza dei greci"* (About the wisdom of the Greeks), [Ed. Cassone e Marzorati, Torino 1836], and in 1844, before she passed away, she managed to give a written manuscript on Plato; it was a *compendium* dedicated to Plato completed in 1844 entitled *"Platone compendiato e commentato* (Plato summarized and commented), [Ed. Elvetica, Capolago 1844].
He also devoted himself to educational and pedagogical studies with interesting publications, *e.g.* "*Riforma della prima educazione" (Reform of the first education),* [Ed. Marietti, Torino 1834]; *"Emilio"* consisting of 12 volumes, [Ed. Marietti, Torino 1821-1823].

Martini's innovation lays in the clear and simple style he employed in his writings [19].

To persuade the stubborn and hesitant individuals about vaccination, Martini examined the most common arguments against it in the population and systematically dismantled them in a straightforward yet comprehensive manner. His goal was to foster dialogue and understanding among those fearful of the practice. This approach involved a carefully crafted communication strategy and the use of gentle, non-confrontational language to avoid harsh tones.
Between 1820 and 1840, the president of the provincial observed that smallpox had become endemic. To prevent a new epidemic emergency, he imposed severe restrictions regarding controls and extended the vaccination mandate to additional groups beyond schoolchildren [25]. Municipal administration employees and those receiving pensions from the Royal Navy they had to provide proof that they and their children had been vaccinated, or else their salaries would be suspended until vaccination was carried out.

The epidemic of 1852 and conclusions

In 1852, a new and rapid pandemic broke out in Genoa, schools and public offices were converted into patient care centers because hospitals were full and additionally, cash rewards were given to mothers who offered their children for the reproduction of the vaccine due to the shortage of fresh serum.
The arrival of cholera in the city in 1854 [26] further worsened the situation. Cholera was not new to the health authorities of the Italian states, having previously caused approximately 150,000 deaths between 1835 and 1838, including three thousand in the Genoa alone [1]. The authorities had to deal with this new emergency [27] which had significant practical repercussions, leading to the reallocation of financial resources originally intended for combacting smallpox to address the cholera emergency. This resulted in a prolonged duration of the smallpox epidemic.
The epidemic finally subsided towards the end of 1854, though new, more contained waves emerged 1856-57.
Several factors contributed to the resurgence:

- Insufficient financial resources discouraged doctors from practicing, as they preferred more lucrative private practice;
- Poor training of some medical personnel compromised vaccination success due to improper execution or the use of compromised serum, which was handled by medical personnel;
- Deep-seated mistrust of the medical personnel among the population, which prevented some individuals from being convinced to undergo vaccination;
- Ineffective regulations failed to adequately address negligent doctors and those who violated protocols.

In 1857, the vaccinated population in the province of Genoa amounted to approximately 56.9% of the total. This figure varied widely across the territory due to poor road conditions, which made vaccination in the suburbs challenging, and differing levels of knowledge and management among local authorities and medical personnel. By comparison, the average vaccinated population in the Kingdom of the Two Sicilies in 1851 was 70.4% [8].
The vaccination coverage results were sufficient to avoid high mortality rates but not enough to contain pandemics. This was the situation shortly before the Unification of Italy. It was not until 1888, with the enactment of the Crispi-Pagliani law, that smallpox vaccination became mandatory. Despite this, smallpox continued to affect the peninsula until the late 1900s [28].
Vaccination has been both celebrated and criticized throughout the history of medicine and public health, dating back to Edward Jenner's time in 1798. The concept of injecting a mild form of "disease" into a healthy person faced opposition even before vaccines were discovered. The authors remember also that Bourbon king Ferdinand planned and introduced the first "free large-scale mass vaccination programme" conducted in Italy and one of the first in Europe to counteract smallpox. The vaccination campaign was marked by many difficulties and the efforts made by the Southern Kingdoms governors were huge [9, 10]. The ''ante litteram communication campaign", aimed at convincing the so-called ''hesitant" people and at confuting the opinions, beliefs, views, and behaviours of vaccination opponents, was impressive [29-32].
By 1821, compulsory vaccination had significantly reduced smallpox infections and death rates. Later, several experiences followed this enterprise, even with heated debates and discussions, of course. Smallpox was finally eradicated worldwide only on the 9th December 1979.
The recent health emergency caused by COVID-19 disease and other health emergencies show many connections with well-known epidemics of the past [33, 34].
Understanding how previous outbreaks were managed can provide valuable insights and tools for addressing current and future infectious disease challenges.

Funding

This research received no external funding.

Informed consent statement

Not applicable.

Data availability statement

Not applicable.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

mM and AP: designed the study, MM &AP conceived the manuscript; AP, MM, LV drafted the manuscript; MM, AP and LV: revised the manuscript; DO, MM and AP performed a search of the literature; DO, LV: critically revised the manuscript; AP, MM, LV: conceptualization, and methodology; LV,AP, MM,DO investigation and data curation; AP, MM: original draft preparation; LV: editing. All authors have read and approved the latest version of the paper for publication.

References

[1] Cosmacini G, Storia della medicina e della sanità in Italia. Dalla peste nera ai giorni nostri, Bari: GLF 2016.

[2] Orsini D, Martini M, From inoculation to vaccination: the fight against smallpox in Siena in the 18th and 19th centuries, Infez Med 2020;28:634-641.

[3] Miller G. The adoption of inoculation for small-pox inoculation, England and France. Philadelphia: University of Pennsylvania Press 1957.

[4] Montagu Lady M. Letters written during his travels in Europe, Asia and Africa, printed for T. Becket and P.A. De Hondt, London 1763, 3 volumes and another print: Letters of Lady Mary Wortley Montagu, printed by P. Didot the elder, Paris 1800.

[5] Carpanetto D, Il pregiudizio sconfitto. La vaccinazione in Piemonte nell'età francese 1800-1814. In: Actis Alesina G, Carpanetto D, Ferro M, a cura di. Torino: Società di Studi Buniviani 2004.

[6] Martini M, Brigo F, Rasori G. Vaccination in the 19th century in Italy and the role of the catholic church in public health: a historical overview. J Prev Med Hyg 2022;63:E104-8. https://doi.org/10.15167/2421-4248/jpmh2022.63.1.2518.

[7] Simonetti O, Cosimi L, Cigana M, Penco A, DI Bella S, Martini M. Balto and Togo during the cold winter of Alaska (1925): the two canine heroes in the fight against diphtheria. J Prev Med Hyg 2024;65:E98-104. https://doi.org/10.15167/2421-4248/jpmh2024.65.1.3229.

[8] Tanturri A, L'infausto dono dell'Arabia. Vaiolo e profilassi nel Mezzogiorno preunitario (1801-1861). Milano: Edizioni Unicopli 2014.

[9] Martini M, Bifulco M, Orsini D. Smallpox vaccination and vaccine hesitancy in the Kingdom of the Two Sicilies (1801) and the great modernity of Ferdinand IV of Bourbon: a glimpse of the past in the era of the SARS-COV-2 (COVID-19) pandemic. Public Health 2022;213:47-53. https://doi.org/10.1016/j.puhe.2022.09.012.

[10] Bifulco M, Di Zazzo E, Pisanti S, Martini M, Orsini D. The nineteenth-century experience of the kingdom of the two Sicilies on mandatory vaccination: An Italian phenomenon? Vaccine 2022;40:3452-4. https://doi.org/10.1016/j.vaccine.2022.04.052.

[11] Carpanetto D, Università e magistrature sanitarie: il progetto di Michele Buniva nel Piemonte napoleonico. Rivista di Storia dell'Università di Torino 2014;III(1).

[12] Martini M, Calcagno P, Brigo F, Ferrando F. The Story of the plague in the Maritime Republic of Genoa (Italy) (1656-1657): An innovative public health system and an efficacious method of territorial health organization. J Prev Med Hyg 2022;63:E625-9. https://doi.org/10.15167/2421-4248/jpmh2022.63.4.2781.

[13] Cipolla C. M, Contro un nemico invisibile. Epidemie e strutture sanitarie nell'Italia del rinascimento. Bologna: Il Mulino 2007.

[14] Assereto G, Per la comune salvezza dal morbo contagioso. I Controlli di Sanità nella repubblica di Genova. Novi Ligure: Città del silenzio 2011.

[15] Bonino G, Prospero B, Biografia Medica Piemontese. Vol. II. Torino: Tipografia Bianco 1825.

[16] Accademia delle scienze di Torino. Memorie dell'Accademia delle scienze di Torino. Tomo XXIX. Torino: Stamperia Reale 1825.

[17] ASG. Intendenza generale di Genova. Epidemia vaiolosa, 1852, b. 442, fasc. 53, 1852.

[18] ASG. Intendenza generale di Genova. Vaccinazione ed altre pratiche relative alla medicina, 1855-1859, b. 452 fasc. 92.

[19] ASG. Intendenza generale di Genova. Giunta provinciale del vaccino: corrispondenze e disposizioni, b. 439, fasc. 39, 1819-1833.

[20] Parodi M, Martini M. History of vaccine and immunization: Vaccine-hesitancy discussion in Germany in XIX century. Vaccine 2023;41:1989-93. https://doi.org/10.1016/j.vaccine.2023.02.029.

[21] Cipolla C. M, Chi Ruppe I Rastelli a Monte lupo? Bologna: Il mulino 2013.

[22] Tognotti E, Vaccinare i bambini tra obbligo e persuasione: tre secoli di controversie. Il caso dell'Italia. Milano: Franco Angeli editore 2020.

[23] Tisci C. Lo scudo contro il vaiolo. Antonio Miglietta e la profilassi nel regno di Napoli (1801-1826). Lecce: Grifo edizioni 2015.

[24] ASG. Intendenza generale di Genova. Disposizioni per combatterlo: corrispondenza della giunta del vaccino, b. 440, fasc. 40, 1829-1830.

[25] Guglielmino E. Genova dal 1814 al 1849. Gli sviluppi economici e l'opinione pubblica. In: Atti della Regia deputazione di storia patria per la Liguria, Serie del Risorgimento 1940;IV(28).

[26] Freschi F, Storia documentata dell'epidemia di cholera-morbus in Genova nel 1854. Genova: Sordo-Muti 1855.

[27] Costa E. Rendiconto economico-medico-statistico dell'Ospedale di Pammatone nel quinquennio 1840 a tutto il 1844. Genova: Tipografia Ferrando 1846.

[28] Tisci C, L'epidemia di vaiolo in Terra di Bari (1918-1919). In: Campanile B, Dibattista L, Garuccio A, a cura di. Malato di Guerra: Le Patologie fisiche e Mentali della Grande Guerra in Puglia. Roma: Aracne 2016, pp. 107-28.

[29] Jacobson RM, St Sauver JL, Finney Rutten LJ. Vaccine Hesitancy. Mayo Clin Proc 2015;90:1562-8. https://doi.org/10.1016/j.mayocp.2015.09.006.

[30] Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health 2021:194:245-51. https://doi.org/10.1016/j.puhe.2021.02.025.

[31] Orsini D, Bianucci R, Galassi FM, Lippi D, Martini M. Vaccine hesitancy, misinformation in the era of COVID-19: Lessons from the past. Ethics Med Public Health 2022:24:100812. https://doi.org/10.1016/j.jemep.2022.100812.

[32] Rosselli R, Martini M, Bragazzi NL, Watad A. The Public Health Impact of the So-Called "Fluad Effect" on the 2014/2015 Influenza Vaccination Campaign in Italy: Ethical Implications for Health-Care Workers and Health Communication Practitioners. Advances Experim Med Biol 2017;973:125-34. https://doi.org/10.1007/5584_2017_39.

[33] Fauci AS, Morens DM. The perpetual challenge of infectious diseases. N Engl J Med 2012;366:454-61. https://doi.org/doi.org/10.1056/NEJMra1108296]. Erratum in: N Engl J Med 2012;366:868 https://doi.org/10.1056/NEJMra1108296.

[34] Simonetti O, Martini M, Armocida E. COVID-19 and Spanish flu-18: review of medical and social parallelisms between two global pandemics. J Prev Med Hyg 2021;62:E613-20. https://doi.org/10.15167/2421-4248/jpmh2021.62.3.2124.

Received on July 8, 2024. Accepted on July 11, 2024.

Correspondence: Lucia Valchi, Department of Health Sciences, University of Genoa, Via Antonio Pastore 1, 16132, Genova. E-mail: lucia.valchi@hotmail.it

How to cite this article: Martini M, Valchi L, Orsini D, Piccardo A. The fight against smallpox during the Savoy kingdom in Genoa between 1815 and 1859. J Prev Med Hyg 2024;65:E296-E302. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3335

ENVIRONMENTAL HYGIENE

How the Anthropocene is changing bioethics

PAOLO DONADONI[1], ROSAGEMMA CILIBERTI[2]
[1] University of Genoa, Genoa, Italy;
[2] Department of Health Sciences, Section of Bioethics and History of Medicine, University of Genoa, Genoa, Italy

Keywords

Anthropocene • Ethics of the Earth • Bioethics • Environment • One health

Summary

The complex challenges of the Anthropocene imply a careful reconsideration of the ethical boundaries of human morality and a heightened sensitivity to the interconnectedness among all living beings. This means that bioethics, traditionally anchored in interhuman relations within the healthcare domain, is called upon to broaden the scope of its operational horizon, encompassing issues related to interspecific relations, environmental health, sustainability, equitable distribution of natural resources, and responsibility for environmental damages. This article explores the intersection between the anthropocentric era and the ethical challenges arising from our increasing influence on the environment and other life forms with which we share the planet. The teaching of fundamental ethical concepts such as solidarity, social responsibility, and equity becomes crucial for nurturing informed and responsible citizens. In doing so, not only is greater awareness promoted regarding global challenges related to health and the environment, but critical skills are also developed to address them proactively.

Introduction

The complexity of bioethical language: between interdisciplinarity, ambiguity, and conceptual evolution

In bioethics, a field that thrives on interdisciplinarity as a vital source of inspiration, terminology often undergoes changes in both extension and intension when transitioning from one area of knowledge to another. At times, terms are stretched beyond their original technical meanings or are characterized by ambiguity and misunderstandings. The language of bioethics, therefore, inherently possesses certain complexities for specific and natural reasons.

An intrinsic and fascinating characteristic, yet simultaneously a genetic flaw, of bioethical debate is its interdisciplinary nature. Bioethics traverses disparate fields of knowledge that not only intersect but also establish enduring relationships, giving rise to mutual hybridizations [1]. Today, to illustrate briefly, legal discourse discusses "transplants" and "determination of death," medicine addresses "informed consent" and "living wills," while philosophy engages with "stem cells" and "embryos," among others.

In some cases, for instance, words can have different meanings in different contexts (plurality of intentions). Consider the term "donation," which in legal contexts refers both to civil law in private contexts and to the specialized discipline of organ transplantation, with entirely non-overlapping meanings [2, 3].

For those involved in bioethical debate, therefore, it is not automatic to assume that the same words convey the same meanings. But let's start from the beginning: the very term "bioethics," coined as a neologism in the 1970s, still today – though considered part of ordinary language – does not have a content (extension of meaning) that can be unequivocally agreed upon. In fact, it is evolving even in terms of thematic priorities [4].

The broadening of the extension of the term "bioethics"

In bioethical literature from the early millennium, various scenarios are included that do not always address the themes of ecology and our relationship with non-human animals. For example, the topic of animal rights is found in Leone's work but not in Sgreccia's [5, 6]. Tettamanzi addresses the ecological issue (chapter 24), but only briefly touches on animals (see, for example, p. 337 and pp. 407-408, where, while considering legitimate – in the absence of valid alternatives – experimentation on animals for the benefit of humans, he specifies: "especially in the field of experimentation, animals should be recognized as having genuine moral and legal rights, thus ensuring adequate protection for them") [7]. Ciccone and Mori dedicate about ten pages to the topic, while Lecaldano, for "economic reasons of control over the material treated and the need for unity," excludes "issues related to the treatment of non-human animals," although specifying that "there are no solid arguments to exclude non-human animals from moral consideration" [8-10] (p. 5). Engelhardt Jr. devotes barely three pages – he calls it an "excursus" – to animals, inviting us to the morality of non-maleficence, consisting of negative duties of beneficence towards humans (pp. 166-168) [8-11]. These are just a few examples, but sufficient to outline a general picture. Indeed, in light of the discourse on bioethics presented,

it would be intriguing to investigate how Aristotle's ethical principles could enhance the approach to the subject. While contemporary bioethics often emphasizes individual rights and autonomy, Aristotelian ethics offers a perspective grounded in the concept of virtue and the pursuit of the common good. Delving into this connection could lead to a deeper understanding of the moral issues intersecting contemporary biomedicine.

It seems that some issues, namely the critical examination of certain areas of reflection, are preferably found in specialized works rather than in general bioethics manuals. Among the authors who have extensively addressed bioethical issues related to the relationship between humans and animals, we recall, for example, Silvana Castignone and Luisella Battaglia who were among the first to initiate the debate on animal rights in Italy in the 1980s [12-18].

As further evidence of this variety (and, at times, vagueness) in the extension of the term's meaning, it can be observed that other authors include topics rarely found in bioethics manuals. For instance, Ciccone devotes chapters to drug abuse, alcoholism, smoking, and AIDS [19].

Angelini asserts that defining exactly what "bioethics" entails is no easy feat. Its vagueness constitutes a primary source of dissatisfaction [20]. Moreover, referring to bioethics in the singular is not an obvious choice; it seems rather risky. Indeed, it would be extremely challenging to identify a consensus in the theoretical definition of this new "science" within the literature dedicated to its epistemological profile. Likewise, finding a reason for unity within the field of bioethics, both in terms of treaties and public culture, would be complex. However, the unity of the bioethical field does exist to some extent [21]; this unity is guaranteed more by the overall societal context in which bioethics originates than by specific theoretical elaboration.

The term "bioethics" itself expresses a critical aspect of its scope and the determination of its extension [22]. However, what is important to note here is the lack of necessary inclusion (or their minimal development, sometimes almost irrelevant) of ecological themes and our relationship with non-human animals in early Millennium manuals. Will this be the case in mid-Millennium manuals as well? Indeed, the Anthropocene compels us today to no longer ignore the priority of our ecological and interspecific relationships.

New topics will have to rightfully enter the field of bioethics, such as invisible pollution (in marine depths and outer space, areas that escape direct human perception but will be at the center of debate in the near future, for instance, to establish shared guidelines for the use of international waters and space, to address pollution cessation, the necessity of cleanup activities, and to use biodegradable materials...) and the ethical treatment of plants (given that life sciences confirm they possess sensory qualities similar to ours, as well as learning, memory, and thinking capacities), as well as a new balance between sapiens and animals (no longer assimilable to mere objects; moreover, chimpanzees belong to our own tribe, that of hominins, and in mammals, basic structures of consciousness and thought akin to ours are recognized) [23-27].

However, the impact of the Anthropocene on the delineation of bioethical issues cannot be considered confined to ecology in the broad sense, as it involves the emergence of specific profiles of human activities: big data, body hybridization, and personal identity (not only concerning human-animal commingling but also regarding developments in robotics), topics not yet institutionalized in bioethics manuals but which presumably will chart the future paths of this discipline.

The shift in priorities in the bioethical debate

Regarding the second aspect, the shifting priorities in the bioethical debate make it clear that human survival automatically becomes a species priority that precedes any individual priorities related, for example, to the principles of autonomy and self-determination (as a matter of logical, these principles are practically inapplicable if human survival is not ensured first).

The Anthropocene, through the awareness of the fundamental role of interspecific relationality and our interaction with planet Earth, as well as their incorporation into bioethical debate, is likely to overshadow the developmental trajectories that characterized the end of the twentieth century and the beginning of the new millennium: the claims of individual rights and the discipline of intra-human relationships inspired, for example, by the right of choice of the individual or the couple, or decisions arising from the doctor-patient dyad. There will emerge a dual polarity: a planetary and global ecological perspective (which somehow evokes and resumes the impetus of the original bioethics, Potter and the like, for instance) and, within the framework of rediscovered biological familiarity with non-human living beings, the vast acquired (or in the process of being acquired) potentialities for intervention on the foundations of human nature – biological, anthropological, psychological, identity-related – and thus also for legal regulation.

The themes of ecology and our relationship with non-human animals [28] are precisely those that assume greater relevance in terms of the current change in bioethical priorities. This is evidenced by the establishment of dedicated chairs, such as those in Plant Psychology at the University of Padua (Umberto Castiello) and Plant Neurobiology at the University of Florence (Stefano Mancuso), or the chair in Private Law of Animals at the University of Turin (Luciano Olivero). This trend calls for a paradigm shift in the biological, cultural, and philosophical concept of the human being and their place in the balance of planet Earth. This aligns with the spirit of the Italian Recovery and Resilience Plan (PNRR), which sees ecology (and eco-sustainability) as the guiding principle characterizing investment mission No. 2 ("Green revolution and ecological transition"), but actually permeating all others as well.

Considering that Legislative Decree 254/2016 requires listed companies with more than 500 employees and

€40 million in revenue to declare their non-financial statements annually (advancing the concept of ethical capital, which irreversibly undermines the supremacy of GDP and introduces ecological, social, and moral values into the heart of the evaluation system), it is likely that sustainability will become a filter, a precondition, for all investments financed with public funds in the future [29].
Thus, the Anthropocene brings bioethics back to its pragmatic profile, to its economic relevance in terms of the depletion of non-renewable resources and the allocation of economic resources. Every year, the Global Footprint Network, an international sustainability organization focusing on environmental accounting, calculates the planetary ecological footprint and identifies the day when the Earth's capacity to regenerate resources for the current year is exhausted. The Earth Overshoot Day for the world fell on July 28, 2022 (in 2021, it was July 29, and in 2020, it was August 22). On May 15, 2022, however, it was Italy's Overshoot Day, the day when Italy surpasses its ecological footprint (thus consuming nearly 3 planets instead of 1) [30]. The United States leads the ranking: they consume the equivalent of 5 planets [31].

The anthropocene and ethical challenges

The interaction between industrialization, urbanization, and economic development has led to significant improvements in human health, including increased life expectancy, reduced infant mortality, and a decline in extreme poverty. However, these benefits, distributed unevenly, have also resulted in unprecedented exploitation of the Earth's life support systems.
We cannot overlook the contribution of the healthcare sector to this profound alteration of natural ecosystems. Inadequate policies regarding the use and disposal of pharmaceuticals and medical devices can significantly contribute to water and soil pollution, negatively impacting biodiversity and ecosystem health. Similarly, intensive farming and livestock practices, often associated with the healthcare sector, contribute to deforestation, soil erosion, and air and water pollution.
As emphasized by the American ecologist Aldo Leopold, the Ethics of the Earth raises crucial questions that challenge many implicit assumptions of a bioethics focused solely on the present temporal dimension, necessitating a profound reconsideration of the ethical relationship that humans have traditionally established with the Earth community and the ecosystems upon which they necessarily depend [32].
In the materialistic and functionalistic perspective typical of modernity, nature is seen as a mere source of resources to be exploited limitlessly and a dumping ground for activities aimed at maximizing productivity and income. However, not only the recent SARS-CoV-2 pandemic but also the various health emergencies that have occurred over time have highlighted the fragility of the traditional paradigm that allows for any possible use of these resources solely based on mere technical possibility.
As philosopher Isabelle Stengers reminds us, the "intrusion of Gaia" warns us that the Earth is much more than just a reservoir of resources to be exploited; it is a living organism, interconnected and interdependent, responding to human actions and their consequences [33, 34]. This concept challenges us to reconsider our traditional relationship with nature and to revise how we treat it to adopt a more respectful and responsible approach, recognizing its intrinsic value and its capacity for self-regulation.
In a different and necessary perspective, humans –as simple members among other living community members – take on an ethical responsibility towards present and future generations in a broader ecological context, capable of considering the connections between humans and the environment in a more complete and conscious way.
By recognizing the intrinsic value of the community itself, beyond the well-being of its individual members, the Ethics of the Earth moves away from the individualistic approach that often still permeates contemporary bioethical reflection to promote an ethics of interconnectedness, which acknowledges and respects the vitality and balance of the community as a whole.
The issue of equity in the use of resources and the distribution of environmental harms represents another crucial point. Who is responsible for mitigating the negative impacts of the Anthropocene, and how should these responsibilities be distributed? As Leopold reminds us, "A thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise" [35].
An ethical approach to managing the Anthropocene thus requires a cultural and social change. This includes promoting sustainable technologies, responsible environmental policies, and a new paradigm of values focused on the interconnectedness between humanity and the global ecosystem.
In this context, considering ourselves citizens of the Earth community broadens the moral horizons of healthcare, moving beyond an exclusively anthropocentric focus.
This approach implies a broader and more inclusive ethics that recognizes our connection to the entire ecosystem and promotes care not only for humans but also for the Earth and all forms of life inhabiting it. It is indeed a fact that our well-being depends not only on the medical care we receive but also on the quality of the air we breathe, the water we drink, and the soil we cultivate for food. A broader and more inclusive ethics thus entails a commitment to caring not only for individuals' immediate medical needs but also the responsibility to adopt practices and policies that protect and preserve the environment in which we live, ensuring long-term health for all forms of life on Earth. This structural interconnectedness among the various components interacting to determine well-being and health is well expressed in the One Health framework, which proposes an integrated approach to holistically address health threats [36].
The One Health approach, officially recognized by the European Commission and all international organizations as a relevant strategy across various sectors benefiting from collaboration between different disciplines, constitutes an ideal approach to achieve global health as it considers the wide range of factors

emerging from various interactions, thus providing a comprehensive framework. Embracing this perspective also entails a revision of the current concept of "health" identified by the World Health Organization as the ability to adapt and self-manage in the face of physical, emotional, and social challenges (2011), to expressly include the reference to the relationship that humans have with other living beings and with nature in its complexity [37]. Integrating this perspective into the definition of health allows us to better understand the critical role that environmental conservation plays in promoting human well-being and to adopt more holistic and sustainable approaches to global health.

A perspective of justice in healthcare that integrates climate and environmental justice could provide healthcare providers with a more comprehensive and relevant ethical framework for future challenges. The One Health approach could indeed imply not only treating individual diseases but also adopting healthcare policies and practices that reduce negative impacts on the environment and promote long-term sustainability. For example, healthcare services could be more involved in reducing air pollution and greenhouse gas emissions, ensuring that healthcare facilities are environmentally sustainable, and promoting a healthier diet and lifestyle with a positive impact on both human health and the environment.

In this way, healthcare workers can actively contribute to building a more equitable and sustainable future for all by considering the ethical implications of their actions not only for the present but also for future generations and the planet. Viewing ourselves as citizens of the Earth community necessarily broadens the moral horizons of care to encompass the interests of all vulnerable subjects, which include not only those who require special protection due to age, gender, social or cultural status, but also all non-human members exposed to the consequences of our actions.

Towards new forms of education

In an era where the Anthropocene increasingly undermines the delicate balances of the planet's life support systems, bioethics can play a crucial role in educating and guiding the choices and actions of individuals, institutions, and governments. However, its impact will be truly significant only if it is able not only to address the consequences of our exploitation of the natural world but also to profoundly rethink our relationship with it.

By promoting fundamental ethical values such as environmental responsibility and solidarity, bioethics, enriched by the concept of ecoformation – which provides a theoretical framework for understanding the intrinsic link between environmental awareness, individual responsibility, and the promotion of planetary health and the well-being of future generations – can stimulate critical reflection on our behavior towards nature and the implications of our actions for the health of the planet and future generations [38].

Reimagining our relationship with ecosystems also entails accepting the challenge of a profound reconsideration of the conventional conceptual tools of bioethics.

Emergencies such as the recent pandemic have highlighted the complexity of adequately addressing distributive justice issues where access to essential healthcare resources is limited and indivisible. The intricacy of these issues, which involved a group of people at a particular historical moment, has sparked debates and conflicts that have led to official positions being taken, such as those expressed by the Italian National Bioethics Committee (NBC) and the Italian Society of Anaesthesiology and Intensive Care (SIIARTI) [39, 40]. However, the complexity of these issues is expected to intensify when the comparison (extremely delicate and challenging) is not between an elderly and a young subject, easily identifiable within clinical parameters and different and quantifiable life expectancies, but extends to include goods and resources used by a plurality of subjects other than those competing for the allocation of vital resources, which will inevitably be affected, in ways that are difficult to quantify, by the production of materials consumed in the care of the individual.

The principles of distributive justice (GILLON) are effective when dealing with problems involving a defined group of potential beneficiaries and limited available resources influencing only those within this group. However, global environmental issues challenge this paradigm: the impacts of our actions are widespread in time and space, involving a wide range of people, both current and future, in different ways [41].

Even the category of obligations of justice based on human rights, ensuring that communities are not depleted in their resources for pharmaceutical production by more advantaged countries, cannot offer a decisive contribution to such issues. It is not always possible to establish a direct and causal link between healthcare provided to an individual and the violation of communities' rights to access uncontaminated water and environmental resources.

The dispersal of environmental causes and effects means that human actions in one place can have significant impacts on people and ecosystems distant in time and space. This interconnectedness makes it difficult to attribute responsibility and establish a clear ethical basis for our actions. Moreover, the fragmentation of human engagement implies that many of the actions contributing to global environmental problems stem from multiple actors, each playing a partial but significant role.

Addressing each of these factors separately would already be challenging using the resources of contemporary biomedical ethics; however, their convergence presents an even more daunting challenge, perhaps insurmountable with the resources currently available. This criticality implies that even when the "distant other" (in spatial or temporal dimensions, such as future generations) enters our circle of concern, it does not always lead to a corresponding active response from the subjects.

Stephen Gardiner has described this situation as a 'perfect

moral storm,' a lethal condition seemingly without an exit, highlighting the need for new forms of thought and ethical action based on a holistic and inclusive approach, recognizing the complex networks of relationships and interactions among individuals, communities, and the environment. This entails the need to cultivate a perception of environmental issues as morally relevant even when they are not easy to perceive [42].

Instead of focusing solely on individual parts or isolated individuals, the holistic approach acknowledges the importance of relationships and interactions among individuals, the biotic community, and the surrounding environment. This implies not only a revision of our conceptual models and ethical practices but also a profound transformation in our behaviors and policies, so that we can effectively address the interconnected challenges posed by human health and the well-being of the planet.

Climate change, soil and water pollution, and the decline in food resources make Potter's warning about the need for a new 'global bioethics,' based on a new understanding of humanity's position within planetary systems, more relevant than ever.

This innovative anthropological and philosophical perspective, arising from an awareness of the intricate relationships and interactions among humans, animals, and the environment, also calls for a redesign of educational programs capable of transcending rigid disciplinary boundaries and promoting broad and pluralistic thinking.

Considering the intrinsic link between human health and environmental health, bioethical education becomes crucial for developing critical thinking skills necessary to address the complex challenges posed by the Anthropocene.

Teaching bioethics can encourage the development of an interdisciplinary mindset, allowing students to understand the complexities of environmental and health issues through a global and interconnected perspective [43].

This can foster collaboration among different academic disciplines and the pursuit of innovative and sustainable solutions to address emerging challenges related to health and the environment.

This includes the ability to fairly assess the ethical implications of decisions and policies, as well as the ability to collaborate effectively with other disciplines and sectors to develop sustainable and socially just solutions.

Starting from schools, the integration of bioethics into educational curricula can promote awareness of the connection between individual actions and collective impacts on the environment and human health. Through the teaching of fundamental ethical concepts such as solidarity, social responsibility, and equity, students can gain a deeper understanding of global challenges related to health and the environment and develop critical skills to address them proactively.

Healthcare professionals who are aware of the ethical implications of their practices can also play a primary role in engaging the general public in adopting sustainable and responsible behaviors.

Conclusions

The Anthropocene represents a critical phase in human history, necessitating a profound examination of our relationship with planet Earth and its myriad life forms. Environmental alterations resulting from human activity are contributing, for instance, to the rise in malnutrition and the spread of vector-borne and waterborne diseases within a context already marked by severe systemic imbalances. Additionally, it is crucial to acknowledge that modern healthcare, primarily developed in high-income countries and often regarded as a model to emulate, has been influenced by the same perspective threatening the well-being of future generations. This underscores the urgent need to reassess global healthcare systems to address emerging environmental challenges and ensure the protection of public health on a global scale.

Only through a fundamental revision of our ethical approaches and collective commitment to coordinated and monitored human actions can we hope to safeguard the health of current and future generations.

Investing in the education of future generations on ethical issues related to the preservation of our planet can significantly promote a culture of environmental awareness and respect for nature. Sensitizing children from an early age to environmental protection and the construction of more sustainable societies can play a fundamental role in shaping individual behaviors and collective decisions aligned with the conservation of our ecosystem and the well-being of present and future generations.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or notforprofit sectors.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

The text is the result of a collaborative effort among the authors. However, for the sole purpose of scientific authorship attribution, DP is to be credited with the paragraphs: Introduction: The complexity of bioethical language: between interdisciplinarity, ambiguity, and conceptual evolution; The broadening of the extension of the term "bioethics"; The shift in priorities in the bioethical debate. CR is to be credited with the paragraphs: The Anthropocene and Ethical Challenges; Towards new forms of education; Conclusion.

References

[1] Donghi P. Prefazione. In: Corbellini G, Donghi P, Massarenti A, eds. Biblioetica. Dizionario per l'uso. Torino: Einaudi 2006, pp. V-XI.

[2] Mazzoni CM. Liberalità e solidarietà nel dono di organi. Belfagor 2000;55:517-525.

[3] Becchi P. Perché si è parlato di 'donazione' in relazione alla dichiarazione di volontà riguardo al prelievo degli organi e perché, quantunque giuridicamente improprio, sarebbe meglio continuare a farlo. In: Barberis G, Lavanda I, Rampa G, Soro B, eds. La politica economica tra mercati e regole. 1th ed. Soveria Mannelli: Rubettino 2005, pp. 93-102.

[4] Pessina A. Bioetica. L'uomo sperimentale. 1th ed. Milano: Mondadori 1999.

[5] Leone S. Nuovo manuale di bioetica. 1th ed. Roma: Città Nuova 2007.

[6] Sgreccia E. Manuale di bioetica vol. I. 3th ed. Milano: Vita e Pensiero 1999.

[7] Tettamanzi D. Nuova bioetica cristiana. 3th ed. Casale Monferrato: Piemme 2000.

[8] Ciccone L. Bioetica. Storia, principi, questioni. 1th ed. Milano: Ares 2003. pp. 245-254.

[9] Mori M. Manuale di bioetica. 1th ed. Firenze: Le lettere 2011, pp. 392-403.

[10] Lecaldano E. Bioetica. Scelte morali. 1th ed. Roma-Bari: Laterza 1999.

[11] Engelhardt Jr. HT. Manuale di bioetica. 3th ed. Milano: Il Saggiatore 1999.

[12] Castignone S, ed. I diritti degli animali. Prospettive bioetiche e giuridiche. 1th ed. Bologna: Il Mulino 1985.

[13] Castignone S. Nuovi diritti e nuovi soggetti. 1th ed. Genova: Ecig 1996.

[14] Battaglia L. Etica e diritti degli animali. 1th ed. Roma-Bari: Laterza 1997.

[15] Castignone S. Povere bestie. 2th ed. Venezia: Marsilio 1999.

[16] Battaglia L. Dimensioni della bioetica. La filosofia morale dinanzi alle sfide delle scienze della vita. 1th ed. Genova: Name 1999.

[17] Battaglia L. Un'etica per il mondo vivente. Questioni di bioetica medica, ambientale, animale. 1th ed. Roma: Carrocci 2011.

[18] Castignone S, Battaglia L, eds. I diritti degli animali. Atti del convegno nazionale. Genova: Centro di Bioetica 1987.

[19] Ciccone L. Bioetica. Storia, principi, questioni. 1th ed. Milano: Ares 2003.

[20] La bioetica. Questione civile e problemi teorici sottesi. Angelini G, Chiodi M, Lattuada L, Mordacci R, Viafora C, Vigna C, eds. 1th ed. Milano: Glossa 1998.

[21] Picavet E. Une crise des fondements: la controverse du principisme «Principisme» et recherche d'unité en bioéthique. Noesis 2016; 28. Available at: https://journals.openedition.org/noesis/2858#quotation (Accessed on: 04/06/2024).

[22] Neri D. La bioetica in laboratorio. 1th ed. Roma-Bari: Laterza 2001.

[23] Castiello U. La mente delle piante. Introduzione alla psicologia vegetale. 1th ed. Bologna: Il Mulino 2019.

[24] Mancuso S. Plant revolution. 1th ed. Firenze-Milano: Giunti 2017.

[25] Mancuso S, Viola A. Verde brillante. Sensibilità e intelligenza del mondo vegetale. 2th ed. Firenze-Milano: Giunti 2015.

[26] Cauwelaert D. Van. Le emozioni nascoste delle piante. Come si esprimono, comunicano e interagiscono i vegetali. 1th ed. Milano: Feltrinelli 2019.

[27] Vallortigara G. Pensiero della mosca con la testa storta. 1th ed. Milano: Adelphi 2021.

[28] Mouawad W. Anima (trad. it. A. Conti). 1th Roma: Fazi 2015.

[29] D.L. 30.12.2016, n. 254, Attuazione della direttiva 2014/95/UE del Parlamento europeo e del Consiglio del 22 ottobre 2014, recante modifica alla direttiva 2013/34/UE per quanto riguarda la comunicazione di informazioni di carattere non finanziario e di informazioni sulla diversità da parte di talune imprese e di taluni gruppi di grandi dimensioni. G.U. Serie Generale n.7 del 10.1.2017. Available at: https://www.gazzettaufficiale.it/eli/id/2017/01/10/17G00002/sg (Accessed on: 4/06/2024).

[30] Wackernagel M L, Lin D. Earth Overshoot Day. In: Wallenhorst N, Wulf C, editors. Handbook of the Anthropocene. New York: Springer Cham 2023, pp. 569-72. https://doi.org/10.1007/978-3-031-25910-4_90.

[31] Center for Sustainable Systems, University of Michigan. U.S. Environmental Footprint Factsheet. 2023. Pub. No. CSS08-08. Available at: https://css.umich.edu/publications/factsheets/sustainability-indicators/us-environmental-footprint-factsheet (Accessed on: 4/06/2024).

[32] Leopold A. Tutto ciò che è libero e selvaggio. In: Castelletti L, ed. Bologna: Piano B 2022.

[33] Stengers I. Nel tempo delle catastrofi. Resistere alla barbarie a venire. In: Manghi N, ed. 1th ed. Torino: Rosemberg & Sellier 2021.

[34] Lovelock J, Gaia A. New Look at Life on Earth. Oxford: Oxford Landmark Science 1979.

[35] Leopold A. A sand county almanac, and sketches here and there. 1th ed. Oxford: Oxford University Press 1989.

[36] Capps B. One health ethics. Bioethics 2022;36:348-55. https://doi.org/10.1111/bioe.12984.

[37] Ciliberti R, Schiavone V, Alfano L. Bioethics: beyond the boundaries of disciplines Med Hist 2023;7:e2023012.

[38] Pineau G. Genèse De L'écoformation. Du préfixe éco au vert paradigme de formation avec les environnements. 1th ed. Paris: L'Harmattan 2023.

[39] Zeneli A, Brandi G, Di Pasquale G, et al. Identifying ethical values for guiding triage decisions during the COVID-19 pandemic: an Italian ethical committee perspective using Delphi methodology. BMJ Open 2021;11:e043239. https://doi.org/10.1136/ bmjopen-2020-043239.

[40] Gianicolo E, Portaluri M. Sulle raccomandazioni di etica clinica della SIAARTI per il trattamento dei pazienti CoViD-19. Recenti Prog Med 2020;111:697-698. https://doi.org/10.1701/3474.34578.

[41] Gillon R, Raising the profile of fairness and justice in medical practice and policy. J Med Ethics 2020;46:789-90. https://doi.org/10.1136/medethics-2020-10703.

[42] Gardiner SM. A perfect moral storm: the ethical tragedy of climate change. Oxford: Oxford University Press 2011. https://doi.org/10.1093/acprof:oso/9780195379440.001.0001.

[43] Gulino M, Patuzzo S, Baldelli I, et al. Bioethics in Italian medical and healthcare education. A pilot study. Acta Biomedica 2018;89:519-31. https://doi.org/10.23750/abm.v89i4.7238.

Received on March 13, 2024. Accepted on May 28, 2024.

Correspondence: Rosagemma Ciliberti, Department of Health Sciences, Section of Bioethics and History of Medicine, University of Genoa, Genoa, Italy. E-mail: ciliberti@unige.it

How to cite this article: Donadoni P, Ciliberti R. How the Anthropocene is changing bioethics. J Prev Med Hyg 2024;65:E303-E308. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3224


MSD
INVENTING FOR LIFE


Pfizer
Vaccines


Seqirus
A CSL Company


SANOFI PASTEUR


VISMEDERI
ANALYSES FOR LIFE IMPROVEMENT


AstraZeneca