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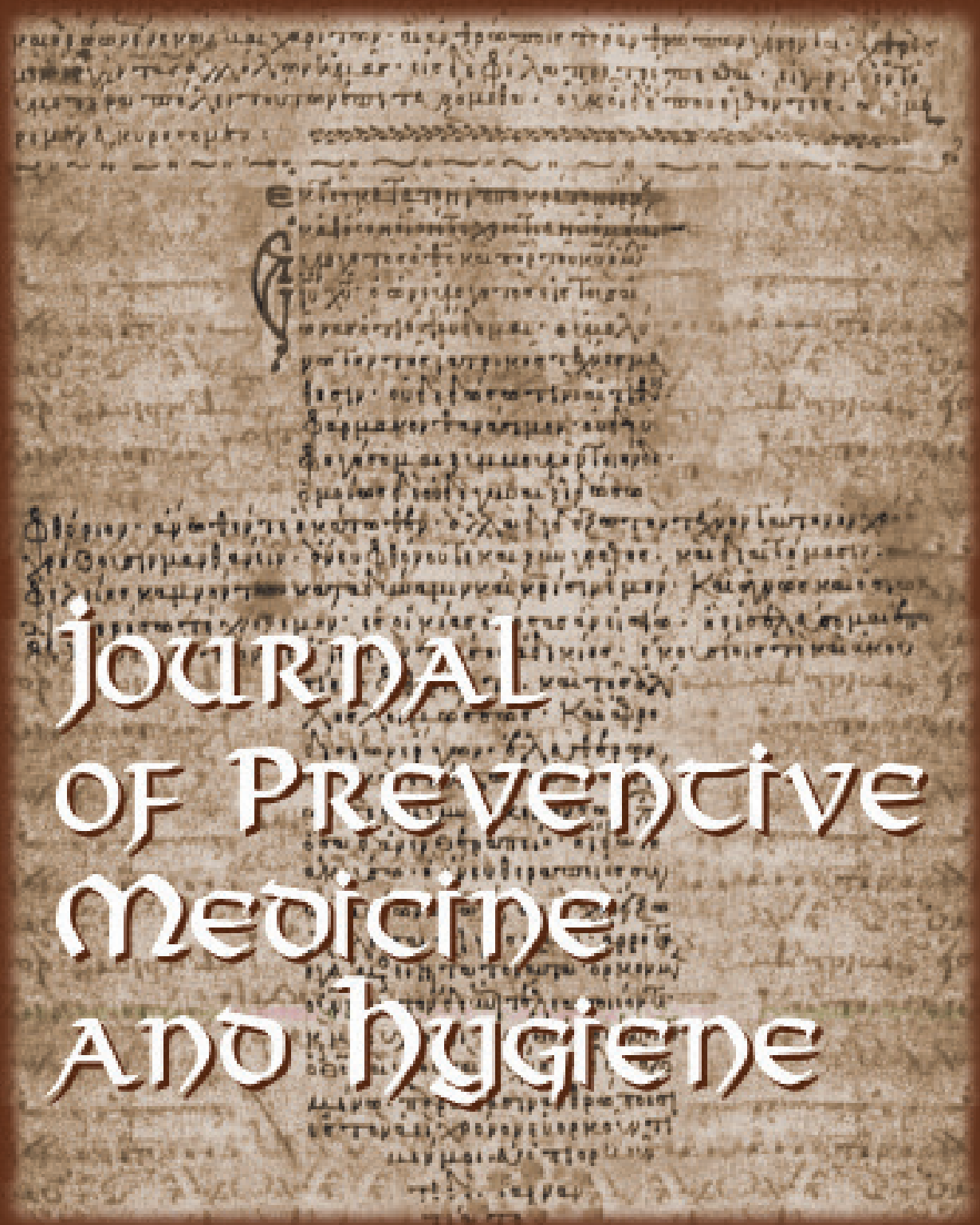

The original document of Hippocrates' oath

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Contents

HEALTH PROMOTION

Telemedicine: the Technological Revolution to Address Healthcare System Shortcomings

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Keywords

Telemedicine • Teleconsultation • National Recovery and Resilience Plan (PNRR)

To the Editors,

In an increasingly complex and challenging healthcare landscape, telemedicine presents an opportunity to improve access to care and ensure that healthcare is always close to citizens [1].

Telemedicine can reduce inequalities, effectively improving access to personalized healthcare services for everyone. However, the result depends not only on the availability of appropriate technological tools but also on the digital literacy of both patients and healthcare personnel [2]. Otherwise, there is a real risk of exacerbating inequalities and compromising equitable access to care.

In Italy, new solutions in telemedicine are increasingly being implemented, radically transforming the doctor-patient relationship, improving access to specific services, and overcoming geographical and temporal limitations.

One area where this tool is being used is the ASL of Latina (Italy): a local health authority in Lazio Region that covers a very large province stretching from Circeo to Sabaudia, including the islands of Ponza and Ventotene [3]. With nearly 600,000 inhabitants, 5 districts, and 4 hospitals in a diverse territory, new technological possibilities are being used to measure and address disparities.

Regarding territorial healthcare a department for the protection of vulnerabilities has been established, comprising a network of consultation offices, a structure dedicated to adult disabilities, a reference point for the migrant population, hospices and palliative care, territorial oncology, and nursing homes. To improve the care of chronic patients, a community nurse has been established.

Telemedicine tools, such as teleconsultation and telemonitoring, which have increasingly gained ground following the COVID-19 pandemic, are playing an increasingly significant role in patient-centered healthcare. In particular, the ASL of Latina boasts a highly developed system for managing heart failure: 2,700 patients are enrolled, and of these, just over a thousand have an implanted device such as a pacemaker and are managed entirely remotely with home tele-visits. A telemonitoring system is in place, verified for 12 hours a day by a hospital cardiologist through an always-active central unit linked to the "Pontine Acute Myocardial Infarction Network". Operating since 2012, the network – aligned with high international standards – relies on the 118 operations center in Latina, with 23 telemedicine systems onboard as many ambulances, emergency rooms with 10 additional telemedicine systems, 24-hour hemodynamics at the central hub, and the intensive cardiac care unit at Santa Maria Goretti Hospital (Latina, Italy), which serves as the central listening, reporting, and teleconsultation center. This makes the hospital the first in Italy for the treatment of acute myocardial infarction according to the ranking by the Italian Society of Cardiology and Hemodynamics, and it ranks among the top ten in Europe, fourth in Italy, and first in Lazio for coronary angioplasty.

A decline in hospitalizations was reached, reconfirmed year after year compared to when this project was not active before 2019. According to the National Outcomes Program editions for the years 2012 and 2018, a clear decline in hospitalizations for acute myocardial infarction was observed. This recorded decline was -7.6% in 6 years. This success derives from the improved management of patients. The combination of heart failure management and the network that has brought electrocardiographs onto ambulances for 10 years, transmitting the trace immediately – even from the islands – to the cardiology operations center for immediate verification if the patient should be taken to the thermodynamic room. Data also show a reduction in the mortality index for heart attack, placing it among the most virtuous regions in Italy for this cause of death. "Mortality for acute myocardial infarction 30 days after hospitalization has indeed dropped from 10% in 2012 to 7% in 2018, practically 30% fewer deaths, meaning 800 lives saved between 2013 and 2018 [4].

Teleconsultation is also used in Liguria Region (Italy) where the San Martino Polyclinic in Genoa is the hub of patients of high complexity care. This organizational model allows the centralization of specific cases.

The hub was alerted by the San Paolo Hospital in

Savona: once the patient was examined, Savona doctors were able to send 1,800 CT images in seconds to the San Martino surgeons via teleconsultation.
Recently, an emergency flight saved a 53-year-old patient with an aortic dissection at risk of rupture and cardiac tamponade. The woman was operated on by cardiac surgeons at the Polyclinic.
Telemedicine can also address current healthcare system shortages: offering online visits can help reduce waiting lists for outpatient appointments, disseminate useful information to the population, and encourage preventive care, reduce costs, and optimize resources by reducing physical appointments when not essential [5]. However, its effectiveness depends on strategic integration into the healthcare system and staff training. At the same time, we cannot rely solely on "remote" solutions to address current healthcare problems such as the shortage of general practitioners. In the immediate term, technological tools can address an emergency situation like this, but in the coming years, careful planning will be necessary: "According to the Italian National Medical Insurance and Welfare Board (Enpam) estimates, as of December 31, 2021, more than 50% of GPs were over 60 years old, and therefore a massive retirement is expected in the coming years: considering a retirement age of 70, about 20,000 GPs should retire by 2031". The effects of this situation are already evident in some areas [6]. This is the case of the Bergamo Health Protection Agency (Italy), which faced a significant shortage of family doctors. Around 20,000 people were left without a primary care physician for more than 18 months. Initially, efforts were made to maintain continuity of care with the opening of temporary clinics staffed by on-call doctors and GPs, but the high influx made it complex to track all services provided. At the same time, it was not simple identify in which time slots the available doctors could take on "extra" patients. Therefore, a platform was created to match the availability of general practitioners with patients "orphaned" of their doctor. The benefits were immediately apparent: patients could book visits not based on their residence but according to their preferences, such as proximity to work, and doctors accessed a direct payment system for services, all managed electronically. Ninety professionals joined, uploading their available hours online: Bergamo residents now have an app to book directly from their smartphones, and 240 local pharmacies participated to assist patients less familiar with technology. In 2023, 9,000 services were provided monthly, 2,000 of which were in the seven community health centers in the area, indicating a growing trend among those who prefer to receive care at their clinics. This is an example how the technology can and should make the Italian healthcare system more efficient. Yet, there is still much to be done in Italy: for this reason, the National Recovery and Resilience Plan (PNRR) allocated 60% of funds to developing digital skills to bridge the gap with more advanced countries in this regard [7]. Previously allocated digitization funds in various regions were never adequately used, and now we must accelerate and recover 'lost time'.

One of the most common problems is the fragmentation of systems and software incapable of communicating with each other. This is precisely what the Abruzzo Region faced after the advent of COVID-19, committing to a dense schedule of digital health in its 2021-2023 three-year plan. It started with training for healthcare personnel, followed by piloting billed services. Efforts were made to facilitate citizen access to choose and possibly revoke their general practitioner, and to create a single booking center (CUP) to address patient healthcare booking difficulties. Significant changes are currently being made to the vaccination registry to unify it and improve screening analysis, ensuring no relevant patient information is overlooked. Additionally, an integrated imaging diagnostics system and a unified platform for laboratory test reporting are being developed, enabling external specialist consultations for certain rare diseases and optimizing resources simultaneously. Consequently, citizens are facilitated in accessing healthcare services, and doctors are provided with new and effective diagnostic platforms.
However, it should not be forgotten that behind artificial intelligence algorithms and teleconsultation or telemedicine, there is always the responsibility of the doctor who must oversee the contribution that innovation can make in terms of higher quality, for example by limiting the possibility of human error [8]. Continuous training for doctors is therefore necessary, supported by engineers to manage these new devices. It is essential that they are European Conformity (CE) certified to ensure their safety. The risks are evident: from respecting patient privacy and the security of personal data, which could be subject to breaches or unauthorized access, to actual malfunctions of medical devices. The digital divide among the population must also be considered, as not everyone can benefit from the advantages of telemedicine, which, if improperly used, can result in a loss of human contact in the doctor-patient relationship, compromising empathy and the necessary doctor-patient relationship. Moreover, technology is costly, and each healthcare manager must identify the priorities for investment to improve their healthcare organization.

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Conflicts of Interest

The authors declare no conflict of interest.

Authors' contributions

All authors contributed equally to the development and preparation of the manuscript.

References

[1] Barbosa W, Zhou K, Waddell E, Myers T, Dorsey ER. Improving Access to Care: Telemedicine Across Medical Domains. Annu Rev Public Health 2021;42:463-81. https://doi.org/10.1146/annurev-publhealth-090519-093711.

[2] Arias López MDP, Ong BA, Borrat Frigola X, Fernández AL, Hicklent RS, Obeles AJT, Rocimo AM, Celi LA. Digital literacy as a new determinant of health: A scoping review. PLOS Digit Health 2023;2:e0000279. https://doi.org/10.1371/journal.pdig.0000279.

[3] ASL Latina. Regione Lazio. Available at: https://www.ausl.latina.it/ (Accessed on: 15/04/2024).

[4] Quotidiano Sanità. Infarto miocardico acuto. L'ospedale di Latina sul podio della classifica nazionale per numero di interventi. Available at: https://www.quotidianosanita.it/lazio/articolo.php?articolo_id=86673. (Accessed on: 15/04/2024).

[5] Haleem A, Javaid M, Singh RP, Suman R. Telemedicine for healthcare: Capabilities, features, barriers, and applications. Sens Int 2021;2:100117. https://doi.org/10.1016/j.sintl.2021.100117.

[6] 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:E236–E44. https://doi.org/10.15167/2421-4248/jpmh2024.65.2.3145

[7] Mudey AB, Dhonde AS, Chandrachood MV. Artificial Intelligence in Healthcare With an Emphasis on Public Health. Cureus 2024;16:e67503. https://doi.org/10.7759/cureus.67503.

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HEALTH PROMOTION

Improving the ONE HEALTH approach: a lesson from SARS-CoV-2 pandemic

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Keywords

SARS-CoV-2 • ONE HEALTH • Surveillance • Zoonosis • Humans and animals• Emergency preparedness

Summary

The emergence of SARS-CoV-2 has underscored the critical need to enhance the ONE HEALTH approach which recognizes the interconnectedness of human, animal, and environmental health. In this review we report on various animal species that were infected by SARS-CoV-2 virus during the pandemic with the aim to contribute to the One Health approach. The SARS-CoV-2 pandemic has highlighted the devastating consequences of zoonotic diseases such as COVID19 and has reiterated the critical role that the health of wildlife, domestic animals, and the environment plays in human health. The pandemic is a lesson learnt on the urgent need for an enhanced ONE HEALTH approach by developing a robust and interconnected global health strategy to effectively prevent and control zoonotic diseases and protect the health of all species on our planet. These efforts are crucial for a sustainable and resilient future for both human and ecological systems.

Introduction

SARS-CoV-2, a highly pathogenic coronavirus in humans, has emerged at the end of 2019 and has caused a devastating pandemic with 771,549,718 confirmed cases, including 6,974,473 deaths, as of 25 October 2023 [1]. Although its origin is still unclear, SARS-CoV-2 has been acknowledged to be a zoonotic virus, meaning that the virus can spread from animals to humans [2]. The most accepted hypothesis behind the COVID-19 pandemic is that the virus originated in a bat species and then spread to humans through a direct spillover event. Additional hypotheses are 1) the circulation of a less-virulent progenitor that over time accumulated mutations and increased its virulence or 2) the involvement of an intermediate host which, having been infected by a bat, was then able to transmit the virus to humans. Although the involvement of an intermediate host has not been confirmed, pangolins and civets have been identified as potential candidates [3-6] (Fig. 1).

As of September 2022, SARS-CoV-2 had been detected in 25 animal species (wild, captive, and domestic animals) from 36 countries. Most of these animals were infected after contact with sick humans, a phenomenon called reverse zoonosis [2, 5, 7, 8]. The main concern during reverse zoonosis is the possible increase of viral virulence due to the many mutations the virus may accumulate during spillover events. These mutations may result in immunity escape factors that when the virus will spread back to humans may lead to disease worsening [5, 7]. The "One Health Concept", first used in 2003-2004 following the emergence of Severe Acute Respiratory Syndrome (SARS) in 2003, recognizes that human health is strictly related to the health of animals, plants, and their shared environment, focusing on the relationship and interconnections among these entities [9-12]. Short after the 2003 SARS epidemic, the emergence and spread of the highly pathogenic avian influenza virus H5N1 [13, 14] contributed to the growing importance of "One Health Concept". The European Commission strongly supports and encourages a One Health approach when it comes to the prevention, preparedness, and response to zoonoses, especially major threats such as avian influenza viruses, West Nile and Ebola viruses. Prevention, robust surveillance, rapid detection and response are crucial when dealing with serious cross-border health threats such as zoonoses [15]. The COVID-19 pandemic has further highlighted the need for an improved One Health Concept that aims to a collaborative, multi-sectoral, and transdisciplinary approach to address potential health threats from the animal-human-environment interface [7, 9, 10, 16-18]. Considering that about 61% of common human pathogens and about 75% of emerging pathogens are of zoonotic origin, mainly from wildlife, surveillance measures of domestic animals as dogs and cats, and of secondary wild reservoir species as mink and white-tailed deer [5] are critical for preventing the emergence of novel SARS-CoV-2 variants as well as of other emerging pathogens. For this reason, the relationship

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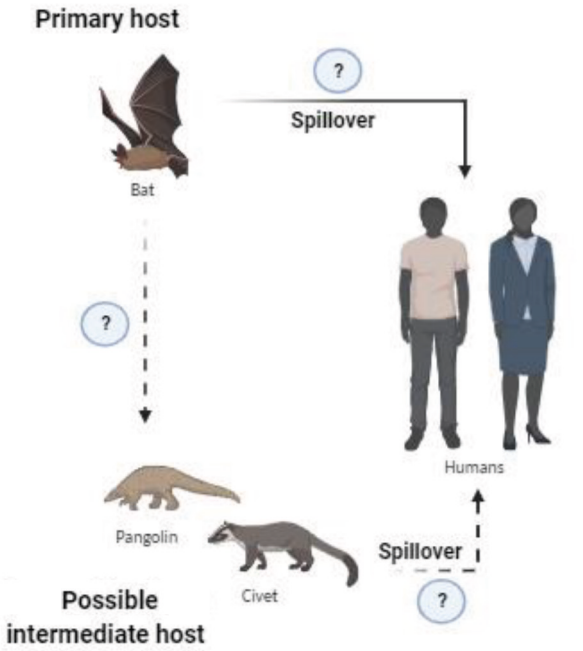
Fig. 1. SARS-CoV-2 zoonotic transmission to humans.



The virus spread from bats to humans through direct spillover (continuous arrow) or through the involvement of an intermediate host (dashed arrows), which was infected by bats and then transmitted the virus to humans (created with BioRender.com).

between the environment and human and animal health is fundamental to understanding and addressing global health challenges [19]. For instance, pollution, climate change, and habitat destruction can lead to the emergence and spread of infectious diseases, affecting both wildlife populations and human communities [20]. Conversely, preserving biodiversity and maintaining healthy ecosystems can provide essential ecosystem services that support human health, such as clean air, water, and food security [21, 22].

The aim of this work was to provide an overview of the various animal species infected by SARS-CoV-2 in order to contribute to the One Health approach.

SARS-CoV-2 infection in pets

Domestic animals, also called pets, are all those which are kept at home for company, such as cats, dogs, ferrets, and hamsters. The COVID-19 pandemic greatly changed the pet-owner relationship. Indeed, while social isolation increased the adoption of pets [23], many pet owners abandoned their animals for fear that they could vehicle the virus [24]. In addition, preventive behavioral measures were taken to avoid direct contact with pets and as a consequence owners became less closely involved with their animals [25].

Experimental studes have shown that pets are susceptible to SARS-CoV-2 infection [26] (Fig. 2). However, their role in the virus transmission cycle is not yet clear.

The first cases of human-animal transmission occurred in Hong Kong in February and March 2020, when two male dogs, one Pomeranian and one German Shepherd, tested positive for SARS-CoV-2 with RT-PCR and serological tests [27]. Serological studies have detected very low SARS-CoV-2 antibody titers in dogs and clinical signs are rarely present. While dogs are the animals living in close contact with humans, their seroprevalence rate is less than 5%, thought it tends to increase when their owners carry a high viral load [28, 29]. In dogs, sex and age seem to play a role in the risk of SARS-CoV-2 infection, and susceptibility to infection increases in male dogs older than year old [30].

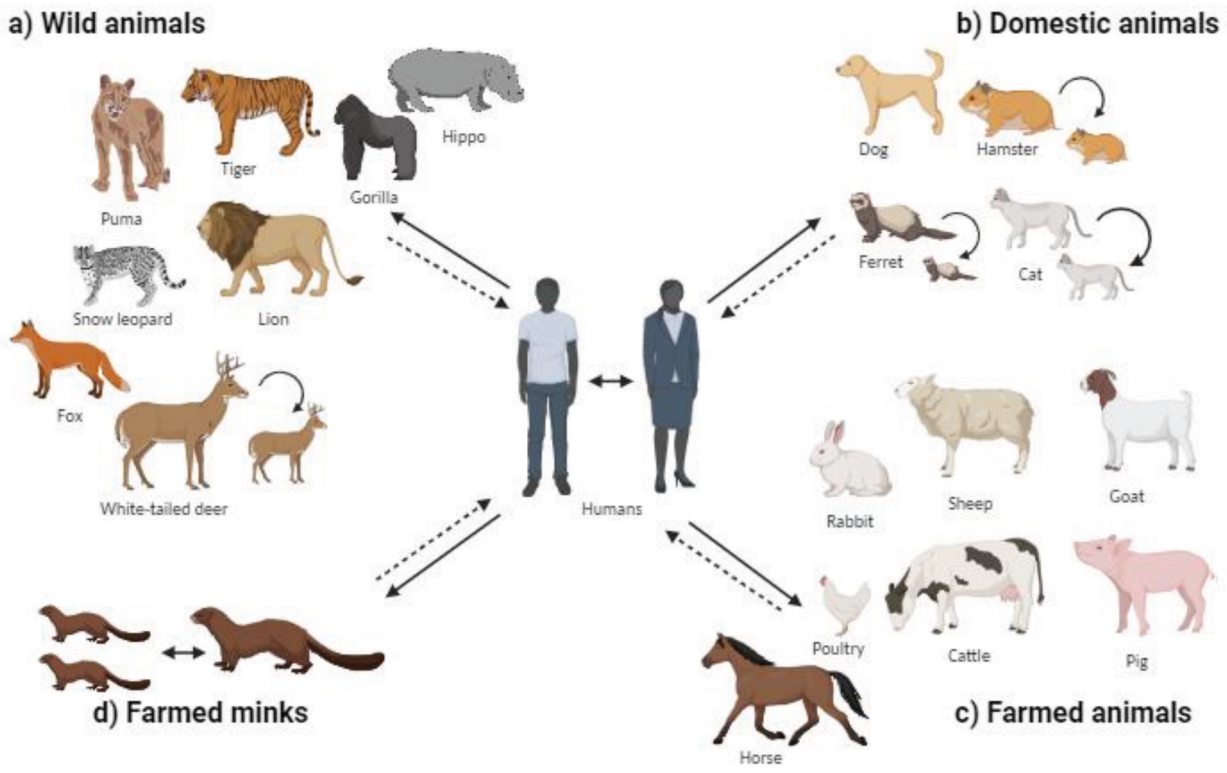
Cats can transmit the virus by air to other naive cats causing infection in the lungs, lymph nodes enlargement, coughing and dyspnea [31]. Cat infection acquired from COVID-19 positive owners has been reported from various countries, confirming human-to-cat SARS-CoV-2 transmission. In a study conducted in Hong Kong, 12% of cats living with infected humans tested positive for SARS-CoV-2 [32]. Similarly, a study conducted in Wuhan (China) found that 14.7% of cats living with infected owners tested positive for the virus. Of these, 10.8% had neutralizing antibodies against SARS-CoV-2 [33]. Cat-to-human transmission seem a rare event with only one case reported in Thailand, where an infected cat of an infected owner sneezed on a veterinarian who became infected [34]. Similar to humans, clinical signs as fever, lethargy, respiratory distress are also observed in cats but are not specific to COVID-19 infection. Younger than one-year cats have a higher risk of infection than dogs of the same age [35].

Cats are more susceptible to infection than dogs, probably because they retain high greater expression of Angiotensin-Converting Enzyme 2 (ACE-2) receptors, the target of the SARS-CoV-2 spike (S) protein in the respiratory tract [36]. Viral persistence in cats is longer (21 days) than in dogs (13 days) [37] and cats' genomic sequence encoding ACE-2 receptor shows 85.5% similarity to that of humans. Only four out of 20 amino acid residues encoding the receptor-binding domain (RBD) of the S protein have been found to differ between cats and humans [38].

Ferrets are susceptible to SARS-CoV-2 infection and have been shown to transmit the virus to other ferrets [39]. In several countries ferrets are kept as pets, but little information is available on SARS-CoV-2 epidemiology in these animals. In a study conducted in Spain in ferrets living with humans infected with SARS-CoV-2 it was found a seroprevalence of 1.6%. None of the seropositive animals showed clinical signs of SARS-CoV-2 infection [40].

Hamsters are considered to be a valuable animal model, as they can develop SARS-CoV-2 infection [41]. Golden Syrian hamsters inoculated nasally with SARS-CoV-2 developed several signs of infection and transmitted the virus to naïve co-housed hamsters [42, 43]. Viral transmission from humans to hamsters was reported after infected Golden Syrian hamsters were shipped from the Netherlands to Hong Kong and sold to different pet shops. The subsequent animal-to-human transmission

Fig. 2. SARS-CoV-2 transmission in various animal species.



The virus has spread from humans to several animal species (reverse zoonotic transmission). Inter-species and intra-species transmission and spill-back to humans have been described (created with BioRender.com).

resulted in more than 80 human cases all of which were attributed to the Delta variant [44, 45].

SARS-CoV-2 in farm animals

SARS-CoV-2 infection has also been described in farm animals (Fig. 2).

Pigs are considered to have a limited susceptibility to SARS-CoV-2 [46]. Under experimental conditions they shown to be resistant to intranasal inoculation of SARS-CoV-2. Indeed, no clinical signs, including increased body temperatures, were observed in these animals [26, 47]. Low level of viral shedding and antibodies against SARS-CoV-2 were found only in 31.3% of experimentally infected pigs [48].

Poultry is also considered at low or no susceptibility to SARS-CoV-2 infection. In a study SARS-CoV-2 was inoculated into chickens, turkeys, ducks, quails and geese and no clinical signs were observed. The virus was not detected in any swab material, and antibodies were not detected in the serum of any species. These results suggest that either SARS-CoV-2 does not replicate in any of the studied poultry species, or that it replicates at too low a level to be detected [49]. Similar findings were reported from other studies performed in chicken [26, 47].

Cattle have little susceptibility to SARS-CoV-2 infection. In one study, as early as 3 days after experimental infection, they displayed a low viral load with a mild but detectable serological response and no cattle-to-cattle transmission was occurred [50]. In another study cows and buffaloes tested negative to RT-PCR for SARS-CoV-2 after contact with their molecular swab-positive owner [51]. Occasionally cattle can be infected and seroconvert after contact with infected humans as found in another study [52]. In sheep, the replication of SARS-CoV-2 in respiratory tissues has been demonstrated [53, 54]. However, limited transmission to other sheep has been reported [53]. Another in vivo study on experimentally infected sheep found no virus or viral RNA in swabs or tissues, but some of them developed low titer of neutralizing antibodies, suggesting a mild infection [55]. A serological investigation on sheep in close contact with humans conducted before and after the pandemic did not find SARS-CoV-2 antibodies, suggesting that sheep are not or little susceptible to SARS-CoV-2 infection [56].

Goats have low susceptibility to SARS-CoV-2 infection. Experimental studies with intranasal inoculation found that animals became positive after 7 days with no changes in body temperature suggesting that goats may have very low susceptibility to SARS-CoV-2 infection [55, 57].

Rabbits are susceptible to SARS-CoV-2 [55, 58]. The infection, despite the positive swab, is asymptomatic, with a low viral replication suggesting that virus transmission among these animals may be less efficient

than in ferrets and hamsters; also, a low viral replication was observed. Finally, a study of more than 100 rabbits showed a very low seroprevalence rate [59]. The spread of the virus and disease in other rabbit breeds or in rabbits of different ages should be further investigated as no data are available [58].

An experimental infection of an adult horse by intranasally administered ancestral SARS-CoV-2 revealed no viral shedding [55]. Some studies involving the molecular detection of SARS-CoV-2 in nasal secretions and/or in feces from healthy horses that had been in contact with infected humans and sick horses revealed no evidence of virus spread [51, 60]. Moreover, a serological survey conducted in China on 18 healthy horses did not detect antibodies against SARS-CoV-2 [61]. However, a study of healthy racehorses found a seroprevalence of 5.9%, suggesting a possible spillover from SARS-CoV-2 infected humans to horses [60]. The seroconversion of a horse after close contact with infected humans confirmed the possible reverse zoonosis occurrence between humans and horses [62]. Finally, in a large seroprevalence study including 1,186 equines it was found that 3.5% of horses had detectable SARS-CoV-2 antibodies without showing clinical signs [63].

The low binding affinity to ACE-2 receptor studied by comparative sequence analysis and functional studies in equines (horses and donkeys) explains the low susceptibility of the species to SARS-CoV-2 infection [64, 65].

SARS-CoV-2 on mink farms

Minks were the first animal population that emerged as a potential source of spillback (the spreading of the virus from humans to animals, also called reverse zoonosis) and secondary spillover (transmission from new animal hosts instead of the original host) during COVID-19 pandemic. The initial infection of these animals was caused by infected humans working in mink farms. An intense and sustained animal-to-animal transmission followed as a result of both the high-density of mink populations and of the high susceptibility of minks to SARS-CoV-2 infection (Fig. 2). This intense intra-species transmission in minks led to the emergence of novel viral variants that spilled over into humans [66].

The first confirmed cases of SARS-CoV-2 in mink were reported in the south-east of the Netherlands during the first pandemic wave [67]. By the end of April 2020, mink from two different farms showed respiratory and gastrointestinal disorders, with a mortality rate of 1.2–2.4%. The infection rapidly spread throughout the farms, with many animals clinically affected. Histological signs of acute interstitial pneumonia and other lung lesions were observed, and viral RNA was detected in the lungs, throat, liver, and intestines of the dead animals [68]. Epidemiological investigations found that SARS-CoV-2 was initially transmitted to minks by humans and then spread widely among mink. Approximately 68% of farm workers or their contacts were subsequently infected with SARS-CoV-2. Viral phylogenetic sequencing confirmed that humans were infected by mink viral strains that differ from the viral strains circulating among humans who had not been in contact with minks [69], providing evidence of mink-to-human transmission [70].

Subsequently, several outbreaks of SARS-CoV-2 infection were reported from mink farms in Europe and North America resulting in high mortality and great economic loss for mink farming [69, 71-75].

A SARS-CoV-2 variant of mink origin, named ‘Cluster 5’, was initially observed in an outbreak in mink and humans in Denmark in June 2020 [76]. The identification of this mink-originating variant led to the mass culling of mink to minimize risks to of wider spreading to humans [77]. In fact, at that time approximately 53% of SARS-CoV-2 strains infecting humans in Denmark were of mink origin, indicating generalized secondary zoonotic transmission had occurred [66]. Outbreaks like those reported in Denmark have persisted throughout the pandemic with the isolation of mink viral strains identical to those isolated in humans [78] and with emergence of other variants of mink origin, such as the Marseille-4 variant (B.1.160) [79]. In addition, transmission from farmed mink to semi-domesticated animals has been documented in the Netherlands [80], and infection from wild minks has been reported in Spain and USA [81, 82], fueling concern about the prospect that a highly susceptible wild animal can become a SARS-CoV-2 reservoir.

Possibly on account of host adaptation, the virus appeared to evolve at a faster rate in mink than in humans [70]. Whole genome sequencing technique has identified about 170 mutations in SARS-CoV-2 samples collected from mink farms, some of which have been found also in humans [83]. The good adaptation of the virus to the mink host led to the emergence of variants, with accumulation over time of point mutations that were repaired early during the spread of the virus in minks enabling the virus to be easily reintroduced into humans [71, 84]. Rabalski et al. [84] found four distinct mutations in the S gene in an isolate taken from a farm worker who tested positive for SARS-CoV-2. This viral variant gave origin to the mink-adapted variant. The detection of mutations in the RBD of the S protein raises concerns about the efficacy of vaccines against human infection by S protein variant strains [72].

SARS-CoV-2 in wild animals

Some studies have reported SARS-CoV-2 spillover from human to wild animals [85] (Fig. 2). The infected wild animal species were primarily in contact with humans in settings of captivity, such as zoos, safari parks, zoological centers, and aquariums [86]. SARS-CoV-2 has been found in 17 animal species belonging to three orders: Artiodactyla, Carnivora, and Primates. Except for two species of the order of Artiodactyla, namely deer, and

one of the order of Primates, the other 14 cases concern species belonging to the order of Carnivora, family of Felidae, with the highest number of species in which the virus has been found [87].

The first case of animal infection by SARS-CoV-2 in the USA was reported in a Malaysian tiger at the Bronx Zoo, New York, as the first case of viral transmission from human to a non-domestic animal [3]. The tiger appears to have been infected by an asymptomatic zookeeper who tested positive for SARS-CoV-2 [88]. Subsequently, the infection was detected in other four tigers and in lions, confirming that SARS-CoV-2 can be transmitted to various species of felines [3].

The emergence of the Delta variant (B.1.617.2), first identified in India in October 2020, prompted the assessment of its possible circulation in wild animals, such as lions [89]. In May 2021 the occurrence of natural infection by the Delta variant was reported in Asian lions, in the Arignar Anna Zoological Park in Chennai (India), where four of thirteen lions had symptoms of SARS-CoV-2 infection, such as loss of appetite and cough. A total of 11 lions were then tested using RT-PCR, nine were positive for SARS-CoV-2 and two of the positive animals died. Although it appeared that the primary source of infection was an infected person, with the further transmission of the virus occurred for the close contact among animals that share the same habitat [90]. The Delta variant was also found in another two cases of infection in Asian lions [89].

Cases of natural infection in pumas occurred in a private zoo in Johannesburg, South Africa, during the first and second epidemic wave. The first positive case of SARS-CoV-2 was found in a puma with symptoms of anorexia. The second case occurred 24 hours later in another puma with similar symptoms. An investigation on zoo staff was performed and two individuals had positive swab [91].

The first two cases of SARS-CoV-2 infection in snow leopards occurred at Louisville Zoo (Kentucky, USA) in December 2020. Again, the infection appears to have been caused by a zookeeper who tested positive to SARS-CoV-2. Later, SARS-CoV-2 infection cases in snow leopards were reported in California, Nebraska, South Dakota, and Illinois due to human-to-animal transmission [87].

In 2021, the transmission of SARS-CoV-2 from man to white-tailed wild deer (Odocoileus virginianus) was documented in the USA [92]. In July 2021, antibodies against SARS-CoV-2 were found in 152 white-tailed deer with a 40% seroprevalence in Michigan, Pennsylvania, Illinois, and New York. In another study between January and March 2021, SARS-CoV-2 was detected in 35.8% out of 360 swabs collected in nine locations in northeastern Ohio. Male and heavier deer were more likely to be infected, especially those living near urban centers where they were more likely to have direct contact with humans through garbage, backyard feeders, and bait stations [93].

In Switzerland, a case of SARS-CoV-2 infection was reported in a red fox during routine surveillance testing [94].

In another study, 283 samples of nasopharyngeal lymph nodes from wild and captive deers were collected in Iowa from April 2020 to January 2021. Of these, 33% were positive on RT-PCR. The majority of the samples were collected between September and December 2020, suggesting that spillover occurs mainly in the hunting season [92]. As more than a third of the deers tested positive to SARS-CoV-2, the authors alerted that a potential new reservoir of SARS-CoV-2 infection might arise.

Naturally acquired infection has also been ascertained in captive gorillas in USA, Czech and Spanish zoos, as a results of direct and indirect contact with SARS-CoV-2 infected humans. Great apes and Western Lowland gorillas displayed visible signs of infection, such as nasal discharge and coughing, and pneumonia-like signs were observed in old apes [66, 95].

Finally, in a zoo in Belgium, hippopotamuses displaying only nasal discharge were found to be swab-positive for SARS-CoV-2. The slight genetic difference between the human and the hippopotamus viruses suggests that humans had infected these animals [96]. Other cases of infection in captive animals have been reported in fishing cats, hyenas, lynxes, mandrills, monkeys, and otters [66].

Conclusions

This work provides an overview on SARS-CoV-2 infection in different animal species. Data were retrieved from both experimental studies and natural infection events occurred during the COVID-19 pandemic.

There is clear evidence that zoonotic spillovers and reverse zoonosis occurred during SARS-CoV-2 pandemic involving humans and animals, providing a comprehensive understanding of the virus transmission dynamics for supporting the improvement of One Health approach strategy.

One Health is a transdisciplinary approach to understanding and addressing complex challenges that involve the health of humans, animals, and the environment [14, 97]. It recognizes that the health of these three interconnected domains is closely linked and that health issues in one domain can have a significant impact on the others. This approach considers health within a unified global perspective (One Health) and it is supported by the evidence that the various outbreaks of new infectious diseases that have periodically occurred during the past five decades are due to zoonotic spillovers [11].

Many species, some of which are in close contact with humans, are susceptible to SARS-CoV-2. The susceptibility of species may change over time and viral variants may continue to emerge with changes in transmission capacity, potentially giving rise to the appearance of new hosts [98]. In the case of mink and deer infection, the adaptation of SARS-CoV-2 via only minimal mutations illustrates the capability of adaptation of this virus to new animal species. In the

most susceptible species, the possibility that new viral mutations emerge will increase the risk of secondary spillover and reverse zoonosis transmission.
In this review we have reported that wild animals were infected by SARS-CoV-2. It is of concern the possibility that a wild animal can become a reservoir of SARS-CoV-2, as it would represent a new potential transmission route for further spread of the virus more difficult to control than the reservoir of domestic animals. An assessment of the current epidemiological situation like the one approached in this review, may serve to recommend options for reviewing the monitoring strategies for SARS-CoV-2 infection in animal species of concern.
In this context, the continuous surveillance of both humans and animals is essential as new variants of SARS-CoV-2 could emerge creating a dynamic landscape of susceptibility and transmission within and between species. Such development could have far-reaching implications for conservation, ecosystem health, food production, economics, and public health. Also, further research is needed to identify potential reservoirs of the virus and to further investigate the human-animal transmission route. Finally, all those animals that are susceptible to the virus, whether domestic, intensively farmed, or wild in captivity, should be vaccinated in order to limit the development of overly diffusive or pathogenic SARS-CoV-2 variants [86, 99]. This approach can help limit the development of overly diffusive or pathogenic SARS-CoV-2 variants. Additionally, enhancing biosecurity measures in animal farming and wildlife management can reduce the risk of spillover events [100, 101]. However, in Europe, vaccination of animals against SARS-CoV-2 was only applied in mink in Finland but is no longer in use due to the limited effectiveness against Omicron variant. Data regarding other possible impact of the vaccination, such as the spread of the virus, the efficacy versus infection and the onset or duration of immunity were incomplete to allow a reliable assessment. Overall, it seems that the vaccine was able to provide a certain degree of protection against severe disease caused by the Delta variant in mink, but it did not prevent infection [102]. Moreover, promoting sustainable agricultural practices can also minimize human-wildlife contact, thereby reducing the risk of zoonotic disease transmission [103].
Overall, the information coming from monitoring programs in animal populations can aid the assessment of risks of virus transmission from animals to humans, with particular regard to the possible selection and emergence of new variants in animal populations, for which humans might be more susceptible or available vaccines less effective [102].
Control of the SARS-CoV-2 pandemic required the adoption of One Health as a collaborative global approach to mitigating the risk to both humans and animals and to uncovering and attenuating the severity of a complex human-animal environmental health problem. However, there road is still long to achieving an optimal institutional coordination and collaboration across various disciplines, a pathway that necessitates the inclusion of social, cultural, and economic components to create a solid One Health approach [104, 105]. Furthermore, establishing interdisciplinary teams that include veterinarians, ecologists, public health professionals, and social scientists can enhance the effectiveness of disease prevention and control strategies [106].
As already reported for Monkeypox virus [107], the implementation of the concept of One Health in all human, animal and environmental spheres could contribute substantially to both to the control of new outbreaks and to strengthen public health preparedness and response.
Finally, educating communities about the importance of One Health and promoting behaviors that reduce the risk of zoonotic transmission can support long-term public health resilience [108, 109].

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Ethics approval

Not required.

Conflicts of interest

Emanuele Montomoli is founder and Chief Scientific Officer of VisMederi srl and VisMederi Research srl. Claudia Maria Trombetta is an external consultant of VisMederi Research srl. The remaining authors have no conflicts of interest to declare.

Authors' contribution

Conceptualization: CMT; Writing - original draft preparation: SM, GG, MGM, BP, CMT; Writing - review and editing: SM, GG, MGM, BP, SV, GM, EM, VM, MC, CMT; Visualization: SM; Supervision: CMT; Project administration: SM, GG. All authors approved the final version of the manuscript. SM and GG contributed equally to this work and share the authorship.

References

[1] World Health Organization. Coronavirus (COVID-19) Dashboard. Available at: https://covid19.who.int/ (Accessed on: 2/11/2023).

[2] Centers for Disease Control and Prevention. Importance of One Health for COVID-19 and Future Pandemics. 2021. Available at: https://archive.cdc.gov/www_cdc_gov/media/releases/2021/s1103-one-health.html (Accessed on: 2/11/2023).

[3] Mahdy MAA, Younis W, Ewaida Z. An Overview of SARS-CoV-2 and Animal Infection. Front Vet Sci 2020;7:596391. https://doi.org/10.3389/fvets.2020.596391.

[4] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3. https://doi.org/10.1038/s41586-020-2012-7.

[5] Sparrer MN, Hodges NF, Sherman T, VandeWoude S, Bosco-Lauth AM, Mayo CE. Role of Spillover and Spillback in SARS-CoV-2 Transmission and the Importance of One Health in Understanding the Dynamics of the COVID-19 Pandemic. J Clin Microbiol 2023;61:e0161022. https://doi.org/10.1128/jcm.01610-22.

[6] Raza S. Analysis of the Spike Proteins Suggest Pangolin as an Intermediate Host of COVID-19 (SARS-CoV-2). Int J Agric Biol 2021;25:639-44. https://doi.org/10.17957/IJAB/15.1711.

[7] Lefrançois T, Malvy D, Atlani-Duault L, Benamouzig D, Druais PL, Yazdanpanah Y, Delfraissy JF, Lina B. After 2 years of the COVID-19 pandemic, translating One Health into action is urgent. Lancet 2023;401:789-94. https://doi.org/10.1016/S0140-6736(22)01840-2.

[8] Istituto Superiore di Sanità. SARS-CoV-2 infection among domestic animals. 2020. Available at: https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-domestic-animals (Accessed on 2/11/2023).

[9] Centers for Disease Control and Prevention. One Health. 2023. Available at: https://www.cdc.gov/onehealth/index.html#:~:text=One%20Health%20is%20a%20collaborative,plants%2C%20and%20their%20shared%20environment (Accessed on 2/11/2023).

[10] World Health Organization. One Health 2023. Available at: https://www.who.int/europe/initiatives/one-health#:~:text=One%20Health%20is%20an%20approach,animal%2Dhuman%2Denvironment%20interface (Accessed on 2/11/2023).

[11] Sironi VA, Inglese S, Lavazza A. The "One Health" approach in the face of Covid-19: how radical should it be? Philos Ethics Humanit Med 2022;17:3. https://doi.org/10.1186/s13010-022-00116-2.

[12] Zumla A, Dar O, Kock R, Muturi M, Ntoumi F, Kaleebu P, Eusebio M, Mfinanga S, Bates M, Mwaba P, Ansumana R, Khan M, Alagaili AN, Cotten M, Azhar EI, Maeurer M, Ippolito G, Petersen E. Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential. Int J Infect Dis 2016;47:5-9. https://doi.org/10.1016/j.ijid.2016.06.012.

[13] Fronteira I, Sidat M, Magalhães JP, de Barros FPC, Delgado AP, Correia T, Daniel-Ribeiro CT, Ferrinho P. The SARS-CoV-2 pandemic: A syndemic perspective. One Health. 2021;12:100228. https://doi.org/10.1016/j.onehlt.2021.100228.

[14] Mackenzie JS, Jeggo M. The One Health Approach-Why Is It So Important? Trop Med Infect Dis 2019;4:88. https://doi.org/10.3390/tropicalmed4020088.

[15] European Commission. Public Health Overview. 2023. Available at: https://health.ec.europa.eu/one-health/overview_en (Accessed on 2/11/2023).

[16] Hobeika A, Stauffer MHT, Dub T, van Bortel W, Beniston M, Bukachi S, Burci GL, Crump L, Markotter W, Sepe LP, Placella E, Roche B, Thiongane O, Wang Z, Guérin F, van Kleef E. The values and risks of an Intergovernmental Panel for One Health to strengthen pandemic prevention, preparedness, and response. Lancet Glob Health 2023;11:e1301-7. https://doi.org/10.1016/S2214-109X(23)00246-2.

[17] Rabozzi G, Bonizzi L, Crespi E, Somaruga C, Sokooti M, Tabibi R, Vellere F, Brambilla G, Colosio C. Emerging zoonoses: the "one health approach". Saf Health Work 2012;3:77-83. https://doi.org/10.5491/SHAW.2012.3.1.77.

[18] Ohia CMD, Uwalaka EC. Covid 19: A Call to One Health Action. Ann Ib Postgrad Med 2021;19:S31-7.

[19] The L. One Health: a call for ecological equity. Lancet 2023;401:169. https://doi.org/10.1016/S0140-6736(23)00090-9.

[20] Pfenning-Butterworth A, Buckley LB, Drake JM, Farner JE, Farrell MJ, Gehman AM, Mordecai EA, Stephens PR, Gittleman JL, Davies TJ. Interconnecting global threats: climate change, biodiversity loss, and infectious diseases. Lancet Planet Health 2024;8:e270-83. https://doi.org/10.1016/S2542-5196(24)00021-4.

[21] Linhares Y, Kaganski A, Agyare C, Kurnaz IA, Neergheen V, Kolodziejczyk B, Kędra M, Wahajuddin M, El-Youssf L, Dela Cruz TE, Baran Y, Pešić M, Shrestha U, Bakiu R, Allard PM, Rybtsov S, Pieri M, Siciliano V, Flores Bueso Y. Biodiversity: the overlooked source of human health. Trends Mol Med 2023;29:173-87. https://doi.org/10.1016/j.molmed.2022.12.002.

[22] Varyvoda Y, Taren D. Considering Ecosystem Services in Food System Resilience. Int J Environ Res Public Health 2022;19:3652. https://doi.org/10.3390/ijerph19063652.

[23] Morgan L, Protopopova A, Birkler RID, Itin-Shwartz B, Sutton GA, Gamliel A, Yakobson B, Raz T. Human–dog relationships during the COVID-19 pandemic: booming dog adoption during social isolation. Humanit Soc Sci Commun 2020;7:155. https://doi.org/10.1057/s41599-020-00649-x.

[24] Parry NMA. COVID-19 and pets: When pandemic meets panic. Forensic Sci Int Rep 2020;2:100090. https://doi.org/10.1016/j.fsir.2020.100090.

[25] Jezierski T, Camerlink I, Peden RSE, Chou JY, Marchewka J. Changes in the health and behaviour of pet dogs during the COVID-19 pandemic as reported by the owners. Appl Anim Behav Sci. 2021;241:105395. https://doi.org/https://doi.org/10.1016/j.applanim.2021.105395.

[26] Shi J, Wen Z, Zhong G, Yang H, Wang C, Huang B, Liu R, He X, Shuai L, Sun Z, Zhao Y, Liu P, Liang L, Cui P, Wang J, Zhang X, Guan Y, Tan W, Wu G, Chen H, Bu Z. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science 2020;368:1016-20. https://doi.org/doi:10.1126/science.abb7015

[27] Sit THC, Brackman CJ, Ip SM, Tam KWS, Law PYT, To EMW, Yu VYT, Sims LD, Tsang DNC, Chu DKW, Perera RAPM, Poon LLM, Peiris M. Infection of dogs with SARS-CoV-2. Nature 2020;586:776-8. https://doi.org/10.1038/s41586-020-2334-5.

[28] de Souza Barbosa AB, Kmetiuk LB, de Carvalho OV, Brandão APD, Doline FR, Lopes SRRS, Meira DA, de Souza EM, da Silva Trindade E, Baura V, Barbosa DS, Brandespim DF, Galhardo JA, Pettan-Brewer C, de Sá Guimarães AM, Dutra V, de Morais HA, Huergo L, Dos Santos AP, Biondo AW. Infection of SARS-CoV-2 in domestic dogs associated with owner viral load. Res Vet Sci 2022;153:61-65. https://doi.org/10.1016/j.rvsc.2022.10.006.

[29] Guo R, Wolff C, Prada JM, Mughini-Gras L. When COVID-19 sits on people's laps: A systematic review of SARS-CoV-2 infection prevalence in household dogs and cats. One Health 2023;16:100497. https://doi.org/10.1016/j.onehlt.2023.100497.

[30] Wang A, Zhu X, Chen Y, Sun Y, Liu H, Ding P, Zhou J, Liu Y, Liang C, Yin J, Zhang G. Serological survey of SARS-CoV-2 in companion animals in China. Front Vet Sci 2022;9:986619. https://doi.org/10.3389/fvets.2022.986619.

[31] Natale A, Mazzotta E, Mason N, Ceglie L, Mion M, Stefani A, Fincato A, Bonfante F, Bortolami A, Monne I, Bellinati L, Guadagno C, Quaranta E, Pastori A, Terregino C. SARS-Cov-2 Natural Infection in a Symptomatic Cat: Diagnostic, Clinical and Medical Management in a One Health Vision. Animals 2021;11:1640. https://doi.org/10.3390/ani11061640.

[32] Barrs VR, Peiris M, Tam KWS, Law PYT, Brackman CJ, To EMW, Yu VYT, Chu DKW, Perera RAPM, Sit THC. SARS-CoV-2 in Quarantined Domestic Cats from COVID-19 House-

holds or Close Contacts, Hong Kong, China. Emerg Infect Dis 2020;26:3071-4. https://doi.org/10.3201/eid2612.202786.

[33] Zhang Q, Zhang H, Gao J, Huang K, Yang Y, Hui X, He X, Li C, Gong W, Zhang Y, Zhao Y, Peng C, Gao X, Chen H, Zou Z, Shi ZL, Jin M. A serological survey of SARS-CoV-2 in cat in Wuhan. Emerg Microbes Infect 2020;9:2013-9. https://doi.org/10.1080/22221751.2020.1817796.

[34] Sila T, Sunghan J, Laochareonsuk W, Surasombatpattana S, Kongkamol C, Ingviya T, Siripaitoon P, Kositpantawong N, Kanchanasuwan S, Hortiwakul T, Charernmak B, Nwabor OF, Silpapojakul K, Chusri S. Suspected Cat-to-Human Transmission of SARS-CoV-2, Thailand, July-September 2021. Emerg Infect Dis 2022;28:1485-8. https://doi.org/10.3201/eid2807.212605.

[35] Patterson EI, Elia G, Grassi A, Giordano A, Desario C, Medardo M, Smith SL, Anderson ER, Prince T, Patterson GT, Lorusso E, Lucente MS, Lanave G, Lauzi S, Bonfanti U, Stranieri A, Martella V, Solari Basano F, Barrs VR, Radford AD, Agrimi U, Hughes GL, Paltrinieri S, Decaro N. Evidence of exposure to SARS-CoV-2 in cats and dogs from households in Italy. Nat Commun 2020;11:6231. https://doi.org/10.1038/s41467-020-20097-0.

[36] Dileepan M, Di D, Huang Q, Ahmed S, Heinrich D, Ly H, Liang Y. Seroprevalence of SARS-CoV-2 (COVID-19) exposure in pet cats and dogs in Minnesota, USA. Virulence 2021;12:1597-609. https://doi.org/10.1080/21505594.2021.

[37] Hamer SA, Pauvolid-Corrêa A, Zecca IB, Davila E, Auckland LD, Roundy CM, Tang W, Torchetti MK, Killian ML, Jenkins-Moore M, Mozingo K, Akpalu Y, Ghai RR, Spengler JR, Barton Behravesh C, Fischer RSB, Hamer GL. SARS-CoV-2 Infections and Viral Isolations among Serially Tested Cats and Dogs in Households with Infected Owners in Texas, USA. Viruses 2021;13:938. https://doi.org/10.3390/v13050938.

[38] Stout AE, Andre NM, Jaimes JA, Millet JK, Whittaker GR. Coronaviruses in cats and other companion animals: Where does SARS-CoV-2/COVID-19 fit? Vet Microbiol 2020;247:108777. https://doi.org/10.1016/j.vetmic.2020.108777.

[39] Richard M, Kok A, de Meulder D, Bestebroer TM, Lamers MM, Okba NMA, Fentener van Vlissingen M, Rockx B, Haagmans BL, Koopmans MPG, Fouchier RAM, Herfst S. SARS-CoV-2 is transmitted via contact and via the air between ferrets. Nat Commun 2020;11:3496. https://doi.org/10.1038/s41467-020-17367-2.

[40] Giner J, Villanueva-Saz S, Tobajas AP, Pérez MD, González A, Verde M, Yzuel A, García-García A, Taleb V, Lira-Navarrete E, Hurtado-Guerrero R, Pardo J, Santiago L, Paño JR, Ruíz H, Lacasta D, Fernández A. SARS-CoV-2 Seroprevalence in Household Domestic Ferrets (Mustela putorius furo). Animals 2021;11:667. https://doi.org/10.3390/ani11030667.

[41] Maurin M, Fenollar F, Mediannikov O, Davoust B, Devaux C, Raoult D. Current Status of Putative Animal Sources of SARS-CoV-2 Infection in Humans: Wildlife, Domestic Animals and Pets. Microorganisms 2021;9:868. https://doi.org/10.3390/microorganisms9040868.

[42] Sia SF, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL, Kaewpreedee P, Perera RAPM, Poon LLM, Nicholls JM, Peiris M, Yen HL. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. Nature 2020;583:834-8. https://doi.org/10.1038/s41586-020-2342-5.

[43] Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, Chan WM, Fan Z, Tsoi HW, Wen L, Liang R, Cao J, Chen Y, Tang K, Luo C, Cai JP, Kok KH, Chu H, Chan KH, Sridhar S, Chen Z, Chen H, To KK, Yuen KY. Simulation of the Clinical and Pathological Manifestations of Coronavirus Disease 2019 (COVID-19) in a Golden Syrian Hamster Model: Implications for Disease Pathogenesis and Transmissibility. Clin Infect Dis 2020;71:2428-46. https://doi.org/10.1093/cid/ciaa325.

[44] Yen HL, Sit THC, Brackman CJ, Chuk SSY, Gu H, Tam KWS, Law PYT, Leung GM, Peiris M, Poon LLM; HKU-SPH study team. Transmission of SARS-CoV-2 delta variant (AY.127) from pet hamsters to humans, leading to onward human-to-human transmission: a case study. Lancet 2022;399:1070-8. https://doi.org/10.1016/S0140-6736(22)00326-9.

[45] Kok KH, Wong SC, Chan WM, Wen L, Chu AW, Ip JD, Lee LK, Wong IT, Lo HW, Cheng VC, Ho AY, Lam BH, Tse H, Lung D, Ng KNH, Au AK, Siu GK, Yuen KY. Co-circulation of two SARS-CoV-2 variant strains within imported pet hamsters in Hong Kong. Emerg Microbes Infect 2022;11:689-98. https://doi.org/10.1080/22221751.2022.2040922.

[46] Meekins DA, Morozov I, Trujillo JD, Gaudreault NN, Bold D, Carossino M et al. Susceptibility of swine cells and domestic pigs to SARS-CoV-2. Emerg Microbes Infect 2020;9:2278-88. https://doi.org/10.1080/22221751.2020.1831405.

[47] Schlottau K, Rissmann M, Graaf A, Schön J, Sehl J, Wylezich C, Höper D, Mettenleiter TC, Balkema-Buschmann A, Harder T, Grund C, Hoffmann D, Breithaupt A, Beer M. SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study. Lancet Microbe 2020;1:e218-25. https://doi.org/10.1016/S2666-5247(20)30089-6.

[48] Pickering BS, Smith G, Pinette MM, Embury-Hyatt C, Moffat E, Marszal P, Lewis CE. Susceptibility of Domestic Swine to Experimental Infection with Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis 2021;27:104-12. https://doi.org/10.3201/eid2701.203399.

[49] Suarez DL, Pantin-Jackwood MJ, Swayne DE, Lee SA, DeBlois SM, Spackman E. Lack of Susceptibility to SARS-CoV-2 and MERS-CoV in Poultry. Emerg Infect Dis 2020;26:3074-6. https://doi.org/10.3201/eid2612.202989.

[50] Ulrich L, Wernike K, Hoffmann D, Mettenleiter TC, Beer M. Experimental Infection of Cattle with SARS-CoV-2. Emerg Infect Dis 2020;26:2979-81. https://doi.org/10.3201/eid2612.203799.

[51] Cerino P, Buonerba C, Brambilla G, Atripaldi L, Tafuro M, Concilio DD, Vassallo L, Conte GL, Cuomo MC, Maiello I, D'Auria J, Cardinale D, Viscardi M, Rofrano G, Gallo A, Brusco P, Pizzolante A, Cicalese V, Galdi P, Galdi L, Vita S, Volzone P, Vuolo GD, Coppola A, Pierri B, Fusco G. No detection of SARS-CoV-2 in animals exposed to infected keepers: results of a COVID-19 surveillance program. Future Sci OA 2021;7:FSO711. https://doi.org/10.2144/fsoa-2021-0038.

[52] Wernike K, Böttcher J, Amelung S, Albrecht K, Gärtner T, Donat K, Beer M. Antibodies against SARS-CoV-2 Suggestive of Single Events of Spillover to Cattle, Germany. Emerg Infect Dis 2022;28:1916-8. https://doi.org/10.3201/eid2809.220125.

[53] Gaudreault NN, Cool K, Trujillo JD, Morozov I, Meekins DA, McDowell C, Bold D, Carossino M, Balaraman V, Mitzel D, Kwon T, Madden DW, Artiaga BL, Pogranichniy RM, Roman-Sosa G, Wilson WC, Balasuriya UBR, García-Sastre A, Richt JA. Susceptibility of sheep to experimental co-infection with the ancestral lineage of SARS-CoV-2 and its alpha variant. Emerg Microbes Infect 2022;11:662-75. https://doi.org/10.1080/22221751.2022.2037397.

[54] Di Teodoro G, Valleriani F, Puglia I, Monaco F, Di Pancrazio C, Luciani M, Krasteva I, Petrini A, Marcacci M, D'Alterio N, Curini V, Iorio M, Migliorati G, Di Domenico M, Morelli D, Calistri P, Savini G, Decaro N, Holmes EC, Lorusso A. SARS-CoV-2 replicates in respiratory ex vivo organ cultures of domestic ruminant species. Vet Microbiol 2021;252:108933. https://doi.org/10.1016/j.vetmic.2020.108933.

[55] Bosco-Lauth AM, Walker A, Guilbert L, Porter S, Hartwig A, McVicker E, Bielefeldt-Ohmann H, Bowen RA. Susceptibility of livestock to SARS-CoV-2 infection. Emerg Microbes Infect 2021;10:2199-201. https://doi.org/10.1080/22221751.2021.2003724.

[56] Villanueva-Saz S, Giner J, Fernández A, Lacasta D, Ortín A, Ramos JJ, Ferrer LM, Ruiz de Arcaute M, Tobajas AP, Pérez MD, Verde M, Marteles D, Hurtado-Guerrero R, Pardo J, Santiago L, González-Ramírez AM, Macías-León J, García-García A, Taleb V, Lira-Navarrete E, Paño-Pardo JR, Ruíz H. Absence of SARS-

CoV-2 Antibodies in Natural Environment Exposure in Sheep in Close Contact with Humans. Animals 2021;11:1984. https://doi.org/doi: 10.3390/ani11071984.

[57] Fernández-Bastit L, Roca N, Romero-Durana M, Rodon J, Cantero G, García Ó, López C, Pérez M, López R, Carrillo J, Izquierdo-Useros N, Blanco J, Clotet B, Pujols J, Vergara-Alert J, Segalés J, Lorca-Oró C. Susceptibility of Domestic Goat (*Capra aegagrus hircus*) to Experimental Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) B.1.351/Beta Variant. Viruses 2022;14:2002. https://doi.org/10.3390/v14092002.

[58] Fernández-Bastit L, Roca N, Romero-Durana M, Rodon J, Cantero G, García Ó, López C, Pérez M, López R, Carrillo J, Izquierdo-Useros N, Blanco J, Clotet B, Pujols J, Vergara-Alert J, Segalés J, Lorca-Oró C. Susceptibility of Domestic Goat (Capra aegagrus hircus) to Experimental Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) B.1.351/Beta Variant. Viruses 2022;14:2002. https://doi.org/10.3390/v14092002.

[59] Mykytyn AZ, Lamers MM, Okba NMA, Breugem TI, Schipper D, van den Doel PB, van Run P, van Amerongen G, de Waal L, Koopmans MPG, Stittelaar KJ, van den Brand JMA, Haagmans BL. Susceptibility of rabbits to SARS-CoV-2. Emerg Microbes Infect 2021;10:1-7. https://doi.org/10.1080/22221751.2020.1868951.

[60] Fritz M, de Riols de Fonclare D, Garcia D, Beurlet S, Becquart P, Rosolen SG, Briend-Marchal A, Leroy EM. First Evidence of Natural SARS-CoV-2 Infection in Domestic Rabbits. Vet Sci 2022;9:49. https://doi.org/10.3390/vetsci9020049.

[61] Lawton KOY, Arthur RM, Moeller BC, Barnum S, Pusterla N. Investigation of the Role of Healthy and Sick Equids in the COVID-19 Pandemic through Serological and Molecular Testing. Animals 2022;12:614. https://doi.org/10.3390/ani12050614.

[62] Deng J, Jin Y, Liu Y, Sun J, Hao L, Bai J, Huang T, Lin D, Jin Y, Tian K. Serological survey of SARS-CoV-2 for experimental, domestic, companion and wild animals excludes intermediate hosts of 35 different species of animals. Transbound Emerg Dis 2020;67:1745-49. https://doi.org/10.1111/tbed.13577.

[63] Pusterla N, Chaillon A, Ignacio C, Smith DM, Barnum S, Lawton KOY, Smith G, Pickering B. SARS-CoV-2 Seroconversion in an Adult Horse with Direct Contact to a COVID-19 Individual. Viruses 2022;14:1047. https://doi.org/10.3390/v14051047.

[64] Lawton K, Keller SM, Barnum S, Arredondo-Lopez C, Spann K, Pusterla N. Seroprevalence of SARS-CoV-2 in 1186 Equids Presented to a Veterinary Medical Teaching Hospital in California from 2020 to 2022. Viruses 2022;14:2497. https://doi.org/doi: 10.3390/v14112497.

[65] Liu Y, Hu G, Wang Y, Ren W, Zhao X, Ji F, Zhu Y, Feng F, Gong M, Ju X, Zhu Y, Cai X, Lan J, Guo J, Xie M, Dong L, Zhu Z, Na J, Wu J, Lan X, Xie Y, Wang X, Yuan Z, Zhang R, Ding Q. Functional and genetic analysis of viral receptor ACE2 orthologs reveals a broad potential host range of SARS-CoV-2. Proc Natl Acad Sci USA 2021;118:e2025373118. https://doi.org/10.1073/pnas.2025373118.

[66] Damas J, Hughes GM, Keough KC, Painter CA, Persky NS, Corbo M, Hiller M, Koepfli KP, Pfenning AR, Zhao H, Genereux DP, Swofford R, Pollard KS, Ryder OA, Nweeia MT, Lindblad-Toh K, Teeling EC, Karlsson EK, Lewin HA. Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates. Proc Natl Acad Sci U S A 2020;117:22311-22. https://doi.org/10.1073/pnas.2010146117.

[67] Pappas G, Vokou D, Sainis I, Halley JM. SARS-CoV-2 as a Zooanthroponotic Infection: Spillbacks, Secondary Spillovers, and Their Importance. Microorganisms 2022;10:2166. https://doi.org/10.3390/microorganisms10112166.

[68] Oreshkova N, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Hakze-van der Honing RW, Gerhards N, Tolsma P, Bouwstra R, Sikkema RS, Tacken MG, de Rooij MM, Weesendorp E, Engelsma MY, Bruschke CJ, Smit LA, Koopmans M, van der Poel WH, Stegeman A. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Euro Surveill 2020;25:2001005. https://doi.org/10.2807/1560-7917.ES.2020.25.23.2001005. Erratum in: Euro Surveill 2021;26. https://doi.org/10.2807/1560-7917.ES.2021.26.12.210325c.

[69] Molenaar RJ, Vreman S, Hakze-van der Honing RW, Zwart R, de Rond J, Weesendorp E, Smit LAM, Koopmans M, Bouwstra R, Stegeman A, van der Poel WHM. Clinical and Pathological Findings in SARS-CoV-2 Disease Outbreaks in Farmed Mink (Neovison vison). Vet Pathol 2020;57:653-7. https://doi.org/10.1177/0300985820943535.

[70] Lu L, Sikkema RS, Velkers FC, Nieuwenhuijse DF, Fischer EAJ, Meijer PA, Bouwmeester-Vincken N, Rietveld A, Wegdam-Blans MCA, Tolsma P, Koppelman M, Smit LAM, Hakze-van der Honing RW, van der Poel WHM, van der Spek AN, Spierenburg MAH, Molenaar RJ, Rond J, Augustijn M, Woolhouse M, Stegeman JA, Lycett S, Oude Munnink BB, Koopmans MPG. Adaptation, spread and transmission of SARS-CoV-2 in farmed minks and associated humans in the Netherlands. Nat Commun 2021;12:6802. https://doi.org/10.1038/s41467-021-27096-9.

[71] Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, van der Spek A, Tolsma P, Rietveld A, Brouwer M, Bouwmeester-Vincken N, Harders F, Hakze-van der Honing R, Wegdam-Blans MCA, Bouwstra RJ, GeurtsvanKessel C, van der Eijk AA, Velkers FC, Smit LAM, Stegeman A, van der Poel WHM, Koopmans MPG. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science 2021;371:172-7. https://doi.org/10.1126/science.abe5901.

[72] Rabalski L, Kosinski M, Smura T, Aaltonen K, Kant R, Sironen T, Szewczyk B, Grzybek M. Severe Acute Respiratory Syndrome Coronavirus 2 in Farmed Mink (Neovison vison), Poland. Emerg Infect Dis 2021;27:2333-9. https://doi.org/10.3201/eid2709.210286.

[73] Fenollar F, Mediannikov O, Maurin M, Devaux C, Colson P, Levasseur A, Fournier PE, Raoult D. Mink, SARS-CoV-2, and the Human-Animal Interface. Front Microbiol 2021;12:663815. https://doi.org/10.3389/fmicb.2021.663815.

[74] Boklund A, Hammer AS, Quaade ML, Rasmussen TB, Lohse L, Strandbygaard B, Jørgensen CS, Olesen AS, Hjerpe FB, Petersen HH, Jensen TK, Mortensen S, Calvo-Artavia FF, Lefèvre SK, Nielsen SS, Halasa T, Belsham GJ, Bøtner A. SARS-CoV-2 in Danish Mink Farms: Course of the Epidemic and a Descriptive Analysis of the Outbreaks in 2020. Animals 2021;11:164. https://doi.org/10.3390/ani11010164.

[75] Eckstrand CD, Baldwin TJ, Rood KA, Clayton MJ, Lott JK, Wolking RM, Bradway DS, Baszler T. An outbreak of SARS-CoV-2 with high mortality in mink (Neovison vison) on multiple Utah farms. PLoS Pathog 2021;17:e1009952. https://doi.org/10.1371/journal.ppat.1009952.

[76] Badiola JJ, Otero A, Sevilla E, Marín B, García Martínez M, Betancor M, Sola D, Pérez Lázaro S, Lozada J, Velez C, Chiner-Oms Á, Comas I, Cancino-Muñoz I, Monleón E, Monzón M, Acín C, Bolea R, Moreno B. SARS-CoV-2 Outbreak on a Spanish Mink Farm: Epidemiological, Molecular, and Pathological Studies. Front Vet Sci 2022;8:805004. https://doi.org/10.3389/fvets.2021.805004.

[77] Hammer AS, Quaade ML, Rasmussen TB, Fonager J, Rasmussen M, Mundbjerg K, Lohse L, Strandbygaard B, Jørgensen CS, Alfaro-Núñez A, Rosenstierne MW, Boklund A, Halasa T, Fomsgaard A, Belsham GJ, Bøtner A. SARS-CoV-2 Transmission between Mink (Neovison vison) and Humans, Denmark. Emerg Infect Dis 2021;27:547-51. https://doi.org/10.3201/eid2702.203794.

[78] Larsen HD, Fonager J, Lomholt FK, Dalby T, Benedetti G, Kristensen B, Urth TR, Rasmussen M, Lassaunière R, Rasmussen TB, Strandbygaard B, Lohse L, Chaine M, Møller KL, Berthelsen AN, Nørgaard SK, Sönksen UW, Boklund AE, Hammer AS, Belsham GJ, Krause TG, Mortensen S, Bøtner A,

Fomsgaard A, Mølbak K. Preliminary report of an outbreak of SARS-CoV-2 in mink and mink farmers associated with community spread, Denmark, June to November 2020. Euro Surveill 2021;26:2100009. https://doi.org/10.2807/1560-7917.ES.2021.26.5.210009.

[79] Chaintoutis SC, Thomou Z, Mouchtaropoulou E, Tsiolas G, Chassalevris T, Stylianaki I, Lagou M, Michailidou S, Moutou E, Koenen JJH, Dijkshoorn JW, Paraskevis D, Poutahidis T, Siarkou VI, Sypsa V, Argiriou A, Fortomaris P, Dovas CI. Outbreaks of SARS-CoV-2 in naturally infected mink farms: Impact, transmission dynamics, genetic patterns, and environmental contamination. PLoS Pathog 2021;17:e1009883. https://doi.org/10.1371/journal.ppat.1009883.

[80] Fournier PE, Colson P, Levasseur A, Devaux CA, Gautret P, Bedotto M, Delerce J, Brechard L, Pinault L, Lagier JC, Fenollar F, Raoult D. Emergence and outcomes of the SARS-CoV-2 'Marseille-4' variant. Int J Infect Dis 2021;106:228-36. https://doi.org/10.1016/j.ijid.2021.03.068.

[81] Sikkema RS, Begeman L, Janssen R, Wolters WJ, Geurtsvankessel C, de Bruin E, Hakze-van der Honing RW, Eblé P, van der Poel WHM, van den Brand JMA, Slaterus R, La Haye M, Koopmans MPG, Velkers F, Kuiken T. Risks of SARS-CoV-2 transmission between free-ranging animals and captive mink in the Netherlands. Transbound Emerg Dis 2022;69:3339-49. https://doi.org/10.1111/tbed.14686.

[82] Center for Epidemiology & Animal Health. SARS-CoV-2 Epidemiological Study around Infected Mink Farms Summary. 2020.

[83] Aguiló-Gisbert J, Padilla-Blanco M, Lizana V, Maiques E, Muñoz-Baquero M, Chillida-Martínez E, Cardells J, Rubio-Guerri C. First Description of SARS-CoV-2 Infection in Two Feral American Mink (Neovison vison) Caught in the Wild. Animals 2021;11:1422. https://doi.org/10.3390/ani11051422.

[84] Mallapaty S. COVID mink analysis shows mutations are not dangerous - yet. Nature 2020;587:340-1. https://doi.org/10.1038/d41586-020-03218-z.

[85] Rabalski L, Kosinski M, Mazur-Panasiuk N, Szewczyk B, Bienkowska-Szewczyk K, Kant R, Sironen T, Pyrc K, Grzybek M. Zoonotic spill-over of SARS-CoV-2: mink-adapted virus in humans. Clin Microbiol Infect 2022;28:451.e1-451.e4. https://doi.org/10.1016/j.cmi.2021.12.001.

[86] Tan CCS, Lam SD, Richard D, Owen CJ, Berchtold D, Orengo C, Nair MS, Kuchipudi SV, Kapur V, van Dorp L, Balloux F. Transmission of SARS-CoV-2 from humans to animals and potential host adaptation. Nat Commun 2022;13:2988. https://doi.org/10.1038/s41467-022-30698-6.

[87] Islam A, Ferdous J, Islam S, Sayeed MA, Rahman MK, Saha O, Hassan MM, Shirin T. Transmission dynamics and susceptibility patterns of SARS-CoV-2 in domestic, farmed and wild animals: Sustainable One Health surveillance for conservation and public health to prevent future epidemics and pandemics. Transbound Emerg Dis 2022;69:2523-43. https://doi.org/10.1111/tbed.14356.

[88] Wang L, Gyimesi ZS, Killian ML, Torchetti M, Olmstead C, Fredrickson R, Terio KA. Detection of SARS-CoV-2 clade B.1.2 in three snow leopards. Transbound Emerg Dis 2022;69:e3346-51. https://doi.org/10.1111/tbed.14625.

[89] Rodriguez-Morales AJ, Dhama K, Sharun K, Tiwari R, Bonilla-Aldana DK. Susceptibility of felids to coronaviruses. Vet Rec 2020;186:e21. https://doi.org/10.1136/vr.m1671.

[90] Karikalan M, Chander V, Mahajan S, Deol P, Agrawal RK, Nandi S, Rai SK, Mathur A, Pawde A, Singh KP, Sharma GK. Natural infection of Delta mutant of SARS-CoV-2 in Asiatic lions of India. Transbound Emerg Dis 2022;69:3047-55. https://doi.org/10.1111/tbed.14290.

[91] Mishra A, Kumar N, Bhatia S, Aasdev A, Kanniappan S, Sekhar AT, Gopinadhan A, Silambarasan R, Sreekumar C, Dubey CK, Tripathi M, Raut AA, Singh VP. SARS-CoV-2 Delta Variant among Asiatic Lions, India. Emerg Infect Dis 2021;27:2723-5. https://doi.org/10.3201/eid2710.211500.

[92] Koeppel KN, Mendes A, Strydom A, Rotherham L, Mulumba M, Venter M. SARS-CoV-2 Reverse Zoonoses to Pumas and Lions, South Africa. Viruses 2022;14:PAGES??. https://doi.org/10.3390/v14010120.

[93] Kuchipudi SV, Surendran-Nair M, Ruden RM, Yon M, Nissly RH, Vandegrift KJ, Nelli RK, Li L, Jayarao BM, Maranas CD, Levine N, Willgert K, Conlan AJK, Olsen RJ, Davis JJ, Musser JM, Hudson PJ, Kapur V. Multiple spillovers from humans and onward transmission of SARS-CoV-2 in white-tailed deer. Proc Natl Acad Sci USA 2022;119:e2121644119. https://doi.org/10.1073/pnas.2121644119.

[94] Hale VL, Dennis PM, McBride DS, Nolting JM, Madden C, Huey D, Ehrlich M, Grieser J, Winston J, Lombardi D, Gibson S, Saif L, Killian ML, Lantz K, Tell RM, Torchetti M, Robbe-Austerman S, Nelson MI, Faith SA, Bowman AS. SARS-CoV-2 infection in free-ranging white-tailed deer. Nature 2022;602:481-6. https://doi.org/10.1038/s41586-021-04353-x.

[95] Delahay RJ, de la Fuente J, Smith GC, Sharun K, Snary EL, Flores Girón L, Nziza J, Fooks AR, Brookes SM, Lean FZX, Breed AC, Gortazar C. Assessing the risks of SARS-CoV-2 in wildlife. One Health Outlook 2021;3:7. https://doi.org/10.1186/s42522-021-00039-6.

[96] Vercammen F, Cay B, Gryseels S, Balmelle N, Joffrin L, Van Hoorde K, Verhaegen B, Mathijs E, Van Vredendaal R, Dharmadhikari T, Chiers K, Van Olmen TJS, Agliani G, Van den Brand JMA, Leirs H. SARS-CoV-2 Infection in Captive Hippos (Hippopotamus amphibius), Belgium. Animals 2023;13:316. https://doi.org/ 10.3390/ani13020316.

[97] Prata JC, Ribeiro AI, Rocha-Santos T. Chapter 1 - An introduction to the concept of One Health. In: Prata JC, Ribeiro AI, Rocha-Santos T, editors. One Health: Academic Press; 2022, pp. 1-31.

[98] Efsa Panel on Animal Health Welfare, Nielsen SS, Alvarez J, Bicout DJ, Calistri P, Canali E et al. SARS-CoV-2 in animals: susceptibility of animal species, risk for animal and public health, monitoring, prevention and control. EFSA J 2023;21:e07822. https://doi.org/10.2903/j.efsa.2023.7822.

[99] Ehrlich M, Madden C, McBride DS, Nolting JM, Huey D, Kenney S, Wang Q, Saif LJ, Vlasova A, Dennis P, Lombardi D, Gibson S, McLaine A, Lauterbach S, Yaxley P, Winston JA, Diaz-Campos D, Pesapane R, Flint M, Flint J, Junge R, Faith SA, Bowman AS, Hale VL. Lack of SARS-CoV-2 Viral RNA Detection among a Convenience Sampling of Ohio Wildlife, Companion, and Agricultural Animals, 2020-2021. Animals 2023;13:2554. https://doi.org/10.3390/ani13162554.

[100] Jana PK, Majumdar A, Dutta S. Predicting Future Pandemics and Formulating Prevention Strategies: The Role of ChatGPT. Cureus 2023;15:e44825. https://doi.org/10.7759/cureus.44825.

[101] Vora NM, Hannah L, Walzer C, Vale MM, Lieberman S, Emerson A, Jennings J, Alders R, Bonds MH, Evans J, Chilukuri B, Cook S, Sizer NC, Epstein JH. Interventions to Reduce Risk for Pathogen Spillover and Early Disease Spread to Prevent Outbreaks, Epidemics, and Pandemics. Emerg Infect Dis 2023;29:1-9. https://doi.org/10.3201/eid2903.221079.

[102] EFSA Panel on Animal Health and Welfare (AHAW); Nielsen SS, Alvarez J, Bicout DJ, Calistri P, Canali E, Drewe JA, Garin-Bastuji B, Gonzales Rojas JL, Gortázar C, Herskin M, Michel V, Miranda Chueca MÁ, Padalino B, Pasquali P, Roberts HC, Spoolder H, Velarde A, Viltrop A, Winckler C, Adlhoch C, Aznar I, Baldinelli F, Boklund A, Broglia A, Gerhards N, Mur L, Nannapaneni P, Ståhl K. SARS-CoV-2 in animals: susceptibility of animal species, risk for animal and public health, monitoring, prevention and control. EFSA J 2023;21:e07822. https://doi.org/ 10.2903/j.efsa.2023.7822.

[103] Brozek W, Falkenberg C. Industrial Animal Farming and Zoonotic Risk: COVID-19 as a Gateway to Sustainable Change?

A Scoping Study. Sustainability 2021;13:9251. https://doi.org/10.3390/su13169251.

[104] Schmiege D, Perez Arredondo AM, Ntajal J, Minetto Gellert Paris J, Savi MK, Patel K, Yasobant S, Falkenberg T. One Health in the context of coronavirus outbreaks: A systematic literature review. One Health 2020;10:100170. https://doi.org/10.3390/su1316925110.1016/j.onehlt.2020.100170.

[105] Shehata AA, Attia YA, Rahman MT, Basiouni S, El-Seedi HR, Azhar EI, Khafaga AF, Hafez HM. Diversity of Coronaviruses with Particular Attention to the Interspecies Transmission of SARS-CoV-2. Animals 2022;12:378. https://doi.org/10.3390/ani12030378.

[106] Anholt RM, Stephen C, Copes R. Strategies for collaboration in the interdisciplinary field of emerging zoonotic diseases. Zoonoses Public Health 2012;59:229-40. https://doi.org/10.1111/j.1863-2378.2011.01449.x.

[107] Guarducci G, Porchia BR, Lorenzini C, Nante N. Overview of case definitions and contact tracing indications in the 2022 monkeypox outbreak. Infez Med 2022;31:13-9. https://doi.org/10.53854/liim-3101-3.

[108] Destoumieux-Garzón D, Mavingui P, Boetsch G, Boissier J, Darriet F, Duboz P, Fritsch C, Giraudoux P, Le Roux F, Morand S, Paillard C, Pontier D, Sueur C, Voituron Y. The One Health Concept: 10 Years Old and a Long Road Ahead. Front Vet Sci 2018;5:14. https://doi.org/10.3389/fvets.2018.00014.

[109] Danasekaran R. One Health: A Holistic Approach to Tackling Global Health Issues. Indian J Community Med 2024;49:260-3. https://doi.org/10.4103/ijcm.ijcm_521_23.

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HEALTH PROMOTION

Aerobic or Resistance Exercise for maximum Cardiovascular Disease Protection? An Appraisal of the Current Level of Evidence

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Keywords

Muscle stretching exercise • Exercise • Muscle • Skeleton • Health promotion • Cardiovascular disease

Summary

Introduction. *The beneficial role of physical activity on the cardiovascular system has been well established and appreciated. The aim of this narrative review was to present a summary of the latest recommendations for physical activity, and to evaluate the most recent scientific evidence regarding the role of aerobic and or resistance exercise in relation to atherosclerotic cardiovascular disease (ASCVD) risk.*
Methods. *Narrative review; searches were performed in PubMed, Scopus and Google Scholar. The guidelines of major Organizations (i.e., European Society of Cardiology, American College of Cardiology/ American Heart Association, American College of Sports Medicine, and World Heart Federation, World Heart Organization) were also retrieved and presented here.*
Results. *Engagement in regular aerobic exercise is strongly recommended for all people and by all scientific organizations for reducing ASCVD mortality and morbidity. Resistance exercise should be implemented in addition to aerobic, however, its individual effects on ASCVD risk are not well established.*
Conclusions. *A reduction of sedentary behavior at population level reduces the healthcare costs by multiple ways. Effective approaches should be implemented that include behavior theory-based interventions, e.g., goal-setting, re-evaluation of goals, self-monitoring, and feedback. Most important is to encourage activity that individuals enjoy and/or can be included in their daily life.*

Introduction

Leisure time physical activity refers to any bodily movement that results in energy expenditure. This includes a wide range of activities, such as walking, running, dancing, swimming, gardening, *etc*. Physical activity can be structured (like organized sports or exercise routines) or unstructured (like outdoor activities). It is typically categorized into four types: aerobic activities (*e.g.*, jogging, cycling), muscle-strengthening activities (*e.g.,* weightlifting), flexibility activities (*e.g*., stretching, yoga) and balance activities. The beneficial role of physical activity on the cardiovascular system has been well established and appreciated [1, 2]. A series of studies since the 1990s have revealed that in both men and women high levels of leisure time aerobic physical activity reduces the risk of atherosclerotic cardiovascular disease (ASCVD) in a range of about 20 to 30%, compared to the risk of those with low levels of physical activity, while even moderate physical activity was significantly associated with up to 20% reduction of the ASCVD risk, indicating an dose-response relationship [3-6]. These effects were independent of the impact of physical activity on other major cardiovascular risk factors, like hypertension, diabetes, obesity, and dyslipidemia.

These accumulative lines of evidence have been summarized in a number of systematic reviews and meta-analyses. For example, a large-scale meta-analysis from the Global Burden of Diseases project, that evaluated 174 studies from all over the world, reported that higher levels of physical activity were significantly associated with 25% lower risk of ischemic heart disease and 26% lower risk for ischemic stroke. In another meta-analysis that explored the mechanistic effects of physical activity on cardiovascular system and included 57 randomized controlled trials of aerobic exercise intervention of at least moderate intensity, aerobic exercise intervention significantly raised antiatherogenic apolipoproteins and lipoprotein sub-fractions, lowered atherogenic apolipoproteins and lipoprotein sub-fractions and improved atherogenic lipid ratios. [5] A more recent meta-analysis of 148 randomized clinical trials and 36 prospective cohort studies, enhanced previous findings, reporting a 34% increased risk for ASCVD in the population with sedentary behavior, but a 29% ASCVD risk reduction in those who performed long-term physical activity as compared to the sedentary [6].

Despite extensive evidence on the impact of physical activity on cardiovascular health, the question of whether resistance exercise, either as a complement to or replacement for aerobic exercise, can offer similar or even greater protection against ASCVD risk remains a concern. Few studies have explored this relationship, and even fewer reviews have summarized and discussed the findings. Thus, the aim of this narrative review was to present a summary of the latest recommendations for physical activity, and to evaluate the most recent scientific evidence regarding the role of aerobic and or resistance exercise in relation to ASCVD risk.

Methods

Literature search

Although this is a narrative review, the basic principles of systematic reviews were followed, according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [7].

A comprehensive literature search of the MEDLINE (via PubMed), Scopus and Google Scholar databases was carried out, until November 30, 2023. The literature search was performed independently by the authors. Boolean operators (*i.e.*, AND, OR, NOT) were used to make the search specific. The search string included the following keywords, according to MeSH (Medical Subjects Headings): "Physical Activity", "Diet", "Exercise", "Aerobic", "Resistance", "Anaerobic", "Cardiovascular Disease", "Heart", "Risk", "Health". The sensitivity of the search was also verified by back referencing the collected systematic reviews, meta-analysis, and independent studies. A hierarchical approach, *i.e.*, screening the title, abstract followed by the full-text manuscript, was used to search for studies. During the time-limit, references of systematic reviews and meta-analyses on the associations of physical activity and ASCVD risk were also manually searched and included. Duplicates were removed. After further screening, epidemiological studies, randomized controlled trials, and meta-analyses evaluating the independent role of physical activity on ASCVD risk, published the past 10 years, were retrieved, and discussed here.

Moreover, the guidelines of major Organizations (*i.e.*, European Society of Cardiology, American College of Cardiology/ American Heart Association, American College of Sports Medicine, and World Heart Federation, World Heart Organization) were also retrieved and presented here.

Measurement of the intensity of physical activity

At this point it should be noted that in the majority of retrieved studies and recommendations, intensity of physical activities is centered around the rates of energy that is consumed during different activities. These rates are known as Metabolic Equivalent Tasks (METs); one MET is defined as the amount of oxygen consumed while at rest, which is approximately 3.5 milliliters of oxygen per kilogram of body weight per minute (3.5 mL O_2/kg/min). Light-intensity physical activity is considered for activities less than 3 MET, moderate-intensity for activities between 3-6 MET and vigorous-intensity for activities of 7 or more MET [8].

Results

Recommendations by the European Society of Cardiology, American College of Cardiology/American Heart Association

Based on the existing large body of evidence, the latest European Society of Cardiology (ESC) Guidelines (2021) strongly recommend that all adults should be engaged in regular physical activities to reduce all-cause mortality, as well as ASCVD-specific mortality, and morbidity [9]. In particular, it is strongly recommended (Class I, Level A) that adults of all ages should strive for at least 150-300 min a week of moderate-intensity (*i.e.*, 3-6 MET) or 75-150 min a week of vigorous-intensity (*i.e.*, 7 or more MET) aerobic physical activity, or an equivalent combination thereof. It is also recommended that people who cannot achieve at least the lowest levels of physical activity, should stay as active as their abilities and health condition allow and try to reduce sedentary time throughout the day. For older adults or individuals with chronic conditions who cannot achieve 150 min of moderate-intensity physical activity a week, they should be as active as their abilities and health conditions allow. Moreover, performing resistance exercise, in addition to aerobic activity, is recommended on 2 or more days per week to reduce ASCVD as well as all-cause mortality (Class I, Level B). The suggestion is one to three sets of 8-12 repetitions at the intensity of 60-80% of the individual's maximum strength, at a frequency of at least 2 days a week in a variety of different exercises involving each major muscle group. For older adults or deconditioned individuals, it is suggested to start with one set of 10-15 repetitions at 40%-50% of their maximum strength [9].

The 2019 Joint Guidelines by the American College of Cardiology/ American Heart Association regarding physical activity also strongly recommend that all adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle (Class I, Level B). In particular, aerobic exercise for 150 min per week of moderate intensity or 75 min per week for vigorous intensity (or an equivalent combination of moderate and vigorous activity) is strongly recommended to reduce ASCVD risk (Class I, Level B). For individuals unable to meet the minimum physical activity recommendations, engaging in at least moderate physical activity even in less than the recommended amount can be beneficial in reducing ASCVD risk (Class IIa, Level B). In addition, American College of Cardiology/ American Heart Association also recommend that decreasing sedentary behavior may be reasonable to reduce ASCVD risk (Class IIb, Level C).

Regarding resistance physical activity, the American College of Cardiology/ American Heart Association recommend that 90-150 minutes per week to 50%-80% of maximum intensity, of 6 exercises and 10 repetitions per set may significantly reduce blood pressure levels, but there is no mention about ASCVD risk [10].

Recommendations by the American College of Sports Medicine, and US Centers for Disease Control

In line with the ESC guidelines, the American College of Sports Medicine (ACSM) also recommends that adults should engage in, at least moderate-intensity aerobic exercise training, and resistance exercises for about 2 to 3 times per week. [11] In particular, ACSM recommends

engaging in moderate-intensity cardiorespiratory exercise training for at least 30 min per day, for at least 5 days per week (*i.e.*, ≥150 min per week) or vigorous-intensity cardiorespiratory exercise training for at least 25 min per day and a minimum of 3 days per week (*i.e.*, ≥75 min per week), or a combination of moderate- and vigorous-intensity exercise, to achieve a significant cardiovascular protection. These recommendations lead to a total energy expenditure of 500-1000 MET/min per week. In addition, ACSM also recommends that adults should perform resistance exercises in addition to the aerobic exercise, for each of the major muscle groups, and neuromotor exercise involving balance, agility, and coordination, for about 2 to 3 times per week [11]. Improvements in physical condition can be reached with any activity that uses large muscle groups, which can be maintained continuously, and is rhythmical and aerobic in nature, *e.g.*, walking-hiking, running-jogging, cycling-bicycling, cross-country skiing, aerobic dance/group exercise, rope skipping, rowing, stair climbing, swimming, skating, and various endurance game activities, or some combination thereof [11].

The latest guidelines for physical activity by the US Centers for Diseases and Prevention (US CDC) suggest a minimum of 150 minutes of moderate-intensity continuous training (MICT), or 75 minutes of vigorous exercise, or a combination of both to achieve various health benefits per week. An alternative to MICT is high intensity interval training (HIIT), defined as repeated, brief, and intense exercise bouts separated by active recovery. It is noted that HIIT produce a significant surge in VO2max and fat oxidation, improving exercise capacity and reducing health risks [12].

The Position of the World Health Organization

The World Health Organization (WHO) strongly recommends engaging in physical activities for people of all ages. Towards the physical activity recommendations made by the scientific societies, WHO has developed the 2018-2030 *Action Plan For More Active People For A Healthier World* [13]. In this Action Plan WHO considers physical activity as a very important lifestyle behavior across all ages, that can and should be integrated into the settings in which people live, work and play. Walking and cycling are key means of transportation and enable engagement in regular physical activity on a daily basis. Also, active play and recreation is important for early childhood as well as for healthy growth and development in children and adolescents. However, there is no specific distinction between the types of physical activity people should follow.

Moreover, WHO supports that quality physical education and supportive school environments can also provide physical and health literacy for long-lasting healthy, active lifestyles.

Epidemiological studies, randomized controlled trials, and meta-analyses on aerobic versus resistance exercise and ASCVD prevention.

Despite the large body of evidence regarding the effects of physical activity on ASCVD risk, there are few epidemiological studies and randomized controlled trials (RCT), and consequently meta-analyses that have evaluated aerobic versus resistance exercise and ASCVD development or even cardiovascular risk markers.

In a recent meta-analysis Momma et al. evaluated 16 prospective cohort studies that examined the association between muscle-strengthening activities and health outcomes in adults. It reported J-shaped associations with the maximum risk reduction (approximately 10-20%) at 30-60 min/week of muscle-strengthening activities for ASCVD, and all-cause mortality, whereas an L-shaped association showing a significant risk reduction at up to 60 min/week of muscle-strengthening activities was observed for diabetes [14].

In a narrative review Giovannucci et al. [15] summarized the existing evidence from cohort studies on muscle strengthening activities and risk of major chronic diseases, including ASCVD and mortality. It was concluded that engagement in muscle-strengthening activities over 60-150 min per week was associated with reduced risk of ASCVD by approximately 20%-25% reduction, type 2 diabetes by approximately 30%, as well as all-cause mortality by approximately 20-25%.

However, it should be underlined that some studies suggest that higher levels of muscle-strengthening activities (*i.e.,* more than 2.5 h/week) may have less benefit or are even harmful, for ASCVD and all-cause mortality, relative to lower levels of activity [16].

In a current systematic review and meta-analysis Khalafi et al. [17] investigated the effects of a combination of aerobic and resistance training which is described as concurrent training of aerobic and resistance versus aerobic or resistance only, on $VO_{2max/peak}$ and muscular strength, in middle-aged and older adults. They revealed that concurrent training is effective for increasing muscular strength and cardiorespiratory fitness in older adults and does not negatively affect these outcomes as compared to either resistance or aerobic alone. It was also concluded that concurrent training can be effective when aerobic and resistamce are performed during the same sessions or as separate sessions and following medium-term and long-term interventions.

The effect of progressive resistance training (PRT) on aerobic fitness and strength in adults with coronary heart disease was evaluated by Hollings et al. [18]. They investigate in a systematic review and meta-analysis 34 studies and 1,940 participants if Progressive Resistance Training was more effective compared to control, aerobic fitness, and when combined with aerobic training. They found that aerobic fitness was improved similarly after PRT (16.9%) or AT (21.0%) and that combined training resulted in a significant greater improvement in peak work compared to AT (5%). It was concluded that progressive resistance training provides improvements in

cardiorespiratory fitness that are comparable to aerobic training in adults with coronary heart disease [18].

The benefits of combination aerobic and resistance exercise on CVD predisposing factors in individuals with elevated risk was investigated by Schroeder et al. [19]. They compared the effect of 60 min/session aerobic exercise vs 60 min/session resistance training vs 30 min aerobic plus 30 min resistance / session in an 8-week exercise with 3 days/week and equal exercise time in all groups. They found that only in combined training, individuals had significant reductions in blood pressure alongside with increases in cardiorespiratory fitness, body strength, lean body mass. It was concluded that among individuals at an increased risk for CVD, as little as 8-weeks of combined training may provide more comprehensive CVD benefits compared to time-matched aerobic or resistance training alone [19].

The combination of aerobic and inspiratory muscle training versus aerobic training was investigated in patients with chronic heart failure by Adamopoulos et al. [20]. They use the multicenter randomized trial (*i.e.*, Vent-HeFT) which was designed to investigate the potential additive benefits of inspiratory muscle training on aerobic training. The study demonstrated that inspiratory muscle training combined with aerobic training provides additional benefits in functional and serum biomarkers (*i.e.*, respiratory muscle function, dyspnea, quality of life, inflammatory and cardiac) in patients with moderate chronic heart failure. Inspiratory muscle training may strengthens the diaphragm and other respiratory muscles, leading to better lung function and reduced respiratory effort during exercise, enhance oxygen exchange and delivery to the working muscles, which, when combined with aerobic training, leads to better overall exercise performance and endurance, reduce circulating inflammatory markers such as C-reactive protein and cytokines, which are often elevated in chronic heart failure, and reduce the workload on the heart by improving breathing efficiency [20].

At this point it should be highlighted that although endurance exercise offers numerous cardiovascular benefits, patients suffering from ASCVD need to approach it with caution. The increased myocardial stress, potential for ischemic damage, and other factors like electrolyte imbalances can increase their risk for developing arrhythmic events. Careful management, including regular cardiac evaluations, may be necessary to balance the benefits and risks of such intense physical activity [21].

In a systematic review Tambalis et al. [22] investigated the effectiveness of different intensities (moderate and high) of aerobic training as well as the type of exercise (aerobic, resistance, and combined aerobic with resistance) in altering the blood lipids levels of 3,042 participants from the general population (*i.e.*, the ATTICA Study). High-intensity exercise (*i.e.*, 7 or more MET) resulted in improvements in high-density lipoprotein cholesterol but for resistance and combined exercise the results were inconsistent. The heterogeneity between the types of exercise did not allow reliable comparisons, (*i.e.*, aerobic activities, muscle-strengthening activities, flexibility activities and balance activities, in terms of their physiological mechanisms to the human body) [22].

Discussion

In this narrative review we explored the latest recommendations for physical activity and evaluated a selection of the most recent, high-quality scientific evidence, including the recommendations of major health societies, regarding the role of aerobic and or resistance exercise in relation to ASCVD risk. It was confirmed that aerobic exercise is a major cardioprotective lifestyle mean for ASCVD risk reduction that should be recommended to people of all ages. Recent evidence suggests that resistance exercise on the top of aerobic, may further confer to ASCVD risk reduction. However, the effect of only resistance exercise on ASCVD risk is not well understood and appreciated [24].

There are various types of physical activities, with a significant variation in terms of their physiological effects. Aerobic training, the most well-studied type of physical activity and the one most commonly performed, enhances heart and lung function, promotes fat metabolism, and improves overall stamina. Resistance training primarily improves muscular strength and bone density. Balance training activities emphasize flexibility, balance, and coordination, and are particularly important for improving range of motion, reducing injury risk, and enhancing overall functional movement, especially among older adults. High-Intensity Interval Training (HIIT) combines short bursts of intense exercise with periods of rest or low-intensity recovery, can be applied to both aerobic and resistance training and is known for improving both cardiovascular fitness and muscular endurance in a time-efficient manner. Inspiratory muscle training is aimed at strengthening the respiratory muscles, particularly the diaphragm, and it is beneficial for people with conditions like chronic obstructive pulmonary disease (COPD) or heart failure, as it improves breathing efficiency and reduces breathlessness. Heterogeneity in exercise training is crucial for optimizing fitness outcomes and tailoring programs to individual needs [2, 8, 9].

The role of aerobic exercise on the cardiovascular system has been extensively studied. The evidence strongly suggests that aerobic exercise of at least 150 minutes per week reduces blood lipids levels, *i.e.*, total cholesterol, low-density lipoprotein (LDL) cholesterol, as well as triglycerides, and increases high-density lipoprotein (HDL) levels [9, 25]. Moreover, regular aerobic exercise helps in arterial blood pressure reduction in people with hypertension, as well as in blood pressure control and management [9, 26]. Health benefits occurred even at low levels of physical activity; for example, individuals with a total activity level of 600 MET minutes/week (the minimum recommended level) had a 2% lower risk of ASCVD compared with those reporting no physical activity, whereas an increase up to 3600 MET minutes/week the risk was reduced by an additional 19% [4].

Obesity is a major threat for developing ASCVD and diabetes [27]. Aerobic exercise has consistently shown that its importance in body weight control, and reduction in lipid accumulation, and therefore reduction of ASCVD risk [25]. However, energy balance and diet are also of crucial importance for ASCVD, thus, adherence to a healthy dietary pattern should always be recommended together with exercise [10, 29-31].

There are relatively few studies that have shown benefits of engagement in resistance exercise for the reduction of surrogate risk markers for ASCVD. The suggested recommendation by ESC and other major organizations for resistance exercise is one to three sets of 8-12 repetitions at the intensity of 60-80% of the individual's 1 repetition maximum at a frequency of at least 2 days a week in a variety of 8-10 different exercises involving each major muscle group [9]. The mechanisms that resistance exercise affects ASCVD risk have not well studied. Some interventional and experimental studies have shown that resistance exercise, such as weightlifting or bodyweight exercises, increase energy expenditure, improve muscle mass and metabolism, by increasing metabolic rate, which, accordingly, assists in weight management and reduces the risk of obesity, a significant risk factor for CVD. Resistance exercise has also been associated with blood pressure regulation [32]. Regular resistance training can help lower blood pressure by improving blood vessel function and reducing arterial stiffness. Lower blood pressure decreases the workload on the heart and reduces the risk of hypertension [33]. Moreover, several clinical trials have shown that engagement in resistance exercise has improved individuals' lipid profile, by increasing levels of HDL-cholesterol and reducing levels of LDL-cholesterol and triglycerides. Resistance training has also shown that increases insulin sensitivity, allowing cells to better respond to insulin and regulate blood sugar, as well as decreases levels of inflammatory markers, which are strongly associated with the development and progression of ASCVD, as summarized in a review paper by Westcott [34]. There are also few studies that have shown that resistance exercise improves endothelial function [35-37]. However, a significant pressure load imposed on the heart during resistance exercise, may lead to a mild form of cardiac hypertrophy. In addition, a marked rise in blood pressure is secondary to resistance exercise; thus, a high-level resistance may have adverse effect on those with uncontrolled hypertension [37]. Thus, incorporating moderate-level resistance exercise into a well-rounded fitness routine, can significantly reduce the risk of ASCVD and improve overall heart health.

In conclusion, engagement in regular physical activity by adults of all ages for reducing ASCVD mortality and morbidity is strongly recommended by all scientific organizations. Furthermore, the latest ESC Guidelines for ASCVD prevention extend beyond standard recommendations, advising that physical activity should be tailored to the individual and prescribed (as pharmaceutical medication) based on frequency, intensity, duration, type (such as aerobic and/or resistance training), and progression. A reduction of sedentary behavior at population level reduces the healthcare costs by multiple ways. To achieve this, effective approaches should be implemented that include behavior theory-based interventions, *e.g.*, goal setting, re-evaluation of goals, self-monitoring, and feedback. Under this perspective, the important role of healthy diet should never be disregarded or underestimated. The most important factor is to encourage activity that individuals enjoy and/or can included in their daily life.

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ND: performed literature search and wrote the paper; DP: critically reviewed the paper and evaluated the retrieved studies.

References

[1] Lippi G, Sanchis-Gomar F. An Estimation of the Worldwide Epidemiologic Burden of Physical Inactivity-Related Ischemic Heart Disease. Cardiovasc Drugs Ther 2020;34:133-7. https://doi.org/10.1007/s10557-019-06926-5.

[2] Myers J. Cardiology patient pages. Exercise and cardiovascular health. Circulation 2003;107:e2-5. https://doi.org/10.1161/01.cir.0000048890.59383.8d.

[3] Li J, Siegrist J. Physical activity and risk of cardiovascular disease--a meta-analysis of prospective cohort studies. Int J Environ Res Public Health 2012;9:391-407. https://doi.org/10.3390/ijerph9020391.

[4] Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, Veerman JL, Delwiche K, Iannarone ML, Moyer ML, Cercy K, Vos T, Murray CJ, Forouzanfar MH. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016;354:i3857. https://doi.org/10.1136/bmj.i3857.

[5] Wood G, Taylor E, Ng V, Murrell A, Patil A, van der Touw T, Wolden M, Andronicos N, Smart NA. Estimating the Effect of Aerobic Exercise Training on Novel Lipid Biomarkers: A Systematic Review and Multivariate Meta-Analysis of Randomized Controlled Trials. Sports Med 2023;53:871-86. https://doi.org/10.1007/s40279-023-01817-0.

[6] Liang ZD, Zhang M, Wang CZ, Yuan Y, Liang JH. Association between sedentary behavior, physical activity, and cardiovascular disease-related outcomes in adults-A meta-analysis and systematic review. Front Public Health 2022;10:1018460. https://doi.org/10.3389/fpubh.2022.1018460.

[7] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline

for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

[8] Holtermann A, Stamatakis E. Do all daily metabolic equivalent task units (METs) bring the same health benefits? Br J Sports Med 2019;53:991-2. https://doi.org/10.1136/bjsports-2017-098693.

[9] Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, 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. Erratum in: Eur Heart J 2022;43:4468. https://doi.org/10.1093/eurheartj/ehac458.

[10] 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 SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596-e646. https://doi.org/10.1161/CIR.0000000000000678. Erratum in: Circulation. 2019;140:e649-e650. https://doi.org/10.1161/CIR.0000000000000725. Erratum in: Circulation. 2020;141:e60. https://doi.org/10.1161/CIR.0000000000000755. Erratum in: Circulation 2020;141:e774. https://doi.org/10.1161/CIR.0000000000000771.

[11] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, 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.

[12] Tappero JW, Cassell CH, Bunnell RE, Angulo FJ, Craig A, Pesik N, Dahl BA, Ijaz K, Jafari H, Martin R; Global Health Security Science Group. US Centers for Disease Control and Prevention and Its Partners' Contributions to Global Health Security. Emerg Infect Dis 2017;23:S5-14. https://doi.org/10.3201/eid2313.170946.

[13] Global action plan on physical activity 2018-2030: more active people for a healthier world. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://iris.who.int/bitstream/handle/10665/272722/9789241514187-eng.pdf?sequence=1 (Accessed on: 30/04/2024).

[14] Momma H, Kawakami R, Honda T, Sawada SS. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. Br J Sports Med 2022;56:755-63. https://doi.org/10.1136/bjsports-2021-105061.

[15] Giovannucci EL, Rezende LFM, Lee DH. Muscle-strengthening activities and risk of cardiovascular disease, type 2 diabetes, cancer and mortality: a review of prospective cohort studies. J Intern Med 2021;290:789-805. https://doi.org/10.1111/joim.13344.

[16] Miyachi M. Effects of resistance training on arterial stiffness: a meta-analysis. Br J Sports Med 2013;47:393-6. https://doi.org/10.1136/bjsports-2012-090488.

[17] Khalafi M, Sakhaei MH, Rosenkranz SK, Symonds ME. Impact of concurrent training versus aerobic or resistance training on cardiorespiratory fitness and muscular strength in middle-aged to older adults: a systematic review and meta-analysis. Physiol Behav 2022;254:113888.https://doi.org/10.1016/j.physbeh.2022.113888.

[18] Hollings M, Mavros Y, Freeston J, Fiatarone Singh M. The effect of progressive resistance training on aerobic fitness and strength in adults with coronary heart disease: a systematic review and meta-analysis of randomised controlled trials. Eur J Prev Cardiol 2017;24:1242-59. https://doi.org/10.1177/2047487317713329.

[19] Schroeder EC, Franke WD, Sharp RL, Lee DC. Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: a randomized controlled trial. PLoS One 2019;14:e0210292. https://doi.org/10.1371/journal.pone.0210292.

[20] Adamopoulos S, Schmid JP, Dendale P, Poerschke D, Hansen D, Dritsas A, Kouloubinis A, Alders T, Gkouziouta A, Reyckers I, Vartela V, Plessas N, Doulaptsis C, Saner H, Laoutaris ID. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: the Vent-HeFT trial: a European prospective multicentre randomized trial. Eur J Heart Fail 2014;16:574-82. https://doi.org/10.1002/ejhf.70.

[21] Apelland T, Janssens K, Loennechen JP, Claessen G, Sørensen E, Mitchell A, Sellevold AB, Enger S, Onarheim S, Letnes JM, Miljoen H, Tveit A, La Gerche A, Myrstad M; NEXAF investigators. Effects of training adaption in endurance athletes with atrial fibrillation: protocol for a multicentre randomised controlled trial. BMJ Open Sport Exerc Med 2023;9:e001541. https://doi.org/10.1136/bmjsem-2023-001541.

[22] Tambalis K, Panagiotakos DB, Kavouras SA, Sidossis LS. Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: a systematic review of current evidence. Angiology 2009;60:614-32. https://doi.org/10.1177/0003319708324927.

[23] Rao P, Belanger MJ, Robbins JM. Exercise, Physical Activity, and Cardiometabolic Health: Insights into the Prevention and Treatment of Cardiometabolic Diseases. Cardiol Rev. 2022;30:167-78. https://doi.org/10.1097/CRD.0000000000000416.

[24] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315-81. https://doi.org/10.1093/eurheartj/ehw106.

[25] Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. Lipids Health Dis 2017;16:132. https://doi.org/10.1186/s12944-017-0515-5.

[26] Edwards JJ, Deenmamode AHP, Griffiths M, Arnold O, Cooper NJ, Wiles JD, O'Driscoll JM. Exercise training and resting blood pressure: a large-scale pairwise and network meta-analysis of randomised controlled trials. Br J Sports Med 2023;57:1317-26. https://doi.org/10.1136/bjsports-2022-106503.

[27] Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. Circ Res 2016;118:1752-70. https://doi.org/10.1161/CIRCRESAHA.115.306883.

[28] Bellicha A, van Baak MA, Battista F, Beaulieu K, Blundell JE, Busetto L, Carraça EV, Dicker D, Encantado J, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Oppert JM. Effect of exercise training on weight loss, body composition changes, and weight maintenance in adults with overweight or obesity: An overview of 12 systematic reviews and 149 studies. Obes Rev 2021;22:e13256. https://doi.org/10.1111/obr.13256.

[29] Astrup A, Magkos F, Bier DM, Brenna JT, de Oliveira Otto MC, Hill JO, King JC, Mente A, Ordovas JM, Volek JS, Yusuf S, Krauss RM. Saturated Fats and Health: A Reassessment and Proposal for Food-Based Recommendations: JACC State-of-

the-Art Review. J Am Coll Cardiol 2020;76:844-57. https://doi.org/10.1016/j.jacc.2020.05.077.

[30] Elagizi A, Kachur S, Carbone S, Lavie CJ, Blair SN. A Review of Obesity, Physical Activity, and Cardiovascular Disease. Curr Obes Rep 2020;9:571-81. https://doi.org/10.1007/s13679-020-00403-z.

[31] Enkhmaa B, Surampudi P, Anuurad E, Berglund L. Lifestyle Changes: Effect of Diet, Exercise, Functional Food, and Obesity Treatment on Lipids and Lipoproteins. 2018. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, eds. Endotext [Internet]. South Dartmouth, MA: MDText.com, Inc 2000.

[32] Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 2004;36:533-53. https://doi.org/10.1249/01.mss.0000115224.88514.3a.

[33] Patnode CD, Evans CV, Senger CA, Redmond N, Lin JS. Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2017;318:175-93. https://doi.org/10.1001/jama.2017.3303.

[34] Westcott WL. Resistance training is medicine: effects of strength training on health. Curr Sports Med Rep 2012;11:209-16. https://doi.org/10.1249/JSR.0b013e31825dabb8.

[35] Kirkman DL, Lee DC, Carbone S. Resistance exercise for cardiac rehabilitation. Prog Cardiovasc Dis 2022;70:66-72. https://doi.org/10.1016/j.pcad.2022.01.004.

[36] Mcleod JC, Stokes T, Phillips SM. Resistance Exercise Training as a Primary Countermeasure to Age-Related Chronic Disease. Front Physiol 2019;10:645. https://doi.org/0.3389/fphys.2019.00645.

[37] Jørgensen SL, Kierkegaard-Brøchner S, Bohn MB, Høgsholt M, Aagaard P, Mechlenburg I. Effects of blood-flow restricted exercise versus conventional resistance training in musculoskeletal disorders-a systematic review and meta-analysis. BMC Sports Sci Med Rehabil 2023;15:141. https://doi.org/10.1186/s13102-023-00750-z.

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Infectious disease

Knowledge, attitude and practice of Lassa fever prevention among adults in Bali Local Government Area, Taraba State, Nigeria

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Key words

Knowledge • Practice • Attitude • Lassa fever prevention • Nigeria.

Summary

Introduction. *Lassa fever (LF), a public health problem of great importance endemic in West Africa, is an acute and sometimes fatal viral haemorrhagic disease which leads to mortality. The current study assessed the knowledge, attitude and practice of Lassa fever prevention among adults in Bali Local Government Area, Taraba State, Nigeria.*

Methods. *Descriptive study design and Cross sectional study design was used for this study. A simple and systematic random sampling technique was used to draw samples of 399 participants for the study. A structured questionnaire was used for data collection after being validated and its reliability tested. The data collected was analysed using frequencies, percentage the hypotheses were tested using Data analysis was done using SPSS version 21, frequency, mean standard deviation, and chi square were performed to ascertain the value of the variables the hypotheses were tested using chi-square statistics at ≤0.05 level of significance.*

Results. *Findings from the study revealed that75% of the respondents had knowledge of the Lassa fever and the preventive practices. It was also shown that about 66.7% were aware of the varied preventive measures at their disposal. The study further shows that 56% had positive attitudes that could affect their practice of preventive measures of Lassa fever. The acceptability level according to this study was very high (89%) among the adults of Bali L.G.A in Taraba state.*

Conclusions. *The study therefore, recommends that there should be a call for educational intervention to improve the knowledge of Lassa fever among community members in Bali LGA this will help towards its preventive practices. This is based on the expectation that good knowledge of Lassa fever can reduce the rate and spread of the Infection.*

Introduction

It have been documented that the earliest cases of Lassa fever were thought to have occurred between 1920 and 1950, in Nigeria, Sierra Leone and Central African Republic and perhaps in other West African countries [8]. However, the disease became recognized and named in 1960 after two missionary nurses died and a third suffered a grave apparently communicable febrile systemic illness while working in Nigeria. The index patient was working in a mission hospital in Lassa town, Borno State, North-Eastern Nigeria when she fell critically ill and was transferred to Evangel Hospital, Jos Plateau State (now Bingham University Teaching Hospital, Jos) where she subsequently died. The second nurse, who was a staff of Evangel Hospital, cared for the index patient on presentation and she later developed comparable symptoms like the index case culminating in her death days later.

Lassa fever is an acute viral hemorrhagic illness caused by Lassa virus, a member of the virus family "*Arenaviridae*". The disease is endemic in various West African countries including Nigeria where Lassa fever virus infections rate per annum is estimated at 100,000 to 300,000 with approximately 5,000 deaths [17]. Outbreaks of the disease have been reported in various parts of Nigeria since it was first reported in 1969 with the worst outbreak recorded in 2012 where 623 cases including 70 deaths were reported from 19 out of 36 states, and case fatality rate put at 37.9% [31].

The interaction between man and his environment is a major aspect to be considered in understanding the epidemiology of diseases. The transmission of Lassa fever is closely related to environmental factors intricately woven around the vector, the rodent *Mastomysnatalensis* [42, 39]. Other environmental factors such as overcrowding, poor food and personal hygiene and poor housekeeping are implicated in the transmission of the Lassa virus (Public Health Agency of Canada, 2011) [43]. Exposed food items, consumption of uncooked, poorly cooked and inadequately reheated foods are also important risk considerations.

In 2012, there were 1,723 cases and 112 deaths in Nigeria. Last year, 12 people died out of 375 infected, according to the Nigeria Center for Disease Control. Nigeria had an outbreak of Lassa fever in the year 2012 with 1,723 cases, 112 deaths, 201 laboratory-confirmed cases, and a case fatality rate of 6.50 [11, 21]. Between January 1 and April 15, 2018, 1,849 suspected cases have been reported from 21 states (Abia, Adamawa,Anambra,

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Bauchi, Benue, Delta, Ebonyi, Edo, Ekiti, Federal Capital Territory, Gombe, Imo, Kaduna, Kogi, Lagos, Nasarawa, Ondo, Osun, Plateau, Rivers, and Taraba). Out of these, 413 patients were confirmed with Lassa fever, nine were classified as suspected, 1,422 tested negative, and the remaining five laboratory results were pending. Of the 413 confirmed and the nine probable Lassa fever cases, 114 deaths were reported (case fatality rate for confirmed cases is 25.4% and for confirmed and probable cases combined is 27%). As of April, 27 health care workers in seven states (Abia, Benue, Ebonyi, Edo, Kogi, Nasarawa, and Ondo) have been infected since January 1, 2018, eight of whom have died [21].

Taraba State is one of the three high burdened states with frequent occurrences of Lassa fever outbreaks [37]. Abakaliki Local Government Area (LGA) had the highest proportion of confirmed Lassa fever cases during the 2018 and 2019 outbreaks in the State [41]. Researches carried out in places around the country have revealed that knowledge of the disease is deficient among many and inadequate among quite a large population making it hard for people to prevent the incident of an outbreak [24-26, 30]. In response to the poor knowledge of the public, the federal government put up various measures to prevent further spread of the diseases and treatment when it occurs. Such measures are the enhancement of disease surveillance, social health education through mass media, increased the number of diagnostic centers from 6 to 12, and also inaugurated a 15-member multisectoral Lassa fever Eradication Committee charged with fashioning and implementing the multifaceted response strategies against the outbreak [33, 40].

Statement of the Problem

Lassa fever being a highly contagious disease endemic in West Africa, including Nigeria and Taraba state [25, 38] needs a robust public measures including early detection, effective treatment and widespread education on prevention to control its spread and mitigate its impact. The overall regional and global risks are through its primary mode of transmission through contact with food or household items contaminated with rat excreta. Due to drying of food items along high ways and outside houses over the night, constant burning of bushes, poor hygiene practices, and overcrowding in homes which causes logging of baggages and properties these give rise to these rats gaining entrance into the houses, all these factors put together may facilitate the increase in rodent man contact or contamination of food source by infected mastomys rat, it is against this background that the researcher have designed this study todetermine knowledge, attitude, practice of Lassa fever prevention among adult of Bali LGA.

Materials and Methods

Population of the Study

It comprised of all adult in Bali L.G.A where the sample for the study was drawned. The current estimated number of adults 18yrs and above 176,634 was derived by the researcher accordingto Bali Local government Commission.

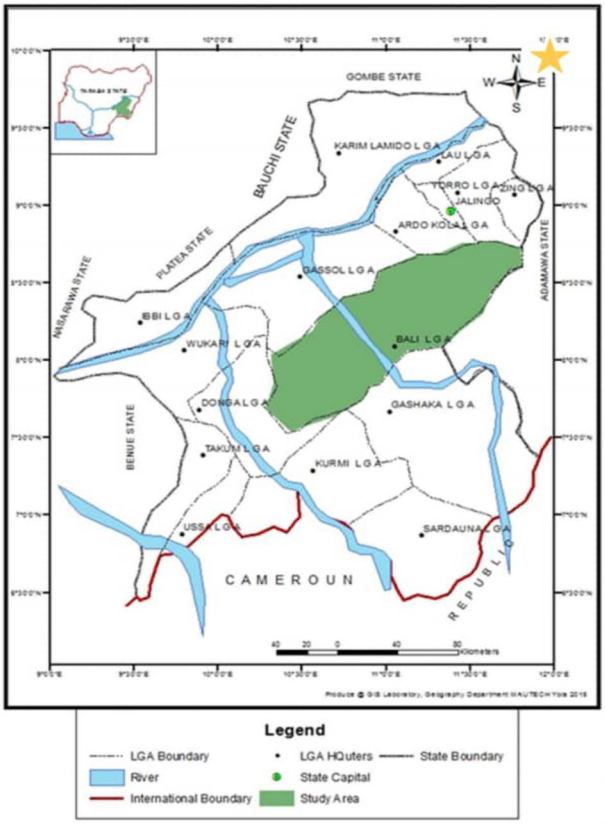
Study Area

Taraba state was carved out from the then defunct Gongola state (now Adamawa state) on the 27th August 1991, by the then Military Administration of General Ibrahim Babangida. The state derived its name from one of the three major rivers in the state and it has a land area of 59400 square kilometers with the headquarter situated in Jalingo. The state is made up of 16 local government areas namely, Ardo Kola, Bali, Jalingo, Zing, Yorro, Lau, Karim Lamido, Wukari, Ibi, Gassol, Gashaka, Sardauna, Kurmi, Donga, Takum, Ussa L.G.A. Bali L.G.A being the main study area for this study is situated in the north central part of the state with headquarter in Bali town about 50 km from Jalingo as shown in Figure 1. It was created in 1976 with population estimated to be 208,935 people at the 2006 census and comprising of Fulani, Mumuye, Jukun, Chamba and other ethnic groups. Bali has a latitude of 8.1554˚ North and longitude 10.9685˚ East. Christianity and Islam are the major religions practiced in Bali L.G.A.

Sample size calculation

Sample size was derived using TaroYamane'formula for finite population.

Fig. 1. Map of Taraba state showing Bali LGA.



Source: Ministry of lands and survey Jalingo, Taraba state.

Using Taro Yamane' formula for finite population.
The Yamane sample size states that:

$$n = N/ (1+N (e) 2)$$

Where: n signifies sample size
N signifies the population size under study (176,634)
e signifies the margin error (it could be 0.10, 0.05 or 0.01)

$$n =176,634/ (1+176,634 (0.05) 2)$$
$$n = 176,634/ (1+34,486(0.0025)$$
$$n =176,634/ (1+441.59)$$
$$n =176,634/ 441.59$$
$$n = 399$$

Sampling Technique

Multi-stage sampling method was used for this study.

In stage one: Selection by cluster

The communities in Bali L.G.A was clustered along existing twenty traditional communities which includes Bali A, Bali B, Mai hula, Sabin dale, Gazabu, Jatau, Sansani, Mayokam, Bakundi, Pangri, Sarkindawa, Ardo tinba, Badokoshi, Aka, Daniya, Dakka, Garba chede, Maigoge, Bayire, Sabon gida.

In Stage two: Selection of communities proportionately

Simple random sampling technique by (balloting without replacement) was used to select both rural and semi-urban communities. Six rural communities were selected which were, Gazabu, Jatau, Sansani, Mayokam, Dakka, Sabon gida and four semi-urban communities were selected which included Bali A, Bayire, Pangri, Bali B. The proportional sample size for each of the selected communities were obtained.

Stage four: Selection of house-hold

This stage involved the selection of the households by systematic random sampling technique. The determined sampling interval for each of the selected communities was employed where 5 was the interval for each selection. The researcher located the centre of each selected communities, divided it into four sections, randomly selected one sector, located the centre of that sector and spun a pen to determine the direction to begin the sampling. The first respondent (head of house hold) sampled was selected by simple random sampling by balloting without replacement. Sampling intervals were obtained for the various communities and it was maintained until the desired number of households was gotten. This was done for three weeks until the desired sample size of 399 respondents was achieved. Written informed consents were obtained from the participants.

Validity of Instruments

The Instrument for data collection was a self-structured questionnaire which was drafted under supervision then went for validation by three experts in the field of Public health, two from Imo state and one from Taraba state. Correction made was used to finalize the instrument for content relevance and appropriateness of language.

Reliability of the Instrument

The questionnaire was administered to 20 respondents with similar characteristics to those in the target population. The reliability of the instrument was tested using Chrombach Alpha Coefficient of Reliability test, and a coefficient of (r = 0.84) was deemed reliable.

Data Collection

A pretested self-structured survey questionnaire was used for data collection, containing closed-ended questions with 4 sections. Section A is the demographic variables of the respondent which is age, gender, marital status, level of education, occupation and religion. Section B contains 10 questions to ascertain their level of knowledge of Lassa fever. Section C contains questions on attitude towards Lassa fever with 10. Section D are the Lassa fever prevention practices which contains 24 questions after being validated and its reliability tested. The questionnaire had a total of 50 closed ended questions on a study on knowledge, attitude and practice of Lassa fever prevention among adults in Bali Local Government Area Taraba State.

Data analysis

Data analysis was performed in IBM-SPSS Statistics version 23. Initial analysis involved construction of frequency distribution and manipulations. The average number of responses was used to compute the overall knowledge and preventive practices in each case and such scores were used to establish a cut-off point scoring 1 per point for each correct answer which were 10 questions, where 7 to 10 is graded as high knowledge, 4-6 as moderate knowledge and below 4 as poor knowledge as well as for the occurrence of preventive practices. The correct answers are indicated on table 4.2 with *. Chi square test (χ^2) was used to test for significant association between the factors and the knowledge or preventive practices. Fisher exact test was conducted at 2 by 2 table where chi-square test assumptions were hard to meet. Statistical tests were performed at 5% level of significant and probability value ($p \leq 0.05$) was used to interpret significance.

Ethical Considerations

Ethical approval to undertake the study was obtained from Research and Ethics Committee of Taraba State Ministry of Health Jalingo, Nigeria. The participants were briefed on the objectives of the study, and their oral and written consent was also obtained before proceeding with the research. It is a descriptive cross-sectional survey, which is a type of design where the researcher does not alter the exposure status but measures the outcome and the exposure(s) in the population under observation. This design was successfully used in related studies of [31, 26].

Results

Table I, shows the demographic status of respondents in Bali LGA, a total of 399 participants were involved in the study but 385 recorded, majority of the participants were within ages 38-47 years 83 (21.6%) and 196 (50.9%) of the respondents are female, Majority of the respondents are married, 231 (60%). In terms of educational attainment, Majority attended secondary education 154 (40%). The participants cut across all religio us faith, 126 (32.7%) are of the Islamic faith, while majority were of the Christian faith with farming as their major occupation.

Table II Present the knowledge of the respondents on Lassa fever prevention. Their knowledge were poor 48.3% as indicated that more than half of the respondents don't know that Lassa fever is a severe disease caused by germ virus, 105 (27.3%) believed that Lassa fever is gotten from eating too much oil. The respondents that are aware that the incubation period of Lassa fever ranges from 1-7 days although are very few, although 175 (45.5%) stated that one can be infected with Lassa fever due to handling food and household items contaminated with rat's faeces and urine. Few were of the opinion that the Lassa fever can be spread through sitting close to an infected person. About 107 (27.8%) affirmed that the disease can cause bleeding and death if not immediately handled. According to 230 (85.8%) of respondents, Lassa fever can be avoided by eliminating rat from the environment, proper environmental hygiene, and protecting food from being contaminated.

Table III shows distribution of respondents by correct knowledge of Lassa Fever Prevention responses Overall knowledge in each case and scores were used to establish a cut-off point scoring 1 per point for each question which were 10 questions, where 7 to 10 is graded as high knowledge 4-6 as moderate knowledge and below 4 as poor knowledge. The classification of knowledge based on High, moderate and poor in percentage is shown in Figure 2 which was determined by scoring the highest score to the correct response and a lower number to a wrong answer. The general average of the total score was calculated to determine the cut-off score (3.24). The average scores of individual scores was also determined.

Table IV, showed that more than half of the respondents strongly agreed and agreed that anyone can be infected with Lassa fever, 29.6% and 33.5% strongly agreed and agreed respectively that Lassa fever is not a spiritual attack. Very few respondents were of the opinion strongly that environmental sanitation can limit rats in the environment, 36.9% of the respondents believed that Lassa fever can best be treated randomly and argued that it can be best treated by the native doctors. Negative and positive attitude was determined by scoring the highest score to the most positive attitude response and a lowest score to the most negative attitude, the general average of the total score was calculated to determine the cut-off score (2.8). The average scores of individual scores was also determined. Figure 3 showed the respondents' percentage level of attitude towards Lassa fever (Score > 2.8 = negative attitude; score ≥ 2.8 = positive attitude).

Tab. I. Distribution of respondent by Socio-economic Characteristics of adults in Bali LGA.

Variables	Frequency (F)	Percent (%)
Age		
18–27	69	17.9
28–37	61	15.8
38–47	83	21.6
48–57	66	17.1
58-67	41	10.6
68-77	17	4.4
78 and above	48	12.5
Total	385	100.0
Gender		
Female	196	50.9
Male	189	49.1
Total	385	100.0
Marital Status		
Divorced	15	3.9
Married	231	60.0
Separated	32	8.3
Single	81	21.0
Widowed	26	6.8
Total	385	100.0
Educational level		
No formal education	79	20.5
Primary	83	21.6
Secondary	154	40.0
Tertiary	69	17.9
Total	385	100.0
Occupation		
Applicant	19	5.0
Business/Trading	75	19.5
Farming	126	32.7
Public/CivilService	99	25.7
Student	66	17.1
Total	385	100.0
Religion		
Christianity	177	46.0
Islam	126	32.7
Traditional worshiper	82	21.3
Total	385	100.0

Table V reveled 32.7% of the respondents are of the opinion that Lassa fever can be prevented by good food protection policy, 36.6% believed that fruits are to be washed thoroughly with water before eating, and half of the respondent said the best way to safe guard your food items from Lassa fever is by eradicating rat and by regular environmental sanitation practice.

Table V also shows that very few respondents cook their food very well before eating on a daily basis. With 28.3% believing that it kills germs when food are prepared very well before eating. 4.2% washes their hands always with soap and water after visiting the toilet, 33.0% washes their hands before eating while very few don't as shown in Table V. Not many take 20 seconds and above for a single session of hand washing as well as using handkerchief to dry off their hands after washing. A

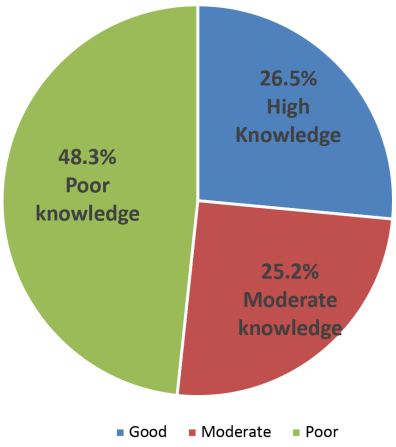
Tab. II. Distribution of respondents by knowledge of Lassa fever prevention.

Variables	Frequency (F)	Percent (%)	Correct answer
What is Lassa fever			
A severe illness caused by germ	126	32.7	*
Another form of malaria	99	25.7	
Disease caused by eating too Much oil	105	27.3	
Fever caused by evil spirit	55	14.3	
Total	385	100.0	
Lassa fever vector			
Monkey	53	13.8	
Mosquito	97	25.2	
None of the above	28	7.3	
Rat	207	53.8	*
Total	385	100.0	
How can Lassa fever be contacted			
Eating over-cooked cow meat	85	22.1	
Items contaminated with rat's faeces and urine	175	45.5	*
None of the above	48	12.5	
Prolonged mosquito bites	77	20.0	
Total	385	100.0	
Early Signs and symptoms of Lassa fever except			
Cough	73	19.0	
Fever	157	40.8	
Headache	58	15.1	
Vomiting	97	25.2	*
Total	385	100.0	
Lassa fever can be prevented through except?			
Eliminating mosquitoes	55	14.3	*
Eliminating rat in the environment	150	39.0	
Proper environmental sanitation	92	23.9	
Protecting food from being contaminated	88	22.9	
Total	385	100.0	
Community ways of controlling Lassa fever			
All of the above	39	10.1	*
Good environmental hygiene	140	36.4	
Keeping cats at home	85	22.1	
Storing grains and food stuffs in rodent-proof containers	121	31.4	
Total	385	100.0	
How can Lassa fever spread			
Contact with the body fluid of infected person	117	30.4	*
Shaking hand	75	19.5	
Sitting close to infected person	137	35.6	
Taking the infected person to hospital	56	14.5	
Total	385	100.0	
What to do one Lassa fever is suspected			
Seek health care immediately	180	46.8	*
Try self-medication first	90	23.4	
Visit a spiritualist	51	13.2	
Watch the situation for sometimes	64	16.6	
Total	385	100.0	
Lassa fever can cause			
All of the above	68	17.7	*
Bleeding	107	27.8	
Death	137	35.6	
Facial swelling	73	19.0	
Total	385	100.0	
How long it takes signs and symptoms to manifest			
1-7 days	94	24.4	
21-28 days	104	27.0	
30-60 days	66	17.1	
7-21 days	121	31.4	*
Total	385	100.0	

Tab. III. Distribution of Respondents by correct knowledge of Lassa Fever Prevention responses.

Variables	Correct		InCorrect		Difference	
	F	%	F	%	F	%
What is Lassa fever?	126	32.7	259	67.3	-133	-34.6
Lassa fever vector?	207	53.8	178	46.2	29	7.6
How can Lassa fever be contacted?	175	45.5	210	54.5	-35	-9.0
Signs and symptoms of Lassa fever?	157	40.8	228	59.2	-71	-18.4
Lassa fever can be prevented through?	331	86.0	54	14.0	277	71.9
Community ways of controlling Lassa fever?	261	67.8	124	32.2	137	35.6
How can Lassa fever spread?	117	30.4	268	69.6	-151	-39.2
What to do when Lassa fever is suspected?	180	46.8	205	53.2	-25	-6.4
Lassa fever can cause?	244	63.4	141	36.6	103	26.8
How long it takes signs and symptoms to manifest?	121	31.4	264	68.6	-143	-37.2

Fig. 2. Level of knowledge of respondents about Lassa fever.



good number of respondents do not hunt for rat or other rodents and do not also eat raw meat or even rodent. Half of the respondents sometimes assist friends and family members who are ill in their activities of daily living as all respondent have never assisted friends or family members who have Lassa fever. Not many always seek health care from the health facility promptly. Good and poor practice was determined by scoring the highest score to the most good practice response and a lowest score to the most poor practice, the general average of the total score was calculated to determine the cut-off score (2.5). The average scores of individual scores was also determined. Figure 4 shows the percentage level of Lassa fever preventive practices by the respondent (Score > 2.5 = negative practice; score ≥ 2.5 = positive practice).

Table VI Shows a cross tabulation of the socio-demographic characteristics of respondents and their knowledge about Lassa fever, results shows a significant relationship between age, gender, marital status, educational status, occupation and religion of respondents and their knowledge about Lassa fever (p-value = < 0.001, 0.042, < 0.001, 0.031, 0.039 and < 0.001 respectively).

Table VII shows the association between the socio demographic characteristics of respondents and their attitude toward Lassa fever disease, results shows a significant relationship between the respondents attitude, educational status and occupation of the respondents (p-value = < 0.001, < 0.001 and 0.049 respectively). No significant relationship was established between attitude and respondents gender, marital status and religion (p-value = 0.201, 0.131 and 0.501 respectively).

Table VIII shows a cross tabulation between knowledge and attitude and knowledge and practice of respondents about Lassa fever. Association was established between knowledge and attitude (p = 0.023) and knowledge and practice (p = 0.033).

Hypotheses Testing

In this study, two null Hypotheses were tested to determine which of the predictor variables produced greater influence on the outcome variable of knowledge and attitudes in the prevention of Lassa fever disease. Chi-square analysis was used in conducting this test at 0.05 level of significance. Decision rule applied was that if $p \leq 0.05$, then the Null Hypotheses will be rejected in favor of alternative hypotheses and if $p \geq 0.05$, then the Null Hypotheses will be accepted and the alternative rejected.

Ho: 1.

There is no significant relationship between knowledge and attitude of Lassa fever prevention among adults of Bali L.G.A in Taraba state

HA: 1.

As suggested by our results (see Table VIII) a significant relationship between knowledge and attitude of Lassa fever prevention among adults of Bali L.G.A in Taraba state was identified (p = 0.033)

Ho: 2.

There is no significant relationship between knowledge and practice of Lassa fever prevention among adults of Bali L.G.A in Taraba state.

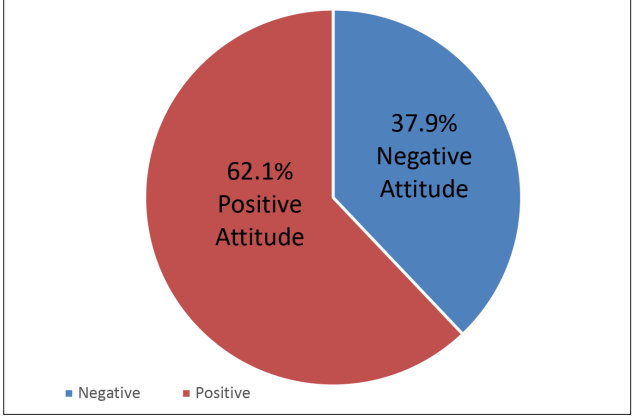
HA: 2.

Results from this study shown above, a p-value of 0.023 less than statistically significant differences at 0.05 level of significance. The null hypothesis is therefore rejected and the alternate hypothesis accepted. Therefore, we

Tab. IV. Distribution of Respondent based on attitude towards Lassa Fever Prevention.

Variables	Frequency (N)	Percent (%)
Anybody no matter the socio-economic status can be infected with Lassa fever		
Strongly Agree	127	33.0
Agree	127	33.0
Strongly disagree	30	7.8
Disagree	101	26.2
Total	385	100.0
Lassa fever is not as a result of spiritual attack		
Strongly Agree	114	29.6
Agree	129	33.5
Strongly disagree	45	11.7
Disagree	97	25.3
Total	385	100.0
Environmental sanitation limits the presence of rats in the Environment		
Strongly Agree	114	29.6
Agree	136	35.3
Strongly disagree	27	7.0
Disagree	108	28.1
Total	385	100.0
Absence of rat in the house is a preventive measure for Lassa fever		
Strongly Agree	114	29.6
Agree	129	33.5
Strongly disagree	45	11.7
Disagree	97	25.2
Total	385	100.0
Body fluid of anyone who is suffering from Lassa fever should be avoided		
Strongly Agree	116	30.1
Agree	132	34.3
Strongly disagree	30	7.8
Disagree	107	27.8
Total	385	100.0
Treatment of Lassa fever should be prompt to reduce the risk of death		
Strongly Agree	102	26.5
Agree	144	37.4
Strongly disagree	35	9.1
Disagree	104	27.0
Total	385	100.0
Lassa fever is not a death sentence		
Strongly Agree	113	29.4
Agree	130	33.8
Strongly disagree	45	11.7
Disagree	97	25.2
Total	385	100.0
Lassa fever should be managed in the health facility by trained health personnel		
Strongly Agree	114	29.6
Agree	129	33.5
Strongly disagree	45	11.7
Disagree	97	25.2
Total	385	100.0
Those who have Lassa fever should not be stigmatized		
Strongly Agree	103	26.8
Agree	144	37.4
Strongly disagree	42	10.9
Disagree	96	24.9
Total	385	100.0
Lassa fever is a very serious illness		
Strongly Agree	114	29.6
Agree	129	33.5
Strongly disagree	45	11.7
Disagree	97	25.2
Total	385	100.0

Fig. 3. Attitude Level of respondents about Lassa Fever.



conclude by saying there is a significant relationship between attitudes and the prevention/control of Lassa fever infection among adults of Bali L.G.A in Taraba state.

Discussion

Summary of main results

Various knowledge variables were used to test their knowledge of the subject matter. Such variables definition of Lassa fever causes of Lassa fever, transmission of Lassa fever, vectors of Lassa fever, incubation and signs/symptoms of Lassa fever. 48.3% of the respondents had a poor knowledge; few of them (26.5%) still had good knowledge of the subject under consideration. These findings are definitely not in line with a study carried out in Nigeria to determine the outbreak of Lassa fever disease [27, 36]. They observed from their study that most of the respondents had high knowledge about the Lassa fever infection especially urban settlers which has been able to help them to adopt some preventive measures against frequent outbreaks. Also NCDC, [38] noted get the fact, get the factual and correct information on Lassa fever from social media, radio, television and

Tab. V. Distribution of respondents by their practice.

Variables	Frequency (N)	Percent (%)
Safeguards your food items in the house		
Always	124	32.2
Never	131	34.0
Sometimes	130	33.8
Total	385	100.0
How can you safe guard your food items from rats		
Covering food items properly	126	32.7
Nothing	37	9.6
Rat poison	76	19.7
Using rat gum	103	26.8
Using rat trap	43	11.2
Total	385	100.0
How often do you carry out environmental sanitation		
Once a month	57	14.8
Once in a week	103	26.8
Once in three week	103	26.8
Once in two week	122	31.7
Total	385	100.0
How do you store your household refuse		
Covered container	225	58.4
Open container	57	14.8
Standard refuse bin	103	26.8
Total	385	100.0
Washes fruits thoroughly with water before eating		
Always	141	36.6
Never	51	13.2
Sometimes	193	50.1
Total	385	100.0
Why do you wash fruits thoroughly before eating		
	51	13.2
I do not wash fruits before eating	82	21.3
No reason	60	15.6
To kill germs that can cause disease	94	24.4
To make it look appetizing	98	25.5
Total	385	100.0

Tab. V (*follows*). Distribution of respondents by their practice.

Variables	Frequency (N)	Percent (%)
If you do not wash fruits thoroughly before eating,why		
	334	86.8
I wash fruits thoroughly before eating	12	3.1
It is not necessary to wash fruits before eating	16	4.2
No reason	9	2.3
Water is not available for washing	14	3.6
Total	385	100.0
Do you cook your food very well before eating		
Never	20	5.2
Always	65	16.9
Sometimes	300	77.9
Total	385	100.0
Why do you cook your food very well before eating		
I do not cook my food very well before eating	88	22.9
No reason	64	16.6
To kill germs that can cause disease	109	28.3
To make the food delicious	104	27.0
Total	385	100.0
Why don't you cook your food very well before eating		
I cook my food very well before eating	370	96.1
I enjoy food that is not cooked to tender	7	1.8
No reason	4	1.0
To save cooking fuel	4	1.0
Total	385	100.0
Washes your hands with soap and water or ash and water after visiting the toilet		
Always	164	42.6
Never	21	5.5
Sometimes	200	51.9
Total	385	100.0
Washes your hands with soap and water or ash and water before eating food		
Always	127	33.0
Never	38	9.9
Sometimes	220	57.1
Total	385	100.0
Washes your hands with soap and water or ash and water when you return home		
Always	127	33.0
Never	38	9.9
Sometimes	220	57.1
Total	385	100.0
Washes your hands with soap and water or ash and water after attending to a sick person		
Always	118	30.6
Never	38	9.9
Sometimes	229	59.5
Total	385	100.0
Washes your hands with soap and water or ash and water after handling dirt/garbage		
Always	107	27.8
Never	38	9.9
Sometimes	240	62.3
Total	385	100.0
How long does your single session of hand washing last		
	20	5.2
10-120 seconds and above seconds	78	20.3
15-19 seconds	6	1.6
20 seconds and above	109	28.3
5-9 seconds	82	21.3
Less than 5 seconds	90	23.4
Total	385	100.0

Tab. V (*follows*). Distribution of respondents by their practice.

Variables	Frequency (N)	Percent (%)
What do you use in drying your hands after washing		
Dryer	24	6.2
Hand towel	95	24.7
Handkerchief	100	26.0
Old clothes	79	20.5
Paper napkin	87	22.6
Total	385	100.0
Do you hunt for rats or other rodents?		
Always	31	8.1
Never	281	73.0
Sometimes	73	19.0
Total	385	100.0
Do you eat raw meat or other rodents?		
Never	306	79.5
Sometimes	79	20.5
Total	385	100.0
If you eat rat meat or other rodents, how do you prepare it for eating?		
	306	79.5
Boiling	21	5.5
Roasting	58	15.1
Total	385	100.0
Assists friends or family members who are ill in their activities of daily living?		
Always	141	36.6
Never	37	9.6
Sometimes	207	53.8
Total	385	100.0
Have assisted in caring for friends or family members who have Lassa fever?		
No	385	100.0
Will you assist in caring for a friend or a family member whom you are aware has lassa fever		
No	75	19.5
Yes	310	80.5
Total	385	100.0
Do you seek health care from the health facility promptly		
Always	83	21.6
Never	7	1.8
Sometimes	295	76.6
Total	385	100.0

Fig. 4. Level of Practice of respondents of Lassa fever prevention..

newspaper; be knowledgeable about how to response to outbreak. This helps minimize fear and will curtail the spread of the infection.

Various attitudes were identified from this study which may have effects on either the outbreak or the spread of Lassa fever disease in a given community. 62.1% of the respondents believed that they are at risk of developing the disease Lassa fever irrespective of their status, race, sex and religious background. This agrees with the findings of [4] in a study titled knowledge, attitudes and practices regarding Lassa fever disease among adults in endemic and non-endemic countries of Liberia. They find out that majority of the respondents in their study believed they are at risk of getting LF; with 52% (231/442) in the non-endemic counties. Also 63.1% of the respondents believed that the disease is not as a result of spiritual attack and that environmental sanitation can

Tab. VI. Association between socio-demographic characteristics and knowledge.

Variables		Knowledge			Total	X^2	p-value
		Good	Moderate	Poor			
Age	18–27	17(24.6)	14(20.3)	38(55.1)	69	445.668	< 0.001
	28–37	15(24.6)	14(23.0)	32(52.5)	61		
	38–47	22(26.8)	23(28.0)	37(45.1)	82		
	48–57	11(16.7)	15(22.7)	40(60.6)	66		
	58-67	21(36.8)	21(36.8)	15(26.3)	57		
	68-77	0(0.0)	1(100.0)	0(0.0)	1		
	78 and above	16(32.7)	9(18.4)	24(49.0)	49		
	Total	102	97	186	385		
Gender	Female	52(26.5)	41(20.9)	103(52.6)	196	625.793	0.042
	Male	50(26.5)	56(29.6)	83(43.9)	189		
	Total	102	97	186	385		
Marital Status	Divorced	3(21.4)	4(28.6)	7(50.0)	14	427.683	< 0.001
	Married	67(28.9)	55(23.7)	110(47.4)	232		
	Separated	9(28.1)	5(15.6)	18(56.3)	32		
	Single	16(19.8)	24(29.6)	41(50.0)	81		
	Widowed	7(26.9)	9(34.6)	10(38.5)	26		
	Total	102	97	186	385		
Educational Status	No formal education	20(25.3)	19(24.1)	40(50.6)	79	523.816	0.031
	Primary	26(31.3)	18(21.7)	39(47.0)	83		
	Secondary	37(24.0)	40(26.0)	77(50.0)	154		
	Tertiary	19(27.5)	20(29.0)	30(43.5)	69		
	Total	102	97	186	385		
Occupation	Applicant	4(21.1)	3(15.8)	12(63.2)	19	550.973	0.039
	Business/Trading	15(19.7)	21(27.6)	40(52.6)	76		
	Farming	29(23.2)	39(31.2)	57(45.6)	125		
	Public/CivilService	44(44.4)	17(17.2)	38(38.4)	99		
	Student	10(15.2)	17(25.8)	39(59.1)	66		
	Total	102	97	186	385		
Religion	Christianity	45(25.4)	43(24.3)	89(50.3)	177	421.790	< 0.001
	Islam	40(28.4)	36(25.5)	65(46.1)	141		
	Traditional worshiper	17(25.4)	18(26.9)	32(47.8)	67		
	Total	102	97	186	385		

greatly limit the occurrence of the disease [4]. However with the poor knowledge of Lassa fever observed among the studied group the overall preventive practices seems to be high 57.7%. Lassa fever preventive practices were also found to be low (45.2%) Findings of this study are in conformity with 51% poor practice toward Lassa fever in a descriptive survey research design done by Abdulkadir and Mohammed in North-Eastern part of Nigeria [22], but the result of the findings are in consistent with66.4% good preventive practices in a descriptive cross-sectional study design by Ossai *et al.*(2020) [23]. The differences in these results could be as a result of different available information about Lassa fever in the areas, and also the location of the study area towards exposure of information about Lassa fever. The study observed that high-risk behaviours and attitudes emanating from societal beliefs among community and households' members have been long associated with the transmission of infectious diseases.

Generalizability

Given the specific characteristics of the study population in Bali Local Government Area, the generalizability of the results may be restricted to similar communities in Taraba State due to comparable socio-economic characteristics. However, to assess the applicability of these findings more broadly, further research involving diverse population is recommended.

Limitation of the Study

On carrying this study, the researcher had limited scope, limited generalizability with different cultural norms and demographics,some of the respondent were reluctant and needed close guide in answering the questionnaire; it took the researcher extra time and effort to stay with respondents to ensure proper filling of the questionnaire.

Implication

The study is believed to have made impact towards informing health policies and strategies at state and national level to improve better surveillance system, community development which can lead to increased awareness towards better preventive practices, the findings of the research can also be used to develop training programs for health care providers in the

Tab. VII. Association between socio-demographic characteristics and attitude.

Variable		Attitude		Total	X^2	p-values
		Negative	Positive			
Age	18–27	29(42.0)	40(58.0)	69	551.618	< 0.001
	28–37	41(67.2)	20(32.8)	61		
	38–47	19(23.2)	63(76.8)	82		
	48–57	50(75.8)	16(24.2)	66		
	58-67	5(8.8)	52(91.2)	57		
	68-77	1(100.0)	0(0.0)	1		
	78 and above	1(2.0)	48(98.0)	49		
	Total	146	239	385		
Gender	Female	102(52.0)	94(48.0)	196	4579.69	0.201
	Male	44(23.3)	145(76.7)	189		
	Total	146	239	385		
Marital Status	Divorced	3(21.4)	11(78.6)	14	9306.36	0.131
	Married	91(39.2)	141(60.8)	232		
	Separated	17(53.1)	15(46.9)	32		
	Single	30(37.0)	51(63.0)	81		
	Widowed	5(19.2)	21(80.8)	26		
	Total	146	239	385		
Educational Status	No formal education	41(51.9)	38(48.1)	79	465.233	< 0.001
	Primary	25(30.1)	58(69.9)	83		
	Secondary	74(48.1)	80(51.9)	154		
	Tertiary	6(8.7)	63(91.3)	69		
	Total	146	239	385		
Occupation	Applicant	19(100.0)	0(0.0)	19	463.892[a]	0.049
	Business/Trading	22(28.9)	54(71.1)	76		
	Farming	36(28.8)	89(71.2)	125		
	Public/CivilService	42(42.4)	57(57.6)	99		
	Student	27(40.9)	39(59.1)	66		
	Total	146	239	385		
Religion	Christianity	82(46.3)	95(53.7)	177	43201.9[a]	0.501
	Islam	45(31.9)	96(68.1)	141		
	Traditional worshiper	19(28.4)	48(71.6)	67		
	Total	146	239	385		

Tab. VIII. Association of Knowledge, Attitude and Practice Towards Lassa Fever Prevention.

Variable		Knowledge			Total	X^2	p-value
		Good	Moderate	Poor			
Attitude	Negative	21(14.4)	43(29.5)	82(56.2)	146	6342.62	0.023
	Positive	81(33.9)	54(22.6)	104(43.5)	239		
	Total	102	97	186	385		
Practice	Good	59(26.6)	54(24.3)	109(49.1)	222	8646.21	0.033
	Poor	43(26.4)	43(26.4)	77(47.2)	163		
	Total	102	97	186	385		

state towards response to Lassa fever outbreak. It can be used for intervention that address and modify risk behaviors.

Conclusions

Lassa fever virus outbreak, a poverty-related infectious diseases outbreak remains a public health threat and burden on vulnerable populations in West Africa and Nigeria in particular. Robust and sustainable leadership commitment and investment of all stakeholders and affected communities in Lassa fever outbreaks prevention and containment is crucial and requires strengthening integrated Lassa fever outbreak surveillance quality data gathering to support evidence data sharing, contextual local and regional outbreak early warning alert, preparedness and response systems. Collaborative 'One Health' approach operational research is needed in understanding spatio-geographical risk factors patterns, reservoir(s) mapping and phylogenetic in guiding evidence-based, appropriately tailored, timely integrated programs, strategic interventions

and implementation against the zoonotic disease epidemics and pandemics threats in Nigeria. Moreover, fostering local community to regional re-merging and emerging epidemics and pandemics data sharing, coordinated invasive pathogens epidemiology surveillance and early warning indicators metrics capacity building, monitoring and evaluation is crucial for timely and quality risk communication and operational research.

Suggestion for Further Studies

Similar studies could be carried out in other LGA.A more elaborate research on environmental health education programmes should be undertaken to cover a wider geographical area of Taraba State.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest statement

We declare no conflict of interest.

Authors' contributions

CN: Concept. SI: Methodology. BN: Proof Reading. LI: Formatting. GA: Data collection.

References

[1] Adewuyi G M, Fowotade A, Adewuyi B T. Lassa Fever: Another Infectious Menace. Afr J Clin Exp Microbiol 2009;10:144-55. https://doi.org/10.4314/ajcem.v10i3.43407

[2] Blumberg L, Enria D, Bausch DG.Viral Haemorrhagic Fevers, In: Manson's Tropical Diseases. Saunders 2014.

[3] Dahmane A, van Griensven J, Van Herp M, Van den Bergh R, Nzomukunda Y, Prior J, Alders P, Jambai A, Zachariah R. Constraints in the diagnosis and treatment of Lassa Fever and the effect on mortality in hospitalized children and women with obstetric conditions in a rural district hospital in Sierra Leone. Trans R Soc Trop Med Hyg 2014;108:126-32. https://doi.org/10.1093/trstmh/tru009.

[4] Dolopei D, Amo-Addae M, Adewuyi P, Himiede W, Fulton S, Lawubah, Woods O, Gbearr O, Deodeh V.K, Sanley A, Kullie M.W, Tamatia G, Muyan J, Gbabow L, Bunnah T.G, Sackie A, Duo H, Leyhen D, Paye E, Phebe T. Knowledge, attitudes and practices (KAP) regarding Lassa fever disease among adults in endemic and non-endemic Counties of Liberia, 2018: A Cross-sectional study. J Interv Epidemiol Public Health 2021;4:9. https://doi.org/10.11604/JIEPH.supp.2021.4.1.1081.

[5] Ireye F, Ejiyere H, Aigbiremolen A O, Famiyesin O E, Rowland-Udoh E A, Ogeyemhe C O, Okudo I, Onimisi AB. Knowledge, Attitude and Infection Prevention and Control Practices Regarding Lassa Fever among Healthcare Workers in Edo State, Nigeria. Int J Prev Treat 2019;8:21-7 https://doi.org/10.5923/j.ijpt.20190801.03.

[6] Haas WH, Breuer T, Pfaff G, Schmitz H, Kohler P, Asper M. Imported Lassa fever in Germany: Surveillance and management of contact persons. Clin Infect Dis 2003;36:1254-7. https://doi.org/10.1086/374853.

[7] McCormick JB, Fisher-Hoch SP. Lassa fever. Curr Top Microbiol Immunol 2002;262:75-109. https://doi.org/10.1007/978-3-642-56029-3_4.

[8] Merson L, Bourner J, Jalloh S, Erber A, Salam AP, Flahault A, Olliaro PL. Clinical characterization of Lassa fever: A systematic review of clinical reports and research to inform clinical trial design. PLoSNegl Trop Dis 2021;15:e0009788. https://doi.org/10.1371/journal.pntd.0009788.

[9] Mofolorunsho K C. Outbreak of lassa fever in Nigeria: Measures for prevention and control. Pan African Medical Jorunal 2016;23(210). https://doi.org/10.11604/pamj.2016.23.210.

[10] Mylne AQ, Pigott DM, Longbottom J, Shearer F, Duda KA, Messina JP, Weiss DJ, Moyes CL, Golding N, Hay SI. Mapping the zoonotic niche of Lassa fever in Africa. Trans R Soc Trop Med Hyg 2015;109:483-92. https://doi.org/10.1093/trstmh/trv047.

[11] Nigeria Centre for Disease Control. Experts Meet to Discuss Lassa Fever Control. Wkly Epidemiol Rep 2017:1-12. Available at: http://www.ncdc.gov.ng/reports/weekly (Accessed on: 5/09/2017).

[12] Ogoina D. Lassa fever:A clinical and epidemiological review. Niger Delta Jorunal Medical Research 2015;1:16-22.

[13] Ogboghodo EO, Adam VY, Omuemu VO, Okojie OH. Knowledge, Attitude and Preventive Practices Against Lassa Fever Among Residents in a Rural Community in Southern Nigeria. West Afr J Med 2019;36:165-71.

[14] Richmond JK, Baglole DJ. Lassa fever: epidemiology, clinical features, and social consequences. BMJ 2003;327:1271-5. https://doi.org/10.1136/bmj.327.7426.1271.

[15] Tambo E, Ugwu EC, Ngogang JY. Need of surveillance response systems to combat Ebola outbreaks and other emerging infectious diseases in African countries. Infect Dis Poverty 2014;3:29. https://doi.org/10.1186/2049-9957-3-29.

[16] WHO. Clinical Management of Patients with Viral Haemorrhagic Fever: A Pocket Guide for the Front-line Health Worker. Interim Emergency Guidance-Generic Draft For West African Adaptation 2014. Available at: https://iris.who.int/bitstream/handle/10665/130883/WHO_HSE_PED_AIP_14.05.pdf?sequence=2 (Accessed on: 14/08/2023).

[17] WHO. Introduction to lassa fever managing infectious hazard 2015. Available at:https://cdn.who.int/media/docs/default-source/documents/emergencies/health-topics---lassa-fever/lassa-fever-introduction.pdf?sfvrsn=b1b96509_2&download=true (Accessed on: 01/7/2023).

[18] WHO.IMAI District Clinician Manual: Hospital Care for Adolescentsand Adults. Guidelines for the Management of Common Illnesses with Limited Resources 2011. Available at: http://

apps.who.int/iris/bitstream/10665/77751/1/9789241548281_Vol1_eng. pdf (Accessed on: 22/07/2023).

[19] WHO, NCDC. Technical Guidelines for Integrated Disease Surveillance and Response in Nigeria. Abuja; March 2013. Available at: https://ncdc.gov.ng/themes/common/docs/protocols/4_1476085948.pdf (Accessed on: 16/08/2023).

[20] WHO, CDC. Technical Guidelines for Integrated Disease Surveillance and Response in the African Region. Brazzaville and Atlanta 2010. Available at: https://www.afro.who.int/sites/default/files/2017-06/IDSR-Technical-Guidelines_Final_2010_0.pdf (Accessed on: 16/08/2023).

[21] World Health Organization. Lassa fever-Nigeria. Disease Outbreak News 2018. Availableat: http://www.who.int/csr/don/20-april-2018-lassa-fever-nigeria/en/ (Accessed on: 5/07/2023).

[22] Abdulkadir S, MohammedAS. Assessment of knowledge of Lassa fever among residents in North-Eastern Nigeria. Int J Health Scie Res 2019:197-202.

[23] Ossai, E.N., Onwe, O.E., Okeagu, N.P., Ugwuoru, A., Laura, Eze, T. K. &Nwede, A. S.Knowledge and preventive practices against Lassa fever among heads of households in Abakaliki metropolis Southeast Nigeria: A cross-sectional study. Proc Singap Healthc 2020;29:73-80. https://doi.org/10.1177/2010105819899120.

[24] Aigbiremolen AO, Duru CB, Awunor NS, Abejegah C, Abah SO, Asogun AD. Knowledge and application of infectious disease control measures among primary care workers in Nigeria: the Lassa fever example. Int J Basic, Appl Innov Res 2012;1:122-129.

[25] Akinwumi AA, Ademola AO, Oladimeji A E, Abiodun O C, Oghenevo A G, Adebola A O, Olarewaju O P, Olayinka AA, Ojo B F. Knowledge of Lassa fever among students of a college of education: Call for inclusion in curriculum. J Adv Med Med Res 2016;16;1-8. https://doi.org/10.9734/BJMMR/2016/26857.

[26] Akunne M O, Isah A, Anene-Okeke C G, Oguejiofor F A. Assessment of knowledge of Lassa fever infection among the undergraduate students of University of Nigeria, Nsukka, Enugu State, Nigeria. Int Res J Pharm Med Sci 2018;1:6-9. https://doi.org/10.5281/zenodo.2538556.

[27] Amoran O, Onwube O. Infection control and practice of standard precautions among healthcare workers in northern Nigeria. J Glob Infect Dis 2013;5;156-63. https://doi.org/10.4103/0974-777X.122010.

[28] Centers for Disease Control and Prevention (2019, January). Lassa fever. Available at: https://www.cdc.gov/vhf/lassa/index.html (Accessed on: 29/8/2023).

[29] Fidelis C, Olajolumo J. Assessment of the level of knowledge and universal cross-infection control practices against Lassa fever among health workers in Sokoto, Nigeria: A hospital survey during Lassa fever outbreak in Nigeria. Int J Adv Med Health Res 2018;5:57-65. https://doi.org/10.4103/IJAMR.IJAMR_11_18.

[30] Ighedosa SU., Asemota O, Aighewi IT., Odigie E A., Usifoh S F., Omorogbe C E., Asemota D O, Osaghae V G, Faboya T N E, Erahuyi O. Knowledge. Attitude and prevention practices of Lassa fever by staff of University of Benin, Benin City. Nigerian Soc Exp Biol J 2017;17:82-90.

[31] Nwonwu E U, Alo C, Una A F, Madubueze U C, Eze I, Eze N C, Ogbonnaya L U,Akamike I C.Knowledge of Lassa fever and its determinants among traders in Izzi community in south-east Nigeria. Arch Curr Res Int 2018;13;1-9. https://doi.org/10.9734/ACRI/2018/39904.

[32] Ossai EN, Onwe OE, Okeagu NP, Ugwuoru AL, Eze TK, Nwede AS. Knowledge and preventive practices against Lassa fever among heads of households in Abakaliki metropolis, Southeast Nigeria: a cross-sectional study. Proc Singap Healthc 2020;29:73-80. https://doi.org/10.1177/2010105819899120.

[33] Reuben C R, Gyar S D. Knowledge, attitudes and practices of Lassa fever in and around Lafia, central Nigeria. Int J Public Health Epidemiol Res 2016;2:14-19.

[34] Usifoh S F, Ighedosa S U, Aighewi I T, Asemota O D, Odigie E A, Faboya T. Impact of Lassa fever on the practice and consumption of stored food by University of Benin Community, in Benin City, Nigeria. J Community Med Prim Health Care. 2018;30:66-76.

[35] World Health Organization (2017, July). Lassa fever: Key fact. Available at:https://www.who.int/news-room/fact-sheets/detail/lassa-fever (Accessed on: 20/07/2023).

[36] World Health Organization. Lassa fever-Nigeria 2018. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/01-march-2018-lassa-fever-nigeria-en (Accessed on: 16/7/2023).

[37] Nigeria Center for Disease Control. Press release: NCDC reviews Lassa fever outbreak response amidst reducing number of cases 2019. Available at: https://ncdc.gov.ng/news/164/press-release%3A-ncdc-reviews-lassa-fever-outbreak-response-amidst-reducing-number-of-cases (Accessed on: 7/10/2023).

[38] Olayiwola J O,Bakarey A S. Epidemiological Trends of Lassa Fever Outbreaks and Insights for Future Control in Nigeria. Int J Trop Dis Health 2017;24:1-14. https://doi.org/10.9734/IJTDH/2017/32823.

[39] Kelly JD, Barrie MB, Ross RA, Temple BA, Moses LM, Bausch DG. Housing equity for health equity: a rights-based approach to the control of Lassa fever in post-war Sierra Leone. BMC Int Health Hum Rights 2013;2:2. https://doi.org/10.1186/1472-698X-13-2.

[40] Wogu JO. Mass media awareness campaign and the prevention of the spread of Lassa fever in the rural communities of Ebonyi State, Nigeria: Impact evaluation. J Public Health Afr 2018 21;9:882. https://doi.org/10.4081/jphia.2018.882.

[41] Usuwa IS, Akpa CO, Umeokonkwo CD, Umoke M, Oguanuo CS, Olorukooba AA, Bamgboye E, Balogun MS. Knowledge and risk perception towards Lassa fever infection among residents of affected communities in Ebonyi State, Nigeria: implications for risk communication. BMC Public Health 2020;20:217. https://doi.org/10.1186/s12889-020-8299-3.

[42] Lecompte E, Fichet-Calvet E, Daffis S, Koulémou K, Sylla O, Kourouma F, Doré A, Soropogui B, Aniskin V, Allali B, Kouassi Kan S, Lalis A, Koivogui L, Günther S, Denys C, terMeulen J. Mastomysnatalensis and Lassa fever, West Africa. Emerg Infect Dis 2006;12:1971-4. https://doi.org/10.3201/eid1212.060812.

[43] Muanya, C. Poor hygiene,poverty, ignorance fuel Lassa Fever epidemic in Nigeria. The Guardian 2016. Available at: http://guardian.ng/sunday-magazine/poor-hygiene-poverty-ignorance-fuel-lassa-fever-epidemic-in-nigeria/ (Accessed on: 19/10/2023).

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Infectious disease

Trend of pathogens and respiratory co-infections in the province of Messina: from pediatric age to senescence

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Keywords

RSV • Surveillance • Adults • Elderly • SARS-CoV-2 • Flu

Summary

Acute respiratory infections (ARI) are a leading cause of global morbidity and mortality and they're primarily caused by viruses such as rhinovirus, coronavirus, and respiratory syncytial virus (RSV), and to a lesser extent by bacteria like Streptococcus pneumoniae and Mycoplasma pneumoniae. The study examines the impact of COVID-19 control measures on the circulation of respiratory pathogens, indicating a reduction in infections during the pandemic period. A retrospective study was conducted on 1,286 patients at the "G. Martino" University Hospital of Messina to evaluate the prevalence of respiratory pathogens. The results showed that SARS-CoV-2, rhinovirus, and RSV are the most frequently isolated pathogens, with a clear seasonality from December to March. Co-infections were detected in 14.1% of cases, predominantly in young children. The study suggests the need for enhanced surveillance strategies to improve the management of respiratory infections and healthcare resources.

Introduction

Acute respiratory tract infections (ARI) are a leading cause of morbidity and mortality globally. They are responsible, particularly in the winter months, for the high number of accesses to the emergency department, hospital admissions, and the prescription of antibiotics [1].

According to the GBD (Global Burden of Disease, Injuries, Risk Factors Study) in 2019 globally, there were 17.2 billion cases of upper respiratory tract infections, with around 10,000 related deaths. It is the sixth leading cause of death for all ages and the main one among children under the age of 5 years old [2].

In the USA there are an estimated 180,000 cases of hospitalization every year with around 14,000 deaths in people over 65 years of age [2].

The causes can be viruses and bacteria and it isn't possible to estimate the real rate of these infections in the light of the purely clinical and non-laboratory diagnosis; nevertheless, according to recent estimates, respiratory infections caused by viruses are around 70% of bacterial ones are around 8%. In the context of viral etiology, according to the same data, *rhinovirus* and *coronavirus* would be responsible for 48% of all Acute Respiratory Failure [3].

In the bacteriological field, the percentage of ARI caused by bacterial agents ranges from 5% to 10%, and the most frequently recurring pathogens were: *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae and Chlamydia pneumoniae* [3].

In the previous season (2022-2023), the ERVISS surveillance network (Synthesis of European Surveillance on Respiratory Viruses) recorded respiratory diseases increase after the summer season, especially after September. In particular, the SARS-CoV-2 trend was characterized by an initial increase up to week 49, followed by a decrease that persists and the COVID-19 severe form has predominantly impacted individuals aged 65 and older. Regarding influenza, week 50 marked the start of the seasonal epidemic in European countries; both type A and type B influenza viruses have been detected, with a higher prevalence of A(H1N1) pdm09 virus in most countries. Unlike previous pathogens, *Respiratory Syncytial Virus* (*RSV)* activity began to increase around week 41, reaching a peak in week 50 followed by a decreasing trend and a greater impact among children aged between 0 and 4 years [4].

In Italy, in December 2023 it has been introduced a new integrated surveillance system (epidemiological and virological) called RespiVirNet represented the evolution of the Influnet and Influweb systems and has been launched to track and potentiate the isolation of viruses linked to influenza-like illnesses (ILIs, defined by the sudden and rapid onset of at least one general symptoms like fever or low-grade fever, malaise/exhaustion, headache, muscle pain and at least one of the respiratory symptoms such as cough, sore throat, labored breathing) and generally of all respiratory viruses. This system, based on general practitioners, pediatricians,

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and regional reference laboratories for respiratory viruses and coordinated by "Istituto Superiore di Sanità" (ISS) with the support of the Italian Ministry of Health, carried out dual surveillance, both epidemiological and the virological. In the latest Influnet report relating to the 2022-23 season, which is the period examined in our study, 27857 clinical samples were collected by the various laboratories with 22.4% (n= 6244) testing positive for the influenza virus (2% type A and 19.8% type B), 6.5% tested positive for SARS-CoV-2, and 21.8% for other respiratory viruses, mostly *RSV* (11.5%) and *Rhinovirus* (about 6%).

As of the time of this writing, the latest available RespiVirNet report is updated to the 4th of February 2024. Among 2781 samples received by laboratories connected to this network, 379 (13.6%) were found positive for *RSV*, 66 (2.3%) for SARS-CoV-2, and 95 (3.41%) for *Rhinoviruses*. Co-circulation of different respiratory viruses contributes to defining the incidence value of ILIs (8,53 cases for 1000 inhabitants); among them, the most prevalent ones were influenza viruses, RSV, SARS-CoV-2, and Rhinoviruses [5].

Every patient admitted to the ICU and/or subjected to ECMO, whose symptoms suggest a case of SARI or ARDS, must be reported via the notification form.

In particular, the definition of SARI (Severe Acute Respiratory Infection) provides hospitalized patient of any age with at least one respiratory sign or symptom (cough, sore throat, respiratory distress) present at the time of admission or in the 48 hours following admission to hospital and at least one systemic sign or symptom (fever or low-grade fever, headache, myalgia, general malaise) or deterioration of general conditions (asthenia, weight loss, anorexia or confusion and dizziness). The definition of ARDS, however, is based on the presence of hospitalized patient of any age with an inflammatory pulmonary syndrome, characterized by diffuse alveolar lesions and increased permeability of the pulmonary capillaries, with non-cardiac pulmonary edema, reduction of pulmonary compliance and bilateral pulmonary infiltrates spread to all segments, severe dyspnea, tachypnea, and cyanosis, despite the administration of oxygen [6].

Microorganisms' epidemiology and clinic

Adenovirus

More than 50 types of Adenoviruses are known to cause infections in humans. These viruses can affect different districts, such as the gastrointestinal (causing acute gastroenteritis) or ocular (causing conjunctivitis); when it affects the respiratory tree, the virus causes ILIs, up to and including bronchitis and pneumonia in severe cases. These infections occur with a seasonality most frequently in winter and spring, affecting the general population at every age group [7].

According to the RespiVirNet report 2024-14, Adenoviridae account for 6.1% of all identified ILIs not attributable to influenza viruses [8].

Human coronaviruses

As of today, seven human coronaviruses have been identified: four of them (229E, NL63, OC43, HKU1) cause an infection with symptoms ranging between the common cold and pneumonia/bronchiolitis; two of them (SARS-CoV-1 and SARS-CoV-2) are responsible for severe respiratory infections with very high transmissibility, and were responsible for the SARS epidemic in 2002-2004 and the COVID-19 pandemic in 2020-2023; the last one (MERS-CoV) causes respiratory ailments very similar to SARS, while transmissibility is influenced by interactions with diseased animals [9].

RespiVirNet 2023-2024 reports distinguish SARS-CoV-2 from other human coronaviruses: the prevalence of these, among the non-influenza viruses responsible for respiratory disorders, was quantified as 26.6% and 5.9%, respectively [8].

Human Metapneumovirus

The *Human Metapneumovirus* (HMPV) was discovered in 2001 and belongs to the *Pneumoviridae* family together with RSV. The symptoms caused by this virus are similar to those of other respiratory viruses, causing affections of the lower and upper respiratory tract, possibly leading to bronchitis or pneumonia. Its circulation is seasonal, occurring in winter and maintaining a detected infection rate until spring [10].

As reported in RespiVirNet's weekly report 2024-14, *Metapneumovirus* accounted for 6.9% of all 14,399 non-influenza respiratory virus identifications from week 2023-46 [8].

Rhinovirus

Rhinoviruses cause 30-35% of adult ILIs and represent the most common cause of Upper Respiratory Tract Infections (common colds), especially in school-age children, in whom 6-8 episodes may occur during the year. Nowadays more than 110 types of Rhinovirus have been identified with different antigenic properties and this great variety of viral antigens is responsible for the frequent recurrence of the infection. The most widespread transmission is via large airborne droplets, but transmission via small aerosolized particles has also been demonstrated. It is estimated that an infected patient is capable of infecting 75% of the members of a family or school group. Rhinovirus epidemics have been documented in indoor environments (such as schools, long-term care facilities, hospitals, neonatal healthcare facilities) and these pathogens are most active in the fall, spring, and summer, with an optimal temperature of 33°C (equal to that of the nasal mucosa) [11-14].

Influenza viruses

Seasonal influenza is a vaccine-preventable disease that each year infects approximately 10-30% of the European population and causes hundreds of thousands of hospitalizations across Europe.

Epidemics occur in the winter months in temperate locations and at different periods of the year in subtropical

and tropical locations. Most influenza virus infections cause mild and self-limiting disease and around one-half of all infections occur with a fever. Older people, younger children, and those with chronic diseases have a greater risk of developing serious complications, such as pneumonia, myocarditis, and encephalitis that may result in death.

Four different types have been identified, all belonging to the *Orthomixoviridae* family:

- types A and B, responsible for classic flu symptoms;
- type C, usually asymptomatic;
- type D, whose possibility of infecting humans is not yet clear.

Influenza A viruses are further divided into subtypes based on molecular differences of the two surface glycoproteins (hemagglutinin and neuraminidase).

The typical influenza epidemiology arises from the marked tendency of influenza viruses to mutate (essentially with two mechanisms: antigenic drift and antigenic shift). This characteristic allows them to evade the host's immune response and therefore make the population more immunologically susceptible and for these reasons, the pathogens spread widely and rapidly.

These molecular variations are an important factor in the preparation of vaccines, whose composition must be updated every year, and, in this light, the surveillance activities are fundamental to selecting the specific strains to be included taking into account what has circulated in previous seasons.

According to the ECDC report the 2022/2023 influenza season marked the return of influenza virus activity at almost pre-pandemic levels in the EU/EEA countries. This season was characterized by an earlier start of the seasonal epidemic and an earlier peak in positivity compared to the four previous seasons [15-17].

Parainfluenza viruses

Parainfluenza viruses belong to the family *Paramyxoviridae* and they can infect terrestrial animals, aquatic mammals, birds, and some reptiles; they, also, include several viruses pathogenic to the human respiratory tract, similar in some aspects to influenza viruses. They differed from them in surface antigen characteristics and size. *Human parainfluenza viruses (hPIV)* are antigenically distinguished into 5 types: 1, 2, 3, 4A, and 4B. All of them cause respiratory infections in humans, although with different epidemiology and clinical picture [18]. *hPIV 1, 2*, and *3* are more prevalent than type *4*; in particular, *hPIV 1* and *2* are associated with "croup" (laryngotracheobronchitis) and upper and lower respiratory disease, while *hPIV 3* causes more bronchiolitis and pneumonia.

Parainfluenza viruses are ubiquitous, and they can infect adults, but the most affect children, in whom the virus results in more severe symptomatology (bronchiolitis, bronchitis, pneumonia). hPIVs, particularly serotype 3, are, after respiratory syncytial virus, the second cause of lower respiratory tract infections in newborns and infants [19, 20]. Forty-one percent of croup cases were associated with these viruses [19]; especially hPIV 1 and hPIV 2 (in lower percentage than type 1) were the most involved. Infection occurs early in life, and serologic data indicate that 50% of one-year-old children and 90% at 5 years have protective antibodies to hPIV 3, 75% to hPIV 1, 60% to hPIV 2, and 50% to hPIV 4 [18, 19]. The seasonality of infections differs according to serotype: hPIV 1 and 2 cause epidemics during autumn and winter; however, episodes of overlapping epidemics caused by the hPIV 1 and hPIV 2 subtypes are possible; hPIV 3 cause sporadic infections throughout the year with a peak in spring; hPIV 4 is present throughout the year but is infrequent and doesn't cause relevant symptoms. Clinically, parainfluenza viruses result in a broad spectrum of lower and upper respiratory tract symptoms: croup, bronchitis, and bronchiolitis were the most common symptoms in children, in addition to cases of coryza, otitis, and pneumonia. In non-immunocompromised adults, on the other hand, parainfluenza viruses lead to simple colds or rhinolaryngitis.

Chlamydia pneumoniae

This intracellular bacterium is a recognized cause of community-acquired pneumonia [21] and it has also been documented in patients with cystic fibrosis [22]. Recent studies have also linked *C. pneumoniae* to bronchitis and asthma [23]. Higher rates of infection were recorded in children compared to adults [24].

The spread of *C. pneumoniae* occurs through direct contact with an airborne transmission or indirectly through fomites [25].

There is currently a resurgence of *C. pneumoniae* infections, after an initial reduction in rates recorded during the SARS-CoV-2 pandemic [26].

Much *C. pneumoniae* infections go unrecognized because they typically manifest as upper respiratory tract infections, often with mild or no symptoms. There isn't typically a discernible seasonal pattern, and outbreaks tend to occur predominantly in crowded environments such as college residence halls and long-term care settings.

Bordetella pertussis and parapertussis

These pathogens cause respectively parapertussis and pertussis (whooping cough), which are highly infectious bacterial diseases involving the respiratory tract whose symptoms are like those of the common cold, including sneezing, runny nose, low-grade fever, and cough with different clinical evolution. Parapertussis is characterized by mild signs and symptoms.

Pertussis, notifiable in Italy, is characterized by epidemic cycles recurring every 2-5 years and represents a public health threat, given its re-emergence despite high vaccination coverage (94% in Italy among children of 24 months old in September 2022) [27, 28].

This resurgence may be attributed to several factors such as improved diagnosis methods, genetic changes in circulating BP, and increased bacterial circulation among adolescents and adults related to the waning of vaccine-induced immunity. Adolescents and adults

are a reservoir for BP and the source of infection to unvaccinated newborns [29].
Furthermore, naïve children represent the most vulnerable group; in fact, literature detected the highest rates of morbidity and complications, such as hospitalization and intensive care unit (ICU) admissions and, consequently mortality. On the other hand, adolescents and adults tend to have a prolonged illness characterized by cough but without other severe symptoms [30].
The greatest disease burden was observed in the paediatric population, linked to the non-immunization or incomplete immunization during the first month of age. In fact, in California, during the 2010 outbreak, the highest rates of disease and hospitalization occurred in infants < 6 months old [28,31]; in the UK, during the 2011-2012 outbreak, the highest incidence and mortality occurred in infants < 3 months old [32].
The pertussis incidence rate in the Italian population aged ≥ 5 years old reported by the ECDC in 2018 was 6.75 per 100,000 in the 5-14 age group and 0.28 per 100,000 in the ≥ 15 age group. In newborns and infants, *Bordetella pertussis* can cause or complicate bronchiolitis; in particular, bronchiolitis-associated morbidity and mortality are higher with concomitant *B. pertussis* infection. However, to date, the pertussis mortality rate in this age group is likely underestimated [33].
According to the systematic review by Macina et al., some comorbidities might increase the risk of developing pertussis. Three studies showed pertussis can lead to increased exacerbations of chronic conditions/illnesses and associated hospitalizations, although one study showed a reduction in the effects of chronic bronchitis. Previous pertussis seemed to contribute to the increased likelihood of developing some respiratory conditions like asthma, and conversely, people with asthma or COPD are at increased risk of severe pertussis requiring further interventions [34].
History of prematurity and an age of less than 3 months emerged as risk factors for the development of fatal pertussis [35].

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of respiratory tract infections, representing community-acquired pneumonia as the major disease-related burden. Infections occur year-round in many different climates worldwide, with epidemics every few years.
The periodic occurrence of epidemics is due to many factors, including the decline of herd immunity or the introduction of new subtypes into the population. The most recent outbreak occurred in late 2019 and early 2020 simultaneously in several countries, predominantly in Europe and Asia. According to previous data the interval between *M. pneumoniae* epidemics in Europe was about 1-3 years.
In 2020 the introduction of non-pharmaceutical interventions (NPIs) against COVID-19 resulted in an abrupt ending of these epidemics and a marked decline in *M. pneumoniae* detection worldwide. In detail, there was a significant reduction in the incidence of *M. pneumoniae* from the pre-pandemic period to the first year after the implementation of NPIs (from 8.61% in 2017-20 to 1.69% in 2020-21), with similar values to the other respiratory pathogens incidence. This value decreased significantly in the second year (0.70%, in 2021-22), when other respiratory pathogens re-emerged as an indicator of community transmission [26].

Respiratory syncytial virus

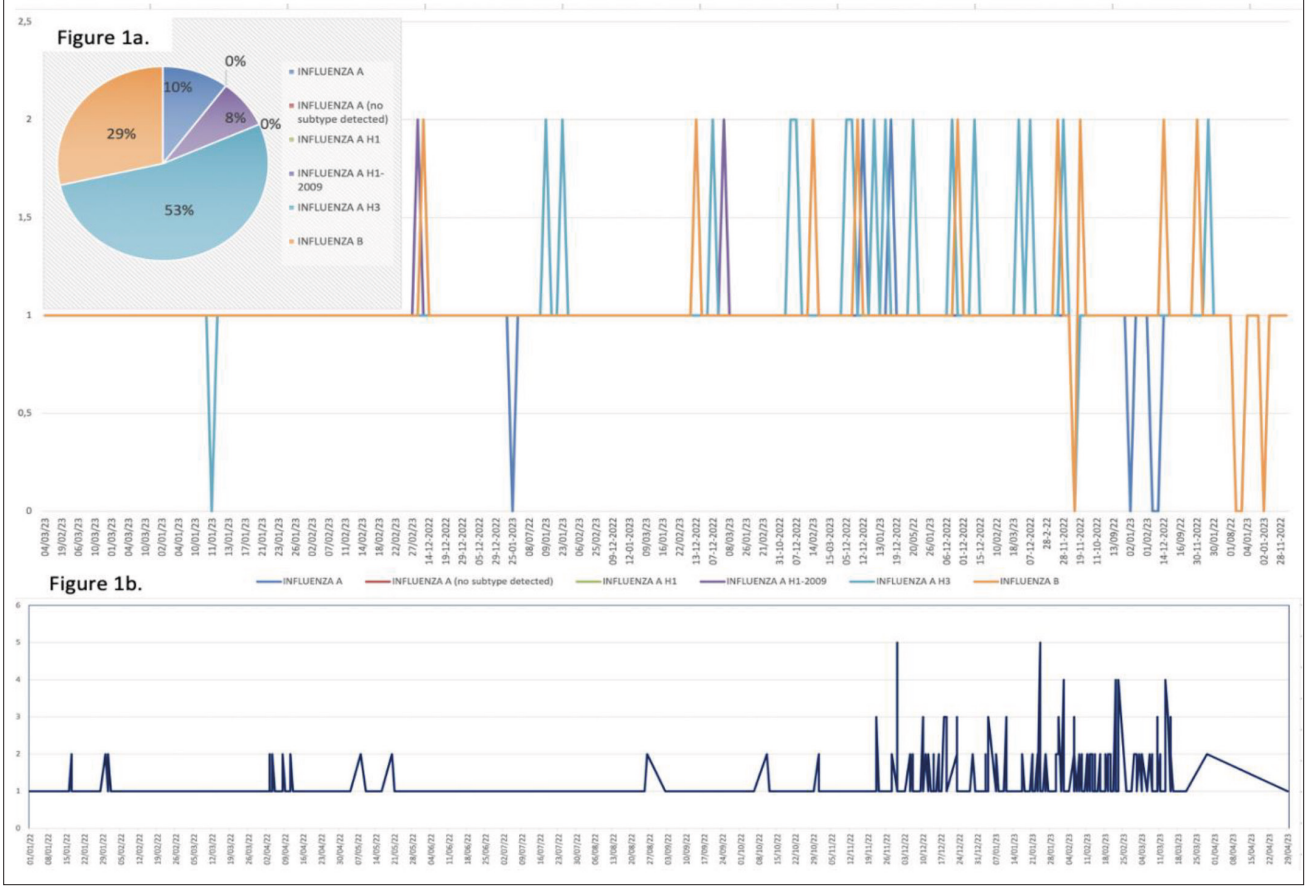
Respiratory syncytial virus is a RNA virus and, until today, two subtypes are recognized, A and B: the first most related to more severe infections and the second one prevalent in pediatric age (10). RSV infection is typically seasonal, with viral circulation typically occurring in the winter period, peaking between December and February [36].
RSV infection generally causes a mild disease, but the severity of the clinical manifestations varies considerably based on age. The most severe forms of the disease are associated with the pediatric age and occur in children under five years of age (especially in infants younger than six months), adults aged 65 years and older and individuals with specific comorbidities [37].
RSV represents the second cause of death globally after malaria, the first cause of death among respiratory infections and the first cause of hospitalization in children under one year of age [38].
Premature infants or those born close to RSV season and/or with bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe acute RSV and related lower respiratory tract infection (LRTI) [39]. Natural infection provides short-lasting immunity, so cases of reinfection are common, particularly those of the upper respiratory tract [40].
Nowadays there are no specific therapies for the treatment of serious RSV infections and the only authorized drug (ribavirin) is complex to manage due to safety issues of use [41].
Therefore, the treatment of severe forms of LRTI is more often limited to symptomatic therapies and supportive measures (hydration and oxygen); a fundamental role is played by primary prevention, given by hygienic-behavioral measures, such as the correct application of hand hygiene, sanitization, social distancing, and the use of monoclonal Abs such as Palivizumab (SYNAGIS) and Nirsevimab (BEYFORTUS) [42]. The first one was the only weapon available for the prevention of RSV infections until the end of 2022, but its indications were limited to children under 24 months of age who had certain conditions that exposed them to a high risk of severe RSV disease (such as ≤ 35 weeks of gestational age and with age < 6 months at the start of the seasonal RSV epidemic; age < 2 years treated in the last 6 months for broncho-pulmonary dysplasia; age < 2 years with hemodynamically significant congenital heart disease) [43].
Furthermore, one dose of Palivizumab provides protection that lasts approximately 1 month, making up to 5 doses of the drug necessary per season, with evident

problems of complete adherence to the prescribed regimen and costs. The use of this monoclonal antibody for the protection of all newborns therefore clashes with insoluble organizational and economic problems [44].
In February 2023, a new monoclonal antibody, Nirsevimab (Beyfortus), was definitively approved by the European Medical Agency (EMA), which has advantages such as a long half-life (protection demonstrated for at least 5 months) and a schedule that involves a single administration (increased compliance). This medication is recommended for all infants younger than 8 months and born during – or at the beginning of – their first RSV season (typically fall to spring) and for some infants aged 8 to 19 months who are at high risk for severe RSV (severely immunocompromised or entering the second RSV season) [45].
Thanks to the availability of Nirsevimab, a universal prevention strategy for RSV diseases appears possible through administration to all cohorts of newborns in the October-March epidemic period, before hospital discharge and the catch-up of non-immunized newborns in the April-September period [46].
Another possible future preventive strategy could be the active immunization, using two prefusion F protein-based recombinant vaccines recently approved by the EMA to prevent LRTI in subjects over 60 years of age [47, 48].
The first authorized preparation (June 2023) (RSVPreF3 OA) is an adjuvanted RSV vaccine containing recombinant respiratory syncytial virus F glycoprotein stabilized in the pre-fusion conformation (RSVPreF3) as the antigenic component. From data in the literature, it emerged that single administration of the vaccine shows a satisfactory safety profile, with an efficacy of approximately 94.1% against severe RSV-related lower respiratory tract disease and 71.7% against RSV-related acute respiratory infection, regardless of RSV subtype and the presence of underlying coexisting conditions [47].
The second authorized preparation (EMA August 2023) is a bivalent vaccine, containing balanced quantities of stabilized prefusion (preF) antigens derived from the two primary subgroups of RSV (RSV A and RSV B), which demonstrated 67% effectiveness in reducing the likelihood of developing RSV-associated lower respiratory tract disease (LRTD) among older adults with two or more symptoms and 86% in reducing the risk of RSV-associated LRTD among individuals with three or more symptoms [48].
This vaccine could be also indicated in mothers during pregnancy (between weeks 24 and 36 of gestation) to protect their children from LRTI (from birth to 6 months of age) [49].
In the final weeks of 2022, the circulation of respiratory syncytial virus (RSV) in the EU intensified, with transmission rates increasing in all population groups and an earlier onset than the usual one [50].
Several EU countries have reported high circulation of RSV and an increase in the number of severe acute respiratory infections (SARI) due to it [50].
Given the growing circulation of RSV and the shortage of available weapons, the ECDC has identified the implementation of surveillance and monitoring systems as one of its priority objectives wherever possible.]. In particular, the specific objectives of the study were to evaluate the circulation of respiratory pathogens in our reality which required hospitalization or access to the emergency/urgency system [50]; we hypothesized that the pandemic period made an important contribution to the epidemiology of respiratory pathogens and we would like to evaluate it.

Methods

A retrospective and monocentric study was conducted, thanks to the collaboration between the Hospital Hygiene Unit and the Microbiology Unit of the University Hospital "G. Martino" of Messina; this study analyzed the prevalence of the various respiratory pathogens found in a cohort of 1286 patients belonging to the several units of our hospital from January 2022 to May 2023 and who carried out a nasopharyngeal swab subsequently analyzed using FilmArray (Biofire RP2.1 by Biomerieux which detects the presence of 19 viruses (*Adenovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A/H1, Influenza A/H1-2009, Influenza A/H3, Influenza B, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Respiratory Syncytial Virus*, SARS-CoV-2 (2019-nCoV), MERS-CoV) and 4 bacteria (*Bordetella pertussis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Bordetella parapertussis*). This test allowed the qualitative detection of the nucleic acid of viruses and bacteria in nasopharyngeal swab samples; it is an integrated platform that combines automated sample preparation, total nucleic acid extraction with nested multiplex PCR and reverse transcriptase PCR, and automatic detection of amplified targets. The FilmArray test used in this study has a sensitivity of 95% and a specificity of 98% for detecting respiratory pathogens and we choose it for this reason respect to other methods.
Inclusion criteria: participants were included if they met the following criteria: they were 18 years or older, undergoing nasopharyngeal swabs, and were able and willing to provide informed consent.
We choice the FilmArray (Biofire RP2.1 by Biomerieux) platform for pathogen detection because it enables simplified test ordering, faster turnaround times, and increased accuracy by minimizing manual data entry.
The data were collected in a structured database. The qualitative data were expressed as absolute and relative frequencies, while the quantitative data were expressed as mean, minimum, maximum, and standard deviation values. The results were stratified according to age, gender, and the number of possibly coexisting pathogens. Furthermore, the temporal trend of the various pathogens in the years under examination was analyzed. Statistical analysis was conducted using Stata software. The

Fig. 1. Seasonality and trend in the number of infections by month for Influenza viruses (Fig. 1a) and RSV (Fig. 1b).



number of co-infections was investigated by stratifying the sample by age and sex. Seasonal trends of each pathogen were also evaluated. Statistical differences in the prevalence of positive samples among pediatric, adult, and elderly patients were assessed."

Results

Our sample consisted of 1286 individuals, aged between 1 month and 99 years (mean age 52.45 ± SD 30.89). The sample was predominantly male (53.92%).

The most frequently isolated pathogens were:

- SARS-CoV-2 (13.76%), is more frequent in males aged between 1 and 17 years;
- Human Rhinovirus (11.35%), is more frequent in males aged between 0 and 16 years;
- RSV (9.10%), is more frequent in patients aged between 0 and 14 years, with equal distribution between genders.

The seasonal trend of each pathogen was also evaluated. For two of the most frequently found pathogens in our sample, *Human Rhinovirus* and *RSV*, the typical seasonality of respiratory viruses was observed, with the highest number of cases occurring from December to March. The trend observed in previous years was also confirmed for SARS-CoV-2.

The infection trends over the two years were analyzed, as shown in Figure 1.

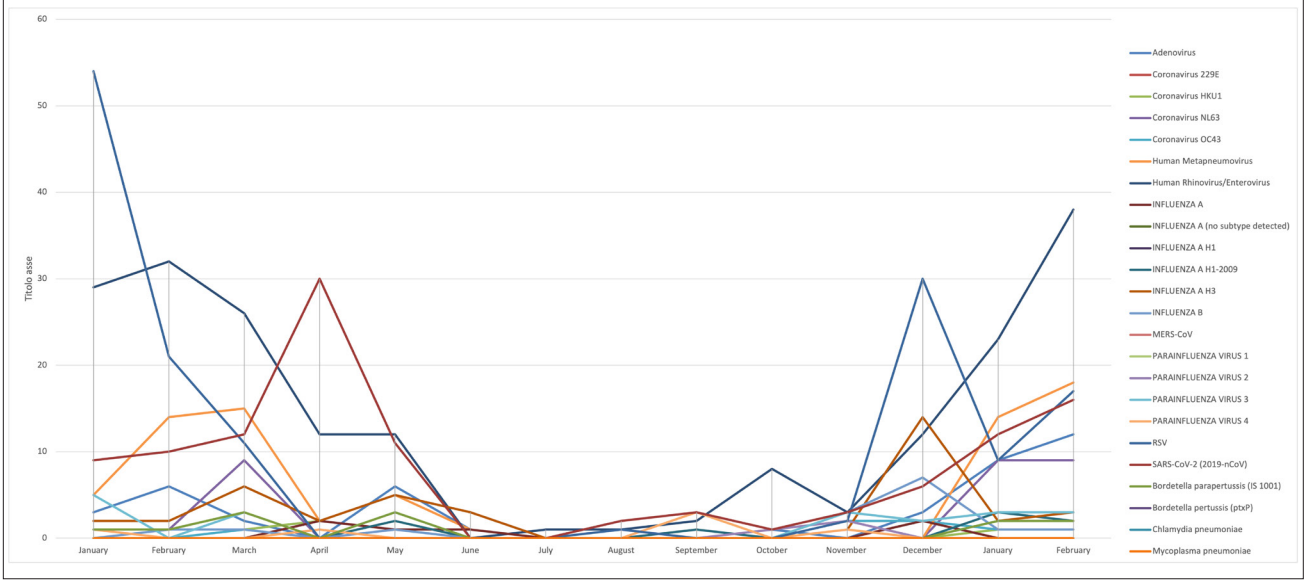
The use of masks and the implementation of isolation and prevention measures to avoid the spread of SARS-CoV-2 led to a reduction in the number of infections.

We also evaluated the presence of statistical differences in the prevalence of positive samples among pediatric, adult, and elderly patients. Significant statistical differences were found (p value = 0.001), with higher prevalence of SARS-CoV-2 in elderly and pediatric patients, and higher prevalence of RSV only in pediatric groups (Tab. I).

Tab. I. Respiratory virus prevalence by age groups.

Age groups	SARS-CoV-2	RSV	Rhinovirus	p value
< 14 years old	5,06%	82,26%	63,52%	0.001
15-64 years old	38,20%	4,84%	20,13%	
>64 years old	56,74%	12,90%	16,35%	

Fig. 2. Seasonality and trend in the number of infections by months for all respiratory pathogens investigated.



The highest percentage of RSV infections was found in the winter period, with an early peak in November (Figs. 1b, 2).

Another data to highlight was the presence of a high prevalence for some bacteria such as *Bordetella parapertussis*, especially in children under 2 years of age (66.67%). No detection of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* was found with an emerging role of *RSV* infection in determining cases of bronchiolitis and pneumonia.

In 14.1% of cases, co-infections were found, predominantly affecting both sexes in the 0-4-year age group. Notably, two patients had five pathogens isolated simultaneously. Furthermore, the number of co-infections was investigated by stratifying the sample by age and sex. From the analysis of the data, it can be seen that the highest percentage of co-infections was detected in the male sex and the age period between 1 and 4 years (mean age = 2.65 ± 2.5 SD; 66% male sex).

The temporal trend of co-infections was also analyzed, with a major peak recorded from November 2022 to March 2023 (see Fig. 3). We detected a value of about 14% of coinfection, especially in pediatric patients (0-4 years); the most frequent coinfection were SARS-CoV-2, RSV, and Rhinovirus.

Discussion

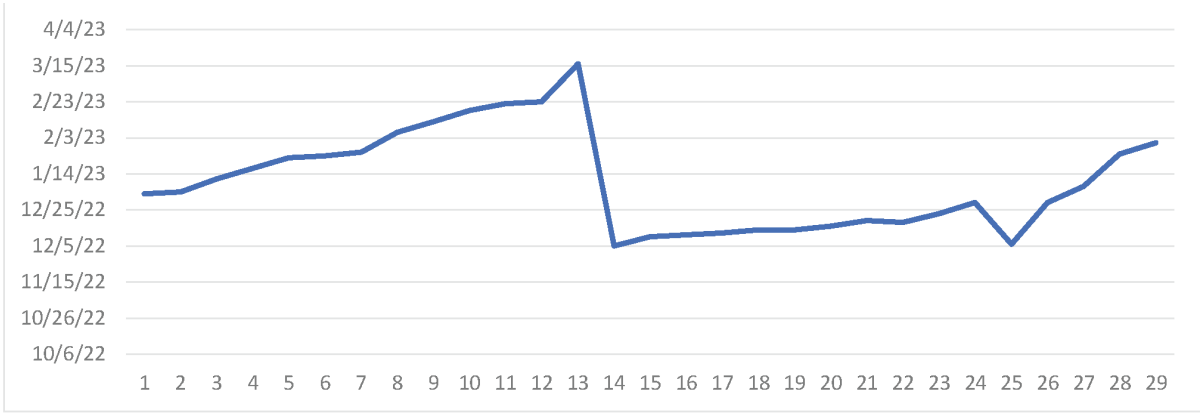
In agreement with national data, our analyses have revealed a greater circulation of the Respiratory Syncytial Virus [5, 11-14]. In our study RSV was the most frequently isolated virus after SARS-CoV-2, influenza A H1N1 virus, and rhinoviruses. Viral and bacterial co-infections were observed in 14.1% of cases, predominantly in children aged 0-4 years. Further studies are needed to understand the interaction between different pathogens and their impact on disease severity." However, these data confirm some recent studies, according to a recent systematic review of the literature in which the authors found 35-40% of pediatric subjects affected. The role of viral-coinfections remained unclear in the severity of RSV-associated respiratory diseases, but several systematic reviews suggested that there isn't an association between disease severity and viral co-infections [51].

In our study, among the epidemiological characteristics, a greater prevalence emerged in the male sex as reported by other authors [52, 53]. However, other studies in the literature have reported a higher prevalence in females [54]. Other epidemiological factors investigated were age and seasonality. The greater prevalence was detected in younger patients, confirming available national data about an higher prevalence in patients under 5 years of age, especially in the presence of comorbidities (*i.e.* bronchopulmonary dysplasia and congenital heart disease, low birth weight) and/or risk factors (preterm birth, artificial breastfeeding, *etc.*). However, older adults and people living with underlying diseases are known to be at a higher risk of respiratory infections, RSV and flu [55]. The peak of the RSV in November that we detected correlates with a recent systematic review of the literature, showing an early temporal peak in December [56].

We found higher values of detection for SARS-CoV-2 in elderly and pediatric patients and for RSV only in pediatric ones ($p < 0.001$), confirming data of a recent systematic review [57].

Another important result of our study is the use of FILMARRAY as a diagnostic tool to facilitates patient management and guide clinical decisions. It has been demonstrated that its use improves the clinical outcome, reducing the use of antibiotics and ICU admission [58]. Another study using this method showed a concordance

Fig. 3. Temporal trend of coinfections.



in defining an early RSV peak in November in the pediatric analyzed population [59]. Furthermore, the resumption of seasonality for RSV indicates how the precautionary measures used have had a major impact on the circulation of RSV and how the application of barrier measures is fundamental in the management of airborne microorganism outbreaks and epidemics [60-67].

RSV detections are less frequent during periods of high influenza activity and RSV incidence may peak 1-2 months earlier [68]. Dynamics such as these make it more difficult to reliably predict the epidemiological trends of ARIs and ILIs. A recent effort in this direction has been set up by the ECDC, with the launch of RespiCast, a platform for real-time forecasts of respiratory disease activity and burden [69].

Although it doesn't focus specifically on RSV, the forecasts provided by this system may help public health workers in drafting an effective prevention campaign.

The coronavirus disease 2019 (COVID-19) pandemic has drastically disrupted the epidemiology of Respiratory Syncytial Virus (RSV) respiratory tract infections in children. Proposed mechanisms include decreased viral immunity in vulnerable age groups caused by the prolonged lack of RSV circulation early in the pandemic, potential SARS-CoV-2-induced immune dysregulation, viral interactions between SARS-CoV-2 and RSV, and modifications in health-seeking behaviors as well as health systems factors [70].

The compilation of precise epidemiological data is also made difficult by a surveillance system against RSV that still needs work. Several European countries still only rely on estimates regarding the burden and incidence of infection [71].

One study examined Belgium's RSV surveillance network and highlighted its inability to accurately predict the epidemiological circulation of the virus. Systems to detect the hospital burden of RSV infections are suggested, with more sentinel hospitals and collection of the treated patients are suggested [71].

As stated previously, the recent approval of vaccines against RSV opens up new scenarios for its prevention. Protection from RSV in newborns will be provided by the administration of the vaccine in pregnant women or by the inoculation of monoclonal antibodies into the child. This approach was tested in a Luxembourg study, where Nirsevimab was administered to 84% of those born between October 2023 and January 2024. The monoclonal antibody was found to be statistically significantly associated with a reduction in hospitalizations, hospital length of stay, and an increase in the mean age of RSV-related cases [72]. In light of these premises, it will be necessary to formulate a new approach that takes into account the peculiarities of each patient group to make the most advantageous choice from an economic and social point of view.

The potential use of one of the two vaccines against RSV during pregnancy clashes with the vaccination hesitancy wall of this population which is very doubtful and sensitive to this topic.

A recent systematic review showed that the source of vaccination information (specialized healthcare worker, family doctor, mass media, non-professionals) is among the main determinants of vaccination hesitancy in pregnant women [73]. The role of the healthcare workers thus becomes increasingly crucial in communicating and responding to patients' doubts, taking care not to downplay their concerns.

Another population that will greatly benefit from the introduction of an effective vaccine is the immunocompromised. RSV was shown to be the fourth most prevalent microorganism in a study investigating transplanted subjects presenting respiratory symptoms [74]. More specifically, patients who had received a hematopoietic stem cell transplant acquired the infection in the nosocomial environment in 50% of cases, a significantly higher percentage than the general population; solid organ transplant recipients, on the other hand, had an incidence of RSV infection of 6-16% [75].

Limitations of the study: one major limitation of our study is its single-center design, which may limit the generalizability of the findings. Additionally, the exclusive use of molecular diagnostics may underestimate the true co-infection rates. Furthermore, the impact of the COVID-19 pandemic on the ARI trend could limit

the results of this study. Moreover, potential biases in Data Collection and Analysis could be discussed.
The COVID-19 pandemic significantly altered the patterns of respiratory infections due to several factors such as lockdowns, social distancing, mask-wearing, changes in healthcare-seeking behavior, and healthcare system priorities. These changes likely led to an underreporting or delay in diagnosing ARIs (Acute Respiratory Infections) and RSV (Respiratory Syncytial Virus) cases during peak pandemic periods. There is also the potential for biases related to immune interactions between SARS-CoV-2 and other viruses (such as RSV), which may have led to atypical patterns of coinfections and viral suppression. The potential immune dysregulation caused by SARS-CoV-2 infection could also have skewed data, leading to inconsistent results that do not align with pre-pandemic trends. A single-center study may not fully capture the diverse epidemiological dynamics of RSV and ARI trends across different geographical locations or healthcare settings. This limitation affects the generalizability of the findings and creates a bias towards the specific population and setting studied. Solely relying on molecular diagnostics (like PCR) can result in biases, as it might underestimate the true rates of viral and bacterial co-infections due to variations in test sensitivity and specificity. Diagnostic methodologies may also differ across studies, affecting the consistency of results and comparisons. Age, gender, seasonality, and comorbidities were identified as influential epidemiological factors. However, there is variability in findings across different studies - for instance, discrepancies in the prevalence of RSV between male and female subjects or the specific age groups most affected. This variability might reflect underlying biases in study design, population demographics, or other unmeasured confounding factors. Changes in health-seeking behavior during the pandemic and modifications in healthcare delivery (*e.g.*, telemedicine vs. in-person visits) could have influenced the detection and reporting rates of RSV and ARIs. Such systemic changes may introduce biases in the dataset, particularly in the assessment of disease burden and the effectiveness of preventive measures.

Conclusions

Although national and European data show an increase in the virus's circulation level, only a small number of subjects with acute respiratory symptoms were tested for RSV. A growing body of evidence demonstrated that perfecting the surveillance system would certainly guarantee a more correct characterization of the epidemiology, contributing to the more appropriate use of medical and pharmacological resources. In most European countries, RSV is not a mandatory reportable disease. However, in 2018 the World Health Organization deemed it appropriate to activate a surveillance system for cases of RSV infection, with particular attention to children under 2 years of age and patients requiring hospitalization, to improve the microbiological diagnosis criteria and precisely outline the characteristics of seasonality, risk groups and spread of the infection.
A significant proportion of studies are likely to underestimate the incidence of RSV infection in older adults, although the effect size is unclear and there is also potential for overestimation. Well-designed studies, together with increased testing for RSV in patients with ARI in clinical practice, are required to accurately capture both the burden of RSV and the potential public health impact of vaccines [76].
Our study sheds light on the burden of RSV-related infections on our local reality. Although the general population was examined, it is the youngest children who are most affected by RSV. As highlighted by data in the literature, our study confirms an early RSV peak in November. The winter seasonality of the disease revealed by the study also argues for more preventive care for those born in this period. The role of viral co-infections in which RSV is involved should be further investigated [77-82].
Our study highlights the need for enhanced surveillance strategies for respiratory infections. We recommend more rigorous preventive measures, such as influenza vaccination and improved hygiene practices.

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Institutional Review Board Statement

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Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of interest statement

The authors declare no conflicts of interest.

Authors' contributions

For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used: Conceptualization, CG and RS; methodology, CG; software, CG; validation, all authors; formal analysis, all authors; investigation, GG, CG, RS; resources, GG, CG, RS; data curation, GG, CG, RS; writing-original draft preparation, GG, CG, RS; writing-review and editing,

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References

[1] Mandelia Y, Procop GW, Richter SS, Worley S, Liu W, Esper F. Dynamics and predisposition of respiratory viral co-infections in children and adults. Clin Microbiol Infect 2021;27:631.e1-631.e6. https://doi.org/10.1016/j.cmi.2020.05.042.

[2] 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;399:2047-2064. https://doi.org/10.1016/S0140-6736(22)00478-0.

[3] Pregliasco F. Influenza and its virus. Italian Journal of Thoracic Diseases (GIMT) 2009;63:171-84+207-20.

[4] WHO European Region Summary. Available at: https://erviss.org (Accessed on: 27/02/2024).

[5] RespiVirNet - Sorveglianza integrata dei virus respiratori - Istituto Superiore di Sanità available at: https://respivirnet.iss.it/pagine/rapportoInflunet.aspx (Accessed on: 27/02/2024).

[6] Istituto Superiore di Sanità - EpiCentro - L'epidemiologia per la sanità pubblica. Available at: https://www.epicentro.iss.it/influenza/definizione-caso (Accessed on: 05/23/2024).

[7] Lynch JP 3rd, Kajon AE. Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention. Semin Respir Crit Care Med 2016;37:586-602. https://doi.org/10.1055/s-0036-1584923.

[8] Rapporto Virologico RespiVirNet, week 2024-14. Available at: https://respivirnet.iss.it/pagine/rapportoInflunet.aspx (Acessed on: 27/05/2024).

[9] Kesheh MM, Hosseini P, Soltani S, Zandi M. An overview on the seven pathogenic human coronaviruses. Rev Med Virol 2022;32:e2282. https://doi.org/10.1002/rmv.2282.

[10] Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an important respiratory pathogen. Int J Infect Dis 2014;25:45-52. https://doi.org/10.1016/j.ijid.2014.03.1394.

[11] Longtin J, Marchand-Austin A, Winter AL, Patel S, Eshaghi A, Jamieson F, Low DE, Gubbay JB. Rhinovirus outbreaks in long-term care facilities, Ontario, Canada. Emerg Infect Dis 2010;16:1463-5. https://doi.org/10.3201/eid1609.100476.

[12] Miller EK, Linder J, Kraft D, Johnson M, Lu P, Saville BR, Williams JV, Griffin MR, Talbot HK. Hospitalizations and outpatient visits for rhinovirus-associated acute respiratory illness in adults. J Allergy Clin Immunol 2016;137:734-43.e1. https://doi.org/10.1016/j.jaci.2015.06.017.

[13] Reese SM, Thompson M, Price CS, Young HL. Evidence of nosocomial transmission of human rhinovirus in a neonatal intensive care unit. Am J Infect Control 2016;44:355-7. https://doi.org/10.1016/j.ajic.2015.10.018.

[14] Gaetano Settimo, Lucia Bonadonna, Paola M.B. Gucci et al for the National Indoor air Study Group 2020, x, 67 p. Indoor air quality in schools: strategies for monitoring chemical and biological pollutants. Rapporti ISTISAN 20/3 - Istituto Superiore di Sanità.

[15] Istituto Superiore di Sanità - EpiCentro - L'epidemiologia per la sanità pubblica. Available at: https://www.epicentro.iss.it/influenza/influenza (Access on: 27/05/2024).

[16] Ryu S, Cowling BJ. Human Influenza Epidemiology. Cold Spring Harb Perspect Med 2021;11:a038356. https://doi.org/10.1101/cshperspect.a038356.

[17] ERVISS WHO European Region Summary. Available at: https://flunewseurope.org/SeasonOverview (Accessed on: 27/05/2024).

[18] Moroni M, D'Arminio Monforte A, Milazzo L. Infezioni dell'apparato respiratorio. In: Moroni M, Esposito R, De Lalla F, eds. Malattie infettive. Milano: Masson s.p.a. 2003, pp. 355-380.

[19] Bellini WJ, Rota PA, Anderson LJ, Paramyxoviruses. In: Collier L, Balows A, Sussmann M, eds. Microbiology and microbial infections (Virology). London: Arnold Edt 1998, pp. 435-452.

[20] Chanock R.M, McIntosh K. Parainfluenza Viruses. In: Fields BN, ed. Virology. New York: Raven Press 1990, pp. 963-984.

[21] Tagini F, Opota O, Greub G. Chlamydia pneumoniae Upsurge at Tertiary Hospital, Lausanne, Switzerland. Emerg Infect Dis 2024;30:810-2. https://doi.org/10.3201/eid3004.231610.

[22] Pittet LF, Bertelli C, Scherz V, Rochat I, Mardegan C, Brouillet R, Jaton K, Mornand A, Kaiser L, Posfay-Barbe K, Asner SA, Greub G. Chlamydia pneumoniae and Mycoplasma pneumoniae in children with cystic fibrosis: impact on bacterial respiratory microbiota diversity. Pathog Dis 2021;79:ftaa074. https://doi.org/10.1093/femspd/ftaa074.

[23] Hahn DL, Schure A, Patel K, Childs T, Drizik E, Webley W. Chlamydia pneumoniae-specific IgE is prevalent in asthma and is associated with disease severity. PLoS One 2012;7:e35945. https://doi.org/10.1371/journal.pone.0035945.

[24] Kumar S, Hammerschlag MR. Acute respiratory infection due to Chlamydia pneumoniae: current status of diagnostic methods. Clin Infect Dis 2007;44:568-76. https://doi.org/10.1086/511076.

[25] Cdc - Chlamydia pneumoniae Infection: Causes and How It Spreads. Available at https://www.cdc.gov/pneumonia/atypical/cpneumoniae/about/causes.html (Accessed on: 27/05/2024).

[26] Meyer Sauteur PM, Beeton ML; European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycoplasma and Chlamydia Infections (ESGMAC), and the ESGMAC Mycoplasma pneumoniae Surveillance (MAPS) study group. Mycoplasma pneumoniae: delayed re-emergence after COVID-19 pandemic restrictions. Lancet Microbe 2024;5:e100-e101. https://doi.org/10.1016/S2666-5247(23)00344-0.

[27] ISS - EpiCentro - L'epidemiologia per la sanità pubblica- Le coperture vaccinali in Italia. Available at: https://www.epicentro.iss.it/vaccini/dati_Ita#pertosse (Accessed on: 27/05/2024).

[28] Fiasca F, Necozione S, Mattei A. Pertussis in Italy: how to protect the "unprotectable"? Hum Vaccin Immunother. 2021 Apr 3;17(4):1136-1141. https://doi.org/10.1080/21645515.2020.1806673.

[29] Fedele G, Stefanelli P. Pertussis in infants and the resurgence of a vaccine preventable disease: what to do? Comment Ann Ist Super Sanita 2017;53:100-3. https://doi.org/10.4415/ANN_17_02_04.

[30] Frassanito A, Nenna R, Nicolai A, Pierangeli A, Tozzi AE, Stefanelli P, Carsetti R, Concato C, Schiavoni I, Midulla F; Pertussis study group. Infants hospitalized for Bordetella pertussis infection commonly have respiratory viral coinfections. BMC Infect Dis 2017;17:492. https://doi.org/10.1186/s12879-017-2567-6.

[31] CDC- Morbidity and Mortality Weekly Report (MMWR). Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5926a5.htm (Accessed on: 07/01/2024).

[32] Fedele G, Carollo M, Palazzo R, Stefanelli P, Pandolfi E, Gesualdo F, Tozzi AE, Carsetti R, Villani A, Nicolai A, Midulla F, Ausiello CM, Pertussis Study Group Parents as source of pertussis transmission in hospitalized young infants. Infection 2017;45:171-8. https://doi.org/10.1007/s15010-016-0943-6.

[33] Walsh PF, Kimmel L, Feola M, Tran T, Lim C, De Salvia L, Pusavat J, Michaelson S, Nguyen TA, Emery K, Mordechai E, Adelson ME. Prevalence of Bordetella pertussis and Bordetella

parapertussis in infants presenting to the emergency department with bronchiolitis. J Emerg Med 2011;40:256-61. https://doi.org/10.1016/j.jemermed.2008.04.048.

[34] Macina D, Evans KE. Pertussis in Individuals with Co-morbidities: a Systematic Review. Infect Dis Ther 2021;10:1141-70. https://doi.org/10.1007/s40121-021-00465-z.

[35] Carloni I, Ricci S, Azzari C, Galletti S, Faldella G, de Benedictis FM. Fatal pertussis in infancy, Italy. J Infect 2017;75:186-9. https://doi.org/10.1016/j.jinf.2017.04.005.

[36] Ciarlitto C, Vittucci AC, Antilici L, Concato C, Di Camillo C, Zangari P, Villani A. Respiratory Syncityal Virus A and B: three bronchiolitis seasons in a third level hospital in Italy. Ital J Pediatr 2019;45:115. https://doi.org/10.1186/s13052-019-0704-0.

[37] Kaler J, Hussain A, Patel K, Hernandez T, Ray S. Respiratory Syncytial Virus: a Comprehensive Review of Transmission, Pathophysiology, and Manifestation. Cureus 2023;15:e36342. https://doi.org/10.7759/cureus.36342.

[38] Graham BS Protecting the Family to Protect the Child: Vaccination Strategy Guided by RSV Transmission Dynamics. J Infect Dis 2014;209:1679-81. https://doi.org/10.1093/infdis/jiu075.

[39] 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.

[40] Jha A, Jarvis H, Fraser C, Openshaw PJM. Respiratory Syncytial Virus. In: Hui DS, Rossi GA, Johnston SL, eds. SARS, MERS and other Viral Lung Infections. Sheffield, UK: European Respiratory Society 2016.

[41] Empey KM, Peebles RS Jr, Kolls JK. Pharmacologic advances in the treatment and prevention of respiratory syncytial virus. Clin Infect Dis 2010;50:1258-67. https://doi.org/10.1086/651603.

[42] Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair S, Jones MA, Thorning S, Conly JM. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev 2011;2011:CD006207. https://doi.org/10.1002/14651858.CD006207.pub4. Update in: Cochrane Database Syst Rev 2020;11:CD006207. https://doi.org/10.1002/14651858.CD006207.pub5.

[43] Position of the Board of the Vaccinal Calendar for Life and of the Italian Society of Neonatology on the possible use of long-half-life monoclonal antibodies for the universal prevention of Respiratory Syncytial Virus (RSV or RSV) diseases in newborns. Available at: http://www.igienistionline.it/docs/2023/03pp.pdf (Accessed on: 27/11/2023).

[44] Garegnani L, Styrmisdóttir L, Roson Rodriguez P, Escobar Liquitay CM, Esteban I, Franco JV. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. Cochrane Database Syst Rev 2021;11:CD013757. https://doi.org/10.1002/14651858.CD013757.pub2.

[45] European Medicines Agency. Beyfortus. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/beyfortus#authorisation-details-section (Accessed on: 27/11/2023).

[46] Jones JM, Fleming-Dutra KE, Prill MM, Roper LE, Brooks O, 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 - United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:920-5. https://doi.org/10.15585/mmwr.mm7234a4.

[47] Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, Schwarz TF, van Zyl-Smit RN, Campora L, Dezutter N, de Schrevel N, Fissette L, David MP, Van der Wielen M, Kostanyan L, Hulstrøm V; AReSVi-006 Study Group. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. N Engl J Med 2023;388:595-608. https://doi.org/10.1056/NEJMoa2209604.

[48] Walsh EE, Pérez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, Polack FP, Llapur C, Doreski PA, Ilangovan K, Rämet M, Fukushima Y, Hussen N, Bont LJ, Cardona J, DeHaan E, Castillo Villa G, Ingilizova M, Eiras D, Mikati T, Shah RN, Schneider K, Cooper D, Koury K, Lino MM, Anderson AS, Jansen KU, Swanson KA, Gurtman A, Gruber WC, Schmoele-Thoma B; RENOIR Clinical Trial Group. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. N Engl J Med 2023;388:1465-77. https://doi.org/10.1056/NEJMoa2213836.

[49] Attaianese F, Guiducci S, Trapani S, Barbati F, Lodi L, Indolfi G, Azzari C, Ricci S. Reshaping Our Knowledge: Advancements in Understanding the Immune Response to Human Respiratory Syncytial Virus. Pathogens 2023;12:1118. https://doi.org/10.3390/pathogens12091118.

[50] European Center for Disease Prevention and Control. Intensified circulation of respiratory syncytial virus (RSV) and associated hospital burden in the EU/EEA – 12 December 2022. ECDC: Stockholm; 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/intensified-circulation-respiratory-syncytial-virus-rsv-and-associated-hospital (Accessed on: 27/22/2023).

[51] Li Y, Pillai P, Miyake F, Nair H. The role of viral co-infections in the severity of acute respiratory infections among children infected with respiratory syncytial virus (RSV): A systematic review and meta-analysis. J Glob Health 2020;10:010426. https://doi.org/10.7189/jogh.10.010426.

[52] Tong S, Amand C, Kieffer A, Kyaw MH. Incidence of respiratory syncytial virus related health care utilization in the United States. J Glob Health 2020;10:020422. https://doi.org/10.7189/jogh.10.020422.

[53] Kim T, Huh JW, Hong SB, Jung J, Kim MJ, Chong YP, Sung H, Doh KH, Kim SH, Lee SO, Kim YS, Lim CM, Koh Y, Choi SH. Epidemiology and Characteristics of Respiratory Syncytial Virus Pneumonia in Critically Ill Adults. Open Forum Infect Dis 2023;10:ofad131. https://doi.org/10.1093/ofid/ofad131.

[54] Gonik B. The Burden of Respiratory Syncytial Virus Infection in Adults and Reproductive-Aged Women. Glob Health Sci Pract 2019;7:515-520. https://doi.org/10.9745/GHSP-D-19-00121.

[55] Tin Tin Htar M, Yerramalla MS, Moïsi JC, Swerdlow DL. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiol Infect 2020;148:e48. https://doi.org/10.1017/S0950268820000400.

[56] Panatto D, Domnich A, Lai PL, Ogliastro M, Bruzzone B, Galli C, Stefanelli F, Pariani E, Orsi A, Icardi G. Epidemiology and molecular characteristics of respiratory syncytial virus (RSV) among italian community-dwelling adults, 2021/22 season. BMC Infect Dis 2023;23:134. https://doi.org/10.1186/s12879-023-08100-7.

[57] Dallmeyer LK, Schüz ML, Fragkou PC, Omony J, Krumbein H, Dimopoulou D, Dimopoulou K, Skevaki C. Epidemiology of respiratory viruses among children during the SARS-CoV-2 pandemic: A systematic review and meta-analysis. Int J Infect Dis 2024;138:10-8. https://doi.org/10.1016/j.ijid.2023.10.023.

[58] Busson L, Bartiaux M, Brahim S, Konopnicki D, Dauby N, Gérard M, De Backer P, Van Vaerenbergh K, Mahadeb B, Mekkaoui L, De Foor M, Wautier M, Vandenberg O, Mols P, Levy J, Hallin M. Contribution of the FilmArray Respiratory Panel in the management of adult and pediatric patients attending the emergency room during 2015-2016 influenza epidemics: An interventional study. Int J Infect Dis 2019;83:32-9. https://doi.org/10.1016/j.ijid.2019.03.027.

[59] Weidmann MD, Green DA, Berry GJ, Wu F. Assessing respiratory viral exclusion and affinity interactions through co-infection incidence in a pediatric population during the 2022 resurgence of influenza and RSV. Front Cell Infect Microbiol 2023;13:1208235. https://doi.org/10.3389/fcimb.2023.1208235.

[60] Bozzola E. Respiratory Syncytial Virus Resurgence in Italy: The Need to Protect All Neonates and Young Infants. Int J Environ Res Public Health 2021;19:380. https://doi.org/10.3390/ijerph19010380.

[61] Fricke LM, Glöckner S., Dreier M., Lange B. Impact of non-pharmaceutical interventions targeted at COVID-19 pandemic on influenza burden - A systematic review. J Infect 2021;82:1-35. https://doi.org/10.1016/j.jinf.2020.11.039.

[62] 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.

[63] Chiapinotto S., Sarria EE, Mocelin HT, Lima JA, Mattiello R., Fischer GB Impact of non-pharmacological initiatives for COVID-19 on hospital admissions due to pediatric acute respiratory illnesses. Paediatrician Breath Rev 2021;39:3-8. https://doi.org/10.1016/j.prrv.2021.04.003.

[64] Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, Le H, Levy A, Moore HC, Blyth CC. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of Coronavirus Disease 2019-Related Public Health Measures. Clin Infect Dis 2021;73:e2829-30. https://doi.org/10.1093/cid/ciaa1906.

[65] 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.

[66] Di Mattia G, Nenna R, Mancino E, Rizzo V, Pierangeli A, Villani A, Midulla F. During the COVID-19 pandemic where has respiratory syncytial virus gone? Pediatr Pulmonol. 2021 Oct;56(10):3106-3109. https://doi.org/10.1002/ppul.25582.

[67] Nenna R, Matera L, Pierangeli A, Oliveto G, Viscido A, Petrarca L, La Regina DP, Mancino E, Di Mattia G, Villani A, Midulla F. First COVID-19 lockdown resulted in most respiratory viruses disappearing among hospitalised children, with the exception of rhinoviruses. Acta Paediatr 2022;111:1399-403. https://doi.org/10.1111/apa.16326.

[68] Piret J, Boivin G. Viral Interference between Respiratory Viruses. Emerg Infect Dis 2022;28:273-81. https://doi.org/10.3201/eid2802.211727.

[69] RespiCast, European Centre for Disease Prevention and Control, European Union Agency. Available at: https://respicast.ecdc.europa.eu/ (Accessed on: 27/05/2024).

[70] Abu-Raya B, Viñeta Paramo M, Reicherz F, Lavoie PM. Why has the epidemiology of RSV changed during the COVID-19 pandemic? EClinicalMedicine 2023;61:102089. https://doi.org/10.1016/j.eclinm.2023.102089.

[71] Raes M, Daelemans S, Cornette L, Moniotte S, Proesmans M, Schaballie H, Frère J, Vanden Driessche K, Van Brusselen D. The burden and surveillance of RSV disease in young children in Belgium-expert opinion. Eur J Pediatr 2023;182:451-60. https://doi.org/10.1007/s00431-022-04698-z.

[72] 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.

[73] Mitchell SL, Schulkin J, Power ML. Vaccine hesitancy in pregnant Women: a narrative review. Vaccine 2023;41:4220-7. https://doi.org/10.1016/j.vaccine.2023.05.047.

[74] Jahn K, Schumann D, Tamm M, Hirsch H, Halter J, Junker L, Strobel W, Savic S, Stolz D. Respiratory viral infection in immunocompromised patients. Eur Resp J 2018;52:PA4694. https://doi.org/10.1183/13993003.congress-2018.PA4694

[75] Villanueva DH, Arcega V, Rao M. Review of respiratory syncytial virus infection among older adults and transplant recipients. Ther Adv Infect Dis 2022;9:20499361221091413. https://doi.org/10.1177/20499361221091413.

[76] Rozenbaum MH, Begier E, Kurosky SK, Whelan J, Bem D, Pouwels KB, Postma M, Bont L. Incidence of Respiratory Syncytial Virus Infection in Older Adults: Limitations of Current Data. Infect Dis Ther 2023;12:1487-504. https://doi.org/10.1007/s40121-023-00802-4.

[77] Venuto R, Giunta I, Cortese R, Denaro F, Pantò G, Privitera A, D'Amato S, Genovese C, La Fauci V, Fedele F, Ceccio C, Squeri R, Facciolà A. The Importance of COVID-19/Influenza Vaccines Co-Administration: an Essential Public Health Tool. Infect Dis Rep 2022;14:987-95. https://doi.org/10.3390/idr14060098.

[78] Genovese C, Costantino C, Odone A, Trimarchi G, La Fauci V, Mazzitelli F, D'Amato S, Squeri R, The Covid-Risk Perception Group. A Knowledge, Attitude, and Perception Study on Flu and COVID-19 Vaccination during the COVID-19 Pandemic: Multicentric Italian Survey Insights. Vaccines (Basel) 2022;10:142. https://doi.org/10.3390/vaccines10020142.

[79] Costantino C, Ledda C, Squeri R, Restivo V, Casuccio A, Rapisarda V, Graziano G, Alba D, Cimino L, Conforto A, Costa GB, D'Amato S, Mazzitelli F, Vitale F, Genovese C. Attitudes and Perception of Healthcare Workers Concerning Influenza Vaccination during the 2019/2020 Season: A Survey of Sicilian University Hospitals. Vaccines (Basel) 2020;8:686. https://doi.org/10.3390/vaccines8040686.

[80] Squeri R, Riso R, Facciolà A, Genovese C, Palamara MA, Ceccio C, La Fauci V. Management of two influenza vaccination campaign in health care workers of a university hospital in the south Italy. Ann Ig 2017;29:223-31. https://doi.org/10.7416/ai.2017.2150.

[81] Genovese C, La Fauci V, Di Pietro A, Trimarchi G, Odone A, Casuccio A, Costantino C, Restivo V, Fantini M, Gori D, Azara A, Deiana G, Castaldi S, Righi E, Palandri L, Panciroli G, Bianco A, Licata F, Cosentino S, Mistretta A, Marranzano M, Ragusa R, Gabutti G, Stefanati A, Prato R, Fortunato F, Martinelli D, Icardi G, Panatto D, Amicizia D, Fabiani L, Moretti A, Di Risio D, Siliquini R, Voglino G, Bert F, Lorini C, Bonaccorsi G, Torre I, Pennino F, Pavia M, Di Giuseppe G, Paolantonio A, Villari P, Marzuillo C, Messina G, Rivieri C, Nante N, Majori S, Tardivo S, Moretti F, D'Amato S, Mazzitelli F, Giunta I, Lo Giudice D, Pantò G, Signorelli C, Squeri R. COVID-19: opinions and behavior of Italian general population during the first epidemic phase. Acta Biomed 2022;93:e2022262. https://doi.org/10.23750/abm.v93i3.12262.

[82] D'Amato S, Squeri R, La Fauci V, Pantò G, Esposito EM, Denaro F, Visalli G, Giunta I, Venuto R, Privitera A, D'Urso L, Cortese R, Mazzitelli F, Ceccio C, Fedele F, Maisano D, Trimarchi G, Genovese C. COVID-19 serological evaluation in a cohort of Vaccinated and Seropositive healthcare workers. Acta Biomed 2021;92(S6):e2021415. https://doi.org/10.23750/abm.v92iS6.12261.

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Infectious disease

Burden of human rabies disease: its potential prevention by means of Rabipur® vaccine

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Keywords

Rabies • Human rabies • Rabies vaccine • Dog bite

Summary

Rabies is a zoonotic viral disease transmitted mainly by bites of infected animals, especially dogs, which are responsible for 99% of human cases. Despite being preventable, it remains a neglected disease in low-income countries, with approximately 60,000 deaths per year, mostly concentrated in Africa and Asia. The real worldwide burden of rabies is probably underestimated, as death-reporting systems are inadequate and active surveillance is limited.
Rabies prevention implies two main, non-exclusive strategies: (i) dog vaccination, in order to interrupt virus transmission to humans, and (ii) human vaccination i.e. pre-exposure prophylaxis (PrEP) and Post-Esposure Prophylaxis (PEP) through the use of purified cell-culture and embryonated egg-based vaccines (CCEEVs).
Rabipur® is one of the available anti-rabies vaccines and is indicated for active immunization in individuals of all ages. Its efficacy and safety have been amply demonstrated.
In rabies-free countries, PrEP is indicated for individuals who face occupational and/or travel-related exposure to the rabies virus in specific settings or over an extended period.
Wider use of human rabies vaccination for PrEP and PEP in conjunction with programs to eradicate rabies from animal populations is the challenging goal in order to reduce the burden of disease and achieve zero rabies.

Introduction

Rabies is a zoonotic viral disease of mammals that is transmitted from animals to humans by exposure to saliva or other sources of infectious virus. Exceptional cases of direct human-to-human transmission and indirect transmission via infected transplants have also been reported [1-3].
After a bite by an affected animal, the virus present in the saliva reaches the peripheral nerves and then the brain. Once the rabies virus infects spinal cord neurons, dissemination proceeds quickly throughout the central nervous system by means of fast axonal transport along neuroanatomical pathways. Many neuronal cell types throughout the central nervous system are infected, whereas infection of non-neuronal cells, including astrocytes, occurs much less commonly [4, 5]. Brain infection results in behavioural changes, probably due to the infection of neurons in limbic areas. Subsequently, the rabies virus spreads away from the central nervous system (centrifugal spread) along neuronal pathways, particularly involving the parasympathetic nervous system, to many organs, including the heart, gastrointestinal tract, adrenal medulla, skin and saliva glands.
While all mammalian species are believed to be susceptible, rabies is mainly detected in dogs, wolves, foxes, coyotes and jackals, raccoons, mongooses, skunks and bats [6]. Dogs are responsible for 99% of human cases [7]. Clinically, rabies is characterized by fitful consciousness, hyperactivity, hallucinations and hydrophobia (furious rabies), or paralysis and coma (paralytic rabies), progressing rapidly and inevitably towards death [8].
Rabies is considered to be a neglected disease, as global and national stakeholders and decision-makers lack awareness of its importance and have not prioritized it. Indeed, global funding agencies do not generally provide funding for rabies elimination efforts; this means that rabies remains under-resourced, especially in the areas most affected by the disease. As a result, the burden rabies persists.
Here, we present a narrative overview on rabies disease, focusing on its clinical, epidemiological burden and the opportunity for prevention by means of Rabipur® vaccine.

Characteristics of rabies virus and clinical symptoms of the disease

The rabies virus is a member of the genus *Lyssavirus*, which belongs to the family of *Rhabdoviridae*; these consist of genetically related enveloped viruses with a single non-segmented negative-stranded RNA [9, 10].
The virus contains multiple copies of five structural proteins: virion transcriptase L, glyocoprotein G, nucleoprotein N, phosphoprotein P, and matrix protein M. The G and M proteins are responsible for blocking apoptosis after infection by virulent street of viruses, which is a protective mechanism for the host. The G protein is a major determinant of viral neurotropism. Mutations in the G protein reduce or eliminate neuroinvasiveness

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without impairing the ability of the virus to multiply in cell culture [11-13]. The G protein of the rabies virus is the main antigen responsible for inducing the production of virus-neutralizing antibodies and for conferring immunity against lethal infection by the rabies virus. Located on the surface of the virion, this glycoprotein plays an important role in the host's immune response and facilitates interaction of the virion with host cell receptors. The incubation period of rabies is reported to range from weeks to years, but mostly lasts 1–2 months on average; indeed, in the majority of cases, incubation takes between 20 and 60 days [14, 15]. Moreover, it has been observed that the incubation period is shorter if the bite occurs in the head rather than in an extremity.

The clinical stages of rabies can be summarized as: incubation, prodrome, acute neurological signs, coma, and death. Once the infection manifests itself clinically, death almost always occurs within 7-10 days. Weakness in the bitten extremities may be evident on primary presentation; subsequently, the disease may progress to either the furious or paralytic form [16-18]. The features of furious rabies are fluctuating consciousness, hydrophobia or aerophobia, inspiratory spasms, and signs of autonomic dysfunction. These may not appear simultaneously, and disappear during coma. Comatose patients with furious rabies may develop flaccid limb weakness, which has frequently been misinterpreted as paralytic rabies. Conversely, ascending weakness of lower motor neurons with only motor disturbance is the initial manifestation of paralytic rabies [17], in which consciousness is preserved until the preterminal phase.

Atypical signs and symptoms of rabies associated with infection by either bat or dog rabies virus variants have been increasingly recognized [15-19]. Transverse myelitis presenting as neuromyelitis optica, and tetanus-like symptoms with locked jaw have been reported [20-22].

Epidemiological burden

The real worldwide burden of rabies is probably underestimated, as death-reporting systems are inadequate and active surveillance is limited [23-25]. Moreover, the widespread unavailability of laboratory diagnosis gives rise to false results, incorrect assessments of rabies epidemiology and, consequently, difficulties in rabies control [26]. Indeed, owing to socio-cultural norms also, laboratory testing of human brain samples is not practical in low- and middle-income countries; hence, the majority of cases of rabies in humans are identified exclusively on the basis of symptoms.

The under-reporting of rabies is complicated by the pathophysiology of the disease itself. Indeed, most individuals with rabies do not present in hospital for diagnosis, since they know that the disease is terminal as soon as the symptoms arise. Moreover, in regions where other diseases with neurological symptoms are common, rabies may be misdiagnosed as these other diseases.

Other methods, such as a probabilistic decision-tree approach, are used in order to calculate the likelihood of a person contracting clinical rabies after being bitten by a dog suspected of having the virus [26]; on the basis of this technique, Knobel et al. argued that canine rabies was responsible for about 55,000 deaths per year across Africa and Asia [23]. However, more data have become available, and the dynamics of the disease has shifted, with a rise in occurrence in some regions and the appearance of rabies in those previously free from the disease [27].

As mentioned above, rabies is an ancient disease with about 60,000 human deaths per year, mostly in Asia and Africa. Most deaths occur in children (approximately 40%), who are more susceptible because of their curious/adventurous nature and their shorter stature, making them more likely to sustain a wound in a higher-risk anatomical location, such as the head [27].

In resource-limited and resource-poor countries, endemic dog rabies, which is sustained by dog-to-dog transmission of the rabies virus, results in an ongoing risk of transmission to humans due to dog bites. Furthermore, rabies in wildlife is still a problem in North America and Europe [27].

According to the latest epidemiological reports, rabies remains a cause for alarm, mainly in Asia, Africa, the Middle East, Latin America and the Caribbean [28-31]. Furthermore, towards the end of the last century, rabies re-emerged in China, and it spread in historically free islands such as Flores and Bali (Indonesia) [31, 32].

Notably, rabies transmission is linked to the socio-economic status of a country, with a high prevalence of the disease being detected in poor areas [26, 33, 34]. Indeed, it has been documented that the incidence and transmission of rabies are negatively correlated with economic development [33-35]. In El Salvador, for example, the country's economic and social crisis has hindered rabies control programs. Furthermore, the capacity for vaccine manufacture and procurement influences the status of rabies in a country [33-35]. Another relevant issue is the high cost of post-exposure rabies programs in developing countries, which is not sustainable by most residents.

Canine and wildlife-mediated rabies burden

A possible strategy for controlling rabies disease is to vaccinate dogs. The cost of vaccinating dogs, which can limit human exposure and curb the spread of the disease, is negligible [36, 37]. However, the lack of funding hinders this action in the developing countries. In the countries where the dog's vaccination is widely implemented good results have been achieved. For example, the United States is one country that has maintained a significant investment in dog vaccination, with the cost being estimated as $0.11/person/year [3, 38].

However, the recent pandemic affected the implementation of mass vaccinations for dogs (interruptions to mass dog vaccination campaigns and disruptions in vaccine supply). Consequently, after the COVID-19 emergency, a sudden spike in rabies cases and dog-bite-induced deaths in India and many other countries were registered. Monitoring canine rabies and wildlife is critical for the control and elimination of disease [39].

Fig. 1. Occurrence of canine rabies [40].

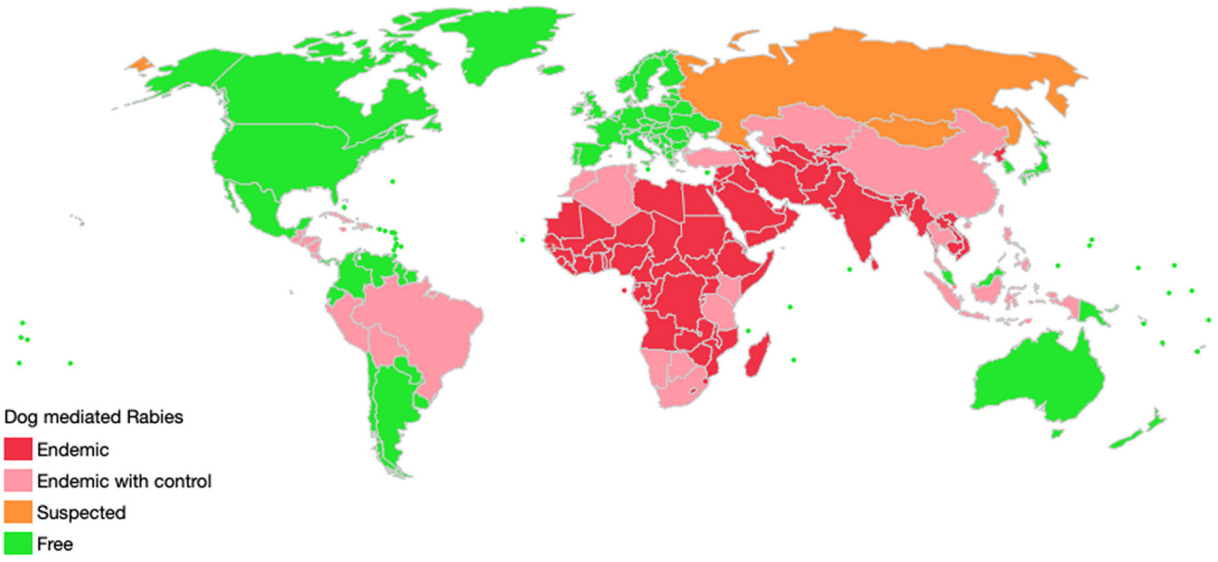


Fig. 2. Occurrence of wildlife-mediated rabies [40].

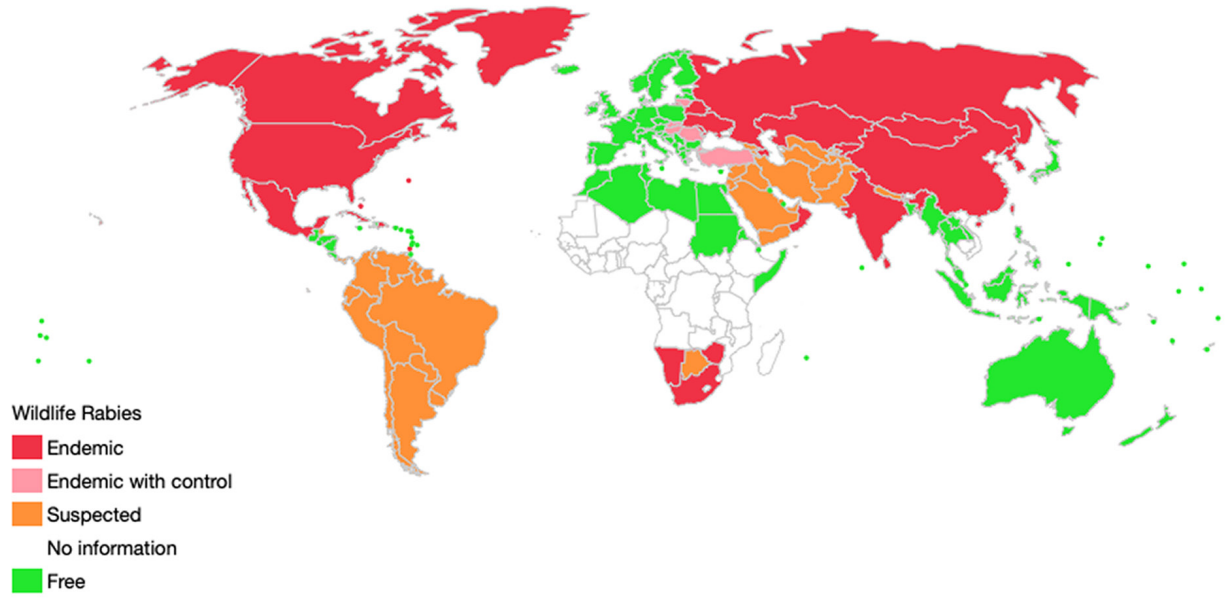


Figure 1 shows the occurrence of canine rabies [40]. Dog-mediated rabies has been eliminated from Western Europe, Canada, the United States, Japan and some Latin American countries. Australia and many Pacific Island nations have always been free from dog-mediated rabies. Nevertheless, these countries may still report imported cases and incur costs for maintaining disease freedom or the surveillance of endemic transmission in wildlife. In South America, efforts to eliminate canine rabies have been enormously successful.

Figure 2 shows the occurrence wildlife-mediated rabies [40]. Other animals, such as bat species, are also reservoirs for the rabies virus. As can be seen, rabies virus vectors and reservoir species are widespread.

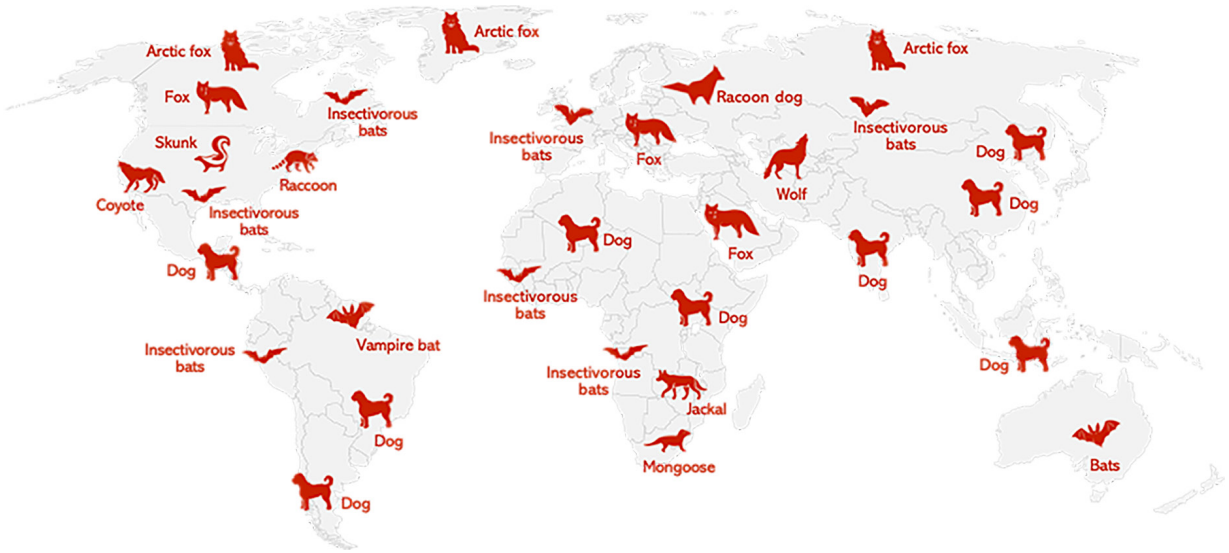
It is well recognized that carnivora (carnivores) and chiroptera (bats) are the canonical mammalian orders responsible for the maintenance and onward transmission of rabies Lyssavirus. However, the role of most species within these orders is not yet completely known and is continually changing as a result of contemporary host shifting (Fig. 3) [41, 42].

Human rabies burden

Figure 4 reports the worldwide prevalence of rabies (human cases per 100,000 pop.). The data refer to 2010 and the 2019-2021 period [43].

Although the number of rabies cases has decreased significantly, the prevalence of the disease is still high in

Fig. 3. Global distribution of mammalian rabies reservoirs and vectors [41, 42].



many countries. In Asia, the continent with highest number of cases, 35,172 human deaths per year are estimated to occur. The cost of Post-Exposure Prophylaxis (PEP) is highest in Asia, with estimates up to US$ 1.5 billion per year. India accounts for 59.9% of rabies deaths in Asia and 35% of deaths globally. In Central Asia and the Middle East, the numbers of human deaths are estimated to be 1,875 and 229 per year, respectively [44]; however, limited information is available on the burden of disease in these areas.

Recently, the age-standardized incidence was evaluated by a Chinese research group [45]; the global incidence was seen to have decreased from 24,745 cases in 1990 to 14,076 cases in 2019. Moreover, the estimated number of rabies cases in 2030 will be close to 5,810. Nevertheless, achieving zero rabies remains a challenging goal [46].

A total of 21,476 human deaths due to dog-mediated rabies [47] are estimated to occur each year in Africa. It is estimated that Africa spends the least on PEP and consequently has the highest human mortality. Improving access to PEP and reducing the prevalence of dog-mediated rabies could save a significant number of lives.

In Latin America and the Caribbean, a concerted effort by the Pan American Health Organization and sustained control in the region has led to a significant decrease in cases of human and dog rabies. Today, bat-mediated rabies accounts for the majority of human cases in the Americas [48].

According to the latest available ECDC report (2022), no human lyssavirus infections were reported in Europe in 2020 and 2021. By contrast, human lyssavirus infections were reported in 2019 and 2018 [49]. However, travel-associated human rabies cases have sometimes occurred in Europe, as reported in recent years. Specifically, in 2018-2019, cases were reported in countries of the European Union, including four travel-related cases and one EU-acquired non-rabies lyssavirus infection caused by European bat lyssavirus 1. In particular, the cases occurred in travelers returning from Morocco (N = 2), Tanzania (N = 1) and India (N = 1). In 2019, France reported an EU-acquired infection due to European bat lyssavirus 1 (EBLV-1) [49]. Finally, one travel-related case was reported in the United Kingdom in 2018.

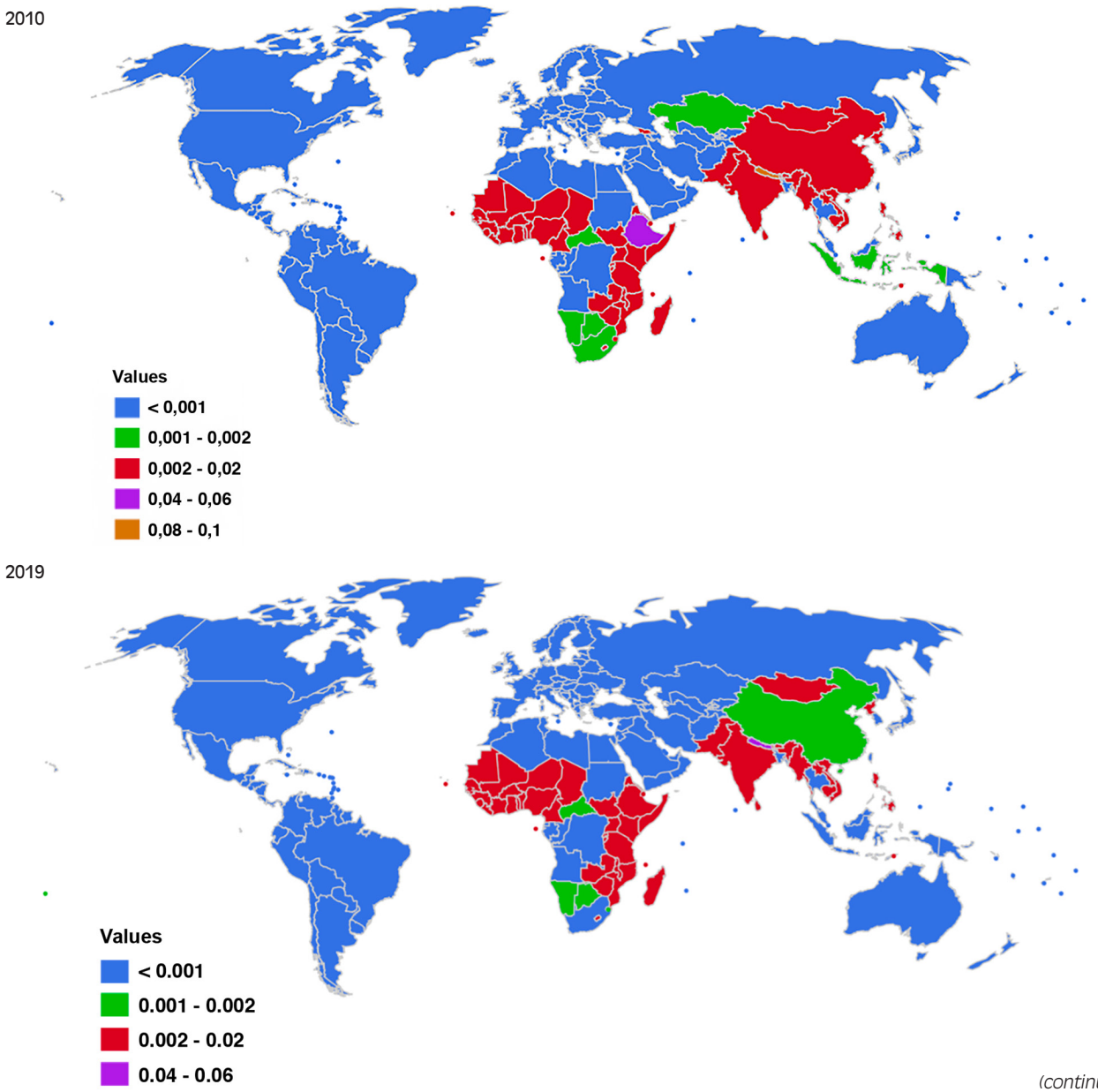
Preventive opportunity in Europe: focus on Rabipur® vaccine

As previously described, rabies is an infection that can be transmitted when a person is bitten, scratched or even just licked by an infected animal, especially if the skin is not intact. Contact with animal traps that have been licked or bitten by infected animals can also cause infections in humans.

Rabies prevention implies two main, non-exclusive strategies: (i) dog vaccination, in order to interrupt virus transmission to humans, and (ii) human vaccination *i.e.* Pre-Exposure Prophylaxis (PrEP) and Post-Exposure Prophylaxis (PEP) through the use of purified cell-culture and embryonated egg-based vaccines (CCEEVs) [46].

The initial rabies vaccine was created by Louis Pasteur in 1885, who used the dried spinal cord of infected rabbits. Subsequently, rabies vaccine production was directed towards sources of virus propagation in materials free from neural tissue. Cell-culture-based and embryonated egg-based vaccines were therefore developed. In embryonated egg-based rabies vaccines, the complete embryo is used for virus propagation. By contrast, cell-culture-based vaccines contain the rabies virus that has been propagated in cell substrates (*e.g.*, primary hamster kidney cells, human diploid cells,

Fig. 4. The worldwide prevalence of rabies (human cases per 100,000 pop.) in 2010, 2019, 2020 and 2021 (available data on August 2024) [43].



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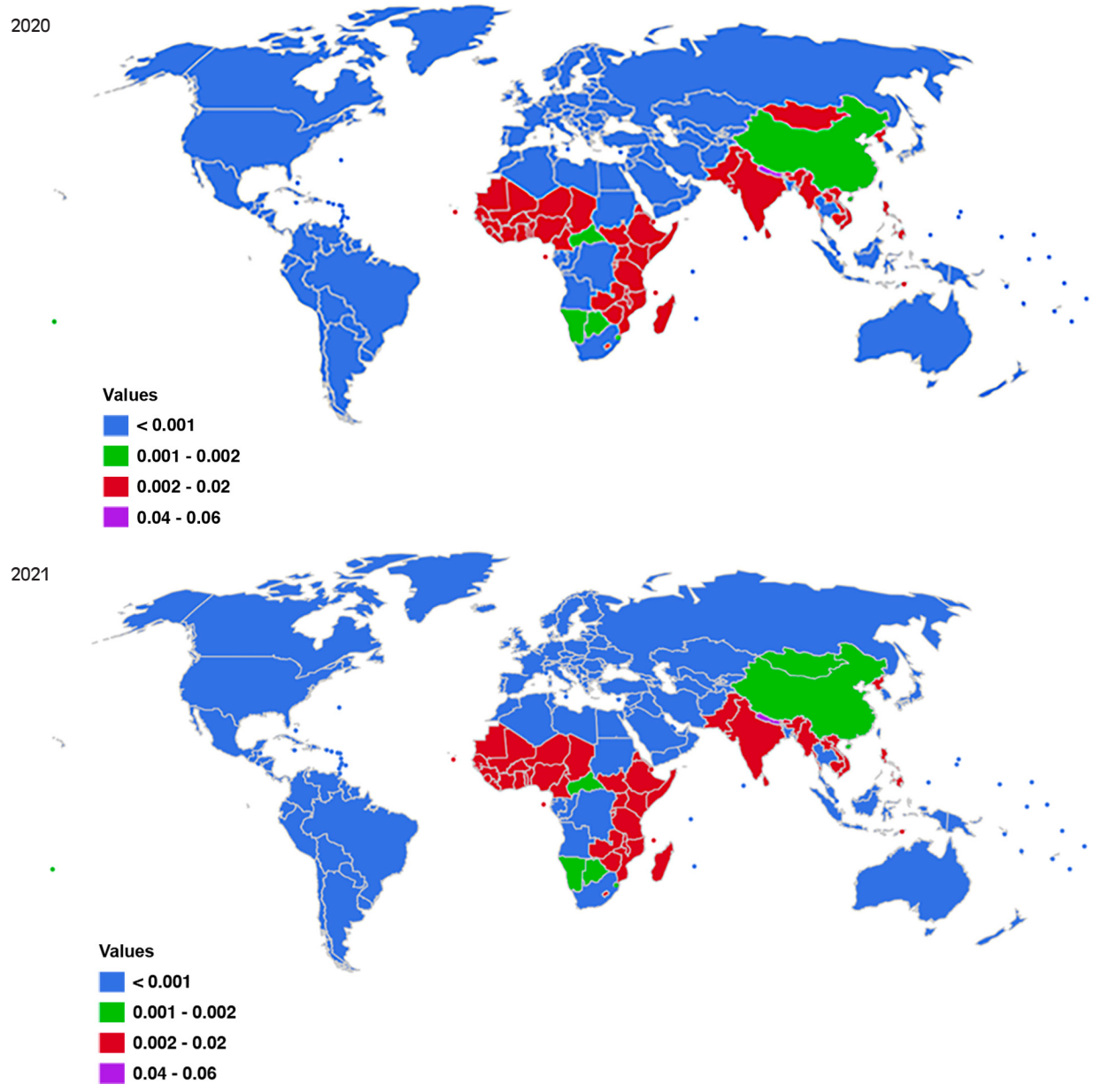
chick embryo cells or Vero cells) [3]. Since 1984, the World Health Organization (WHO) has strongly recommended modern, concentrated, purified CCEEVs [3]. All CCEEVs are able to promptly induce a high level of virus-neutralizing antibody response to the G protein of the rabies virus. The WHO-specified minimum serum antibody concentration of 0.5 International Unit (IU)/mL is widely used as a measure of adequate seroconversion after vaccination. In most individuals, irrespective of age or nutritional status, this level is reached by day 7 to 14 [3].

Rabipur® is an inactivated, purified chick embryo cell culture rabies vaccine for human use. One dose contains ≥ 2.5 IU of rabies antigens in 1.0 mL dose of lyophilised inactivated rabies virus of the Flury low egg passage (LEP) strain, polygeline, salts and sucrose as excipients, and trace amounts of amphotericin B, chlortetracycline, neomycin, human serum albumin and chicken proteins (*e.g.,* ovalbumin) [50].

The vaccine was first approved in Germany in 1984, and subsequently in the UK in 2016. At the time of development of the vaccine, a six-dose Essen regimen of PEP was officially recommended by the WHO. Consequently, Rabipur® was initially assessed in clinical trials involving six 1.0 mL intramuscular (IM) doses for PEP, and was licensed as such. According to WHO guidelines, the PEP six-dose Essen regimen produced an adequate antibody response [3]. Subsequently, the shorter Zagreb regimen used an abbreviated schedule of two doses on Day 0 and one dose on Days 7 and 21 (2-1-1).

Fig. 4 (*follows*). The worldwide prevalence of rabies (human cases per 100,000 pop.) in 2010, 2019, 2020 and 2021 (available data on August 2024) [43].



Rabipur® is indicated for active immunization PrEP and PEP against rabies in individuals of all ages, according to official recommendations [50]. The recommended dose for both primary immunisation and boosters is 1.0 mL.

To date, Rabipur® has been authorized in 15 European Economic Area (EEA) countries and in 8 non-EEA countries: UK, Switzerland, Australia, Canada, Japan, New Zealand, Singapore and the USA.

Pre-exposure prophylaxis of Rabipur® vaccine

Primary immunization involves three doses administered according to the conventional day 0, day 7, day 21 (28) or the rapid regimen (days 0, 3, 7), available in Europe, in unvaccinated individuals (Tab. I). The rapid regimen should only be considered for adults aged 18-65 years who are not able to complete the conventional PrEP regimen within 21 or 28 days before protection is required (Tab. I). Alternatively, in immunocompetent individuals, the one-week regimen with 2 doses can be used: at time 0 and after 7 days. This new product information is available from October 2023 [50] (Tab. I). Evidence for a shortened PrEP regimen is consistent with the latest recommendations from the WHO, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) [51] and several European national rabies guidelines.

The conventional 3-dose regimen should be implemented in immunocompromised individuals. The rapid regimen and the one-week schedule with 2 doses on days

Tab. I. Primary immunization schedules in individuals never previously vaccinated [50].

	Conventional schedule	Accelerated schedule	One-week regimen
1 dose	Day 0	Day 0	Day 0
2 dose	Day 7	Day 3	Day 7
3 dose	Day 21 (28)	Day 7	

0 and 7 may be administered, if accompanied by serological testing at 2-4 weeks after the first rabies vaccine administration, to assess whether an additional vaccine administration is needed. Consultation with an infectious disease specialist or an immunologist is advised.
Booster doses are generally recommended every 2-5 years. The timing of booster administration after vaccination with the rapid regimen has not yet been established. In accordance with official recommendations, serological testing for the presence of antibody titers ≥0.5 IU/mL should be conducted to assess the need for booster doses.
Rabipur® may be used as a booster vaccine in subjects previously immunized with any rabies vaccine derived from human diploid cells [50].
The vaccine may be used for pre-exposure prophylaxis during pregnancy and in breastfeeding women if it is considered that the potential benefit outweighs any possible risk to the fetus and the infant [50].

Post-exposure prophylaxis of Rabipur® vaccine

Regarding PEP, this should begin as soon as possible after exposure.
Table II summarizes recommendations for PEP by type of exposure.
In-post-exposure prophylaxis of previously unvaccinated individuals, the vaccine should be administered according to table III [50].
In previously vaccinated individuals, post-exposure prophylaxis consists of two doses administered on days 0 and 3. Rabies immunoglobulin is not indicated in such cases.
In immunocompromised individuals with category II and III exposures (Tab. II), 5 doses should be given in combination with comprehensive wound management and local infiltration of rabies immunoglobulin.
In view of the almost invariably fatal outcome of rabies, there is no contraindication to post-exposure prophylaxis in pregnancy and in breastfeeding women.

Immunogenicity of Rabipur® vaccine

The immunogenicity of Rabipur® has been assessed in more than 50 clinical trials since 1983, in both PEP and PrEP regimens, using both IM and Intradermal (ID) administration. The trial populations have consisted of adults and children aged ≥12 months [3]. A concise overview of the main studies is provided below.
A double-blind comparative clinical trial carried out by Vodopija I. et al. [52] evaluated the immunogenicity of three tissue culture rabies vaccines by using a commercial human diploid cell vaccine (HDCV) lot as the comparator. Two different vaccination regimens, a pre-exposure schedule, and an abbreviated 2-1-1 post-exposure schedule (two doses of the vaccine applied bilaterally on day 0, with subsequent single doses given on days 7 and 21) were tested. In both regimens, purified chick embryo cell vaccine and purified Vero rabies vaccine induced an antibody response equivalent to that of HDCV. The 2-1-1 regimen rapidly induced a high antibody titre response, peaking on day 14.
Subsequently, a study by Nicholson KG et al. [53] investigated the response and persistence over two years of antibody titres elicited by a purified chick embryo cell culture rabies vaccine and a human diploid cell strain rabies vaccine. An antibody response was detected in all subjects on day 14, the highest titres being found after two intramuscular 1.0 mL doses administered on days 0, 7 and 21. In total, 177 volunteers were enrolled. By comparison, a schedule of immunization on days 0, 28 and 56 induced the highest titres 21 days after the final injection; on both schedules, antibody titres persisted equally over two years. Neutralizing antibody titres were lower after ID vaccination with 0.1 mL than with 1.0 mL IM on days 0, 7 and 21; when given on days 0, 28 and 56, however, the responses were comparable.
Analogously, a study that evaluated the antibody response and duration and the anamnestic response to boosters over a 2-year period found that vaccination with Rabipur® via an IM or ID regimen resulted in an adequate immune response by day 28, which was sustained on day 365 [54]. This clinical trial [54] assessed the immunogenic effects of a purified chick embryo cell (PCEC) rabies vaccine administered ID or IM. Four arms were involved: *i.e*. ID PrEP, IM PrEP, ID Booster, and IM Booster vaccination. In total, 130 adult volunteers participated in the clinical trial. Subjects undergoing IM administration received the vaccine according to the ACIP recommendations: PrEP, three 1 mL (2.5 I.U.) rabies vaccine doses (days 0, 7, and 21) or a routine booster of one 1 mL dose. The ID groups followed the same schedule, but the volume of the doses administered was different [volume of 0.1 mL (0.25 I.U.)]. The researchers found a similar rate of increase in rabies virus neutralizing antibody titres 14-21days after vaccination in both the ID and IM groups. The GMTs values elicited by ID vaccination were slightly lower than those elicited by IM vaccination, in both naïve and booster groups, and these differences were statistically significant. Fourteen days after completing vaccination, all individuals developed neutralizing antibody titres above the minimum arbitrary. Antibodies remained above the set threshold until the end of the trial, 160 days after the completion of vaccination.
Jaijaroensup W et al. [55] investigated the immunogenicity of rabies post-exposure booster injections in subjects who had previously received pre-exposure vaccination.

Tab. II. Recommendations for Post-Exposure Prophylaxis (PEP) [50].

Exposure category	Type of exposure to a rabid animal or suspected domestic or wild exposure [a] or exposure to an animal that cannot be analyzed	Recommended prophylaxis
I	The animal was touched or fed. Licking of intact skin. Contact with secretions or excretions of a rabid animal or human on intact skin.	None, if a reliable history can be gathered.
II	Light bite on unprotected skin. Superficial scratches or abrasions without bleeding.	Administer the vaccine immediately [b]. Discontinue treatment if the animal remains healthy for an observation period of 10 days [c] or if the animal tests negative for rabies on appropriate diagnostic techniques performed in a reliable laboratory.
III	Single or multiple transdermal bites [d] or scratches, licking of damaged skin. Contamination of mucous membranes with saliva (e.g. licks). Exposure to bats [e].	Administer rabies vaccine immediately and rabies immunoglobulin preferably as soon as possible after starting PEP. Rabies immunoglobulin can be injected up to 7 days after administration of the first dose of the vaccine. Discontinue treatment if the animal remains healthy for a 10-day observation period or if the animal tests negative for rabies on appropriate diagnostic techniques performed in a reliable laboratory.

[a] Exposure to rodents, rabbits or hares does not routinely require post-exposure prophylaxis.
[b] If an apparently healthy dog or cat from or one from a low-risk area is placed under observation, postponement of the start of treatment may be justified.
[c] The observation period refers only to dogs and cats. Except for animal species that are threatened or in danger of extinction, other domestic or wild animals suspected of rabies must be euthanized humanely and their tissues examined for rabies antigen by means of appropriate laboratory techniques.
[d] Bites, especially on the head, neck, face, hands and genitals, are considered category III exposures, owing to the abundant innervation of these areas.
[e] Post-exposure prophylaxis should be considered in the case of contact between a human and a bat, unless the exposed person can exclude a bite or scratch, or on exposure of a mucosa.

Tab. III. Post-exposure immunisation regimens for previously unvaccinated individuals [50].

	Essen regimen (5 doses)	Zagreb regimen (4 doses)	Reduced Essen regimen (4 doses)[2]
1st dose	Day 0	Day 0, 2 doses[1]	Day 0
2nd dose	Day 3		Day 3
3rd dose	Day 7	Day 7	Day 7
4th dose	Day 14	Day 21	Day 14
5th dose	Day 28		

[1] One injection in each of the two deltoids or thigh sites.
[2] This shortened Essen regimen may be used as an alternative for healthy, immunocompetent individuals provided they receive wound care plus rabies immunoglobulin in category III (Tab. II) as well as in category II (Tab. II) exposures and a WHO-prequalified rabies vaccine.

Specifically, 138 veterinary students underwent intradermal or intramuscular pre-exposure vaccination. They then received booster injections one year later [55]. One year later, individuals who had undergone intradermal rabies pre-exposure vaccination with 0.1 mL on days 0, 7, and 28 had a lower post-exposure booster antibody response than those who had received the pre-exposure series intramuscularly. A significant number of the former showed an unsatisfactory early anamnestic response. Residual neutralizing antibodies, 1 year after the preexposure vaccination, were also significantly higher in the intramuscular than in the 0.1 mL dose intradermal group. However, all study subjects had antibody titers above the minimum recommended level of 0.5 IU/mL by day 14. The authors concluded that not all subjects who had undergone intradermal pre-exposure vaccination were fully protected during the first 5 days after exposure. Thus, in the case of severe rabies exposure, rabies immunoglobulin injected into bite wounds and followed by a complete post-exposure vaccine series might be indicated.

Starting from the rationale that conventional rabies PrEP and Japanese encephalitis (JE) primary series vaccination regimens each require up to 4 weeks for completion and sometimes may not be feasible in individuals who need these immunizations on short notice, another study [56] investigated an accelerated regimen. Specifically, a Phase 3b study, randomized, controlled, observer-blind study evaluated the immunogenicity of the concomitant administration of a purified chick embryo cell culture rabies vaccine and an inactivated, adsorbed Japanese encephalitis vaccine according to an accelerated (1 week) regimen in comparison with the conventional regimens (4 weeks). A total of 661 healthy adults (18 to ≤65 years) were randomized to the accelerated or conventional vaccine regimens: Rabies + JE-Conventional; Rabies + JE-Accelerated; Rabies-Conventional; JE-Conventional. Independently of the rabies vaccination regimen, ≥97% of subjects reached an adequate levels of rabies virus-neutralizing antibody concentrations

(≥0.5 IU/mL) up to day 57, with percentages of subjects with concentrations ≥ 0.5 IU/mL on day 366 ranging between 68% in the Rabies + JE-Accelerated group and 80% in the Rabies-Conventional group. The Rabies + JE-Accelerated group displayed high JE neutralizing antibody titers at all-time points. These findings provided evidence that the accelerated PrEP rabies and JE vaccination regimens constitute a valid alternative in the short-term to recommended conventional regimens. The concomitant administration of these two vaccines does not compromise immune responses to any of the vaccine antigens, particularly when short-term protection is required.

"Boostability" after single-visit PrEP with rabies vaccine was demonstrated in a randomised controlled non-inferiority clinical trial [57]. Specifically, single-visit IM PrEP induced an anamnestic antibody response that was non-inferior to that of the two-visit IM schedule; single-visit ID PrEP, however, did not. The fold increases in antibody titers elicited by the single-visit IM and the single-visit ID schedule, respectively, were 2.32 (95% CI: 1.43-3.77) and 1.11 (95% CI: 0.66-1.87) times as high as that elicited by the standard schedule.

The 1-year boostability of a three-dose rabies PrEP schedule in individuals undergoing immunosuppressive monotherapy was evaluated in a very recent clinical trial [58]. Individuals on immunosuppressive monotherapy with a conventional immunomodulator or a TNF-alpha inhibitor (TNFi) for a chronic inflammatory disease underwent a three-dose IM PrEP schedule (days 0, 7, 21-28) with 1 mL Rabipur®, followed by a two-dose simulated PEP schedule (days 0, 3) after 12 months. Rabies neutralizing antibodies were assessed at the baseline, on day 21-28 (before the third PrEP dose), day 60, month 12 and month 12 + 7 days. The primary outcome was 1-year boostability, defined as the proportion of patients with a neutralizing antibody titre of ≥0.5 IU/mL at month 12 + 7 days. Secondary outcomes were GMTs and factors associated with the primary endpoint. The 1-year boostability was 90% with a GMT of 6.16 (95% CI: 3.83-9.91). All participants seroconverted at some point in the study. An early response to PrEP (on day 21-28) was significantly associated with 100% boostability (Odds Ratio 51; 95% CI: 5.0-6956, $P < 0.01$). In summary, the vaccination schedule investigated was immunogenic in patients on immunosuppressive monotherapy, with all participants seroconverting at some point in the study, though not all participants were able to mount a quick recall response after boosting (90%).

Good immunogenicity in children and pregnant women has been obtained in several studies [3].

Data from several clinical trials have demonstrated Rabipur® to be immunogenic with an acceptable safety profile in children for both PEP and PrEP. A study in children aged 2-15 years who had single IM doses (1.0 mL) on days 0, 7 and 28 for PrEP showed adequate immune response (≥ 5 IU/mL) by day 14 after vaccination in 100% of children [3, 59]. Similar findings have been observed in children aged 12-18 months receiving IM or ID Rabipur® on days 0, 7 and 28 with concomitant administration of Japanese encephalitis vaccine [3, 60].

A PEP study assessing Rabipur® immunogenicity was carried out in children bitten by either confirmed or suspected rabid animals (mainly dogs, followed by monkeys, cats and mongoose). Two hundred and seventy-one children aged 1-13 years received PEP on Days 0, 3, 7, 14, 30 and 90. The serological response was adequate with a maximum immune response 10–15 days after the last vaccination. The vaccine was well tolerated, and no failures were observed [3, 61].

Another clinical case-study reported on the vaccination with Rabipur® of a newborn baby after her mother developed clinical rabies during pregnancy following a dog bite 3 months prior to giving birth. A healthy baby was delivered, following which the baby received a total of five doses of Rabipur®: 1.0 mL IM at birth and a four-dose series (Days 3, 7, 14 and 30). At the age of 2 years, the child was healthy and developing normally [3, 62].

The administration of Rabipur® in pregnant women for PEP has been documented in a retrospective case series on two pregnant women who had WHO category III exposure to a suspected (Tab. II) rabid animal at gestational week 12. Each of the pregnant women got a total of five doses on days 0, 3, 7, 14 and 28 (Essen regimen) and equine rabies immunoglobulin. Both vaccine and equine rabies immunoglobulin were well tolerated with no reports of systemic or local adverse events. The women had normal deliveries of healthy babies with no evidence of congenital abnormalities [63]. There is a clear consensus that pregnancy is not a contraindication to rabies PEP [3].

Efficacy of Rabipur® vaccine

While immunogenicity of a vaccine is a surrogate parameter of efficacy, vaccine effectiveness can be assessed by investigating survival rate in subjects exposed to confirmed rabies who received the vaccine regimen. Indeed, real survival data are available following administration of Rabipur® to patients who have been exposed to rabies. Giesen A. et al. in their vaccine profile assessment reported that the individuals bitten by proven rabid animals who received Rabipur® survived over the study period (survival rate:100%) [3]. Specifically, a prospective clinical trial assessing the efficacy of a 0.1 mL dose of Rabipur® administered ID was conducted in 113 patients presenting with category III exposure (Tab. II) from laboratory-confirmed rabid animals. Patients were vaccinated and monitored monthly for 1 year post exposure. The vaccine was well tolerated, and no severe adverse events were reported. All patients survived 1 year post exposure, confirming the efficacy of vaccine [64]. This demonstrated efficacy comes from robust data collected from several hundred patients of different ages, including children [3].

There are very rare cases in which clinical rabies has developed in immunologically healthy people despite apparently correct PEP regimen, including wound treatment and timely administration of RIG and vaccine. A systematic review reported few probable vaccine fail-

ure cases in which Rabipur® was administered in one case, Rabipur® and a purified Vero cell rabies vaccine were given in a second case and an unknown vaccine in a third case [3]. More recently, a case of atypical initial clinical rabies symptoms that led to delayed diagnosis was reported. The patient died despite appropriate PEP and administration of Rabipur [3]. Physicians should be advised that immediate and correct PEP management without delay according to official recommendations is essential for patient survival.

Safety of Rabipur® vaccine

Many data have been collected on the safety profile of Rabipur®, including information gathered before vaccine licensing and in the post-authorization period [3, 65].
The main safety results from clinical trials are reported below.
Healthy volunteers from among hospital staff and veterinary students, who were randomly assigned to regimens using purified chick embryo cell PCEC vaccine, alone or together with human rabies immunoglobulin, did not experience severe Adverse Events (AEs), with only mild or moderate injection site pain being reported [66].
Two years later, in 125 patients who had received 3, 5 and 6 doses on days 0, 3, 7, 14, 30 and 90 after exposure to rabid animals, no systemic reactions were registered. Erythema, swelling and pain were among the local reactions reported [67].
Rabipur® administered in a three-dose series and followed by a 2-year booster has proved safe, with tenderness and pain at the injection site (~50%), redness and swelling (~35%), headaches, slight fever and malaise (~20%), joint pain (1.4%) and brief episodes of enlarged nymph nodes (4.3%) being reported [54].
Comparable findings emerged from a study by Briggs DJ et al. [68], in which the safety profile was positively confirmed, the most frequently reported concomitant medical condition being 'allergy' (7.2%).
In 620 healthy volunteers, mild local side-reactions were observed in less than 2% of the vaccinees. No serious general reactions were reported or seen after 2200 injections (except for three cases of urticaria) [69].
A 10-year post-marketing surveillance study was carried out in India; this confirmed the good safety profile of PEP and PrEP with Rabipur®. Specifically, the vaccine was well tolerated in a cohort of 1289 individuals, including children aged ≥1 year. Only 4% of subjects reported AEs, which were mainly mild or moderate. The most frequently reported local adverse reactions were injection-site pain (2.1%) and injection-site induration (1.1%). Mild fever (37.2-37.8°C) occurred in six subjects (0.5%) following the third or fourth vaccination, and lasted 12-24 h [3, 70].
Another relevant post-licensure safety study was conducted in the USA from 1997 to 2005. This showed that, on approximately 1.1 million doses of vaccine, 336 AEs were reported after Rabipur® administration, approximately 30 events per 100,000 doses. Twenty-four (7%) of the AEs were considered serious by the reporters; there were no reports of death. The authors concluded that the evaluation of Vaccine Adverse Event Reporting System reports did not suggest a high frequency or unusual pattern of serious or other medically important AEs, and that most AEs were non-serious and consistent with pre-licensure safety data [65].
Many decades of global use of Rabipur® has confirmed the safety and tolerability profile observed in clinical trials. The overall rate of reports of adverse reactions is approximately 12.3 events per 100,000 doses. The vast majority (nearly 80%) of events reported in Asia, Europe and the USA were non-serious reactions recorded during clinical trials. The most often reported symptoms are: systemic reactions, such as headache, dizziness, influenza-like illness and associated symptoms (*e.g.*, fever, asthenia and myalgia), and local injection-site-related reactions (*e.g.,* redness, swelling and pain) [3, 50].
Rabipur® is generally well tolerated in children. The studies reported typical adverse reactions as fever, fatigue, and pain and redness at the injection site. No serious adverse reaction related to the vaccine occurred [3].

Rabies as a travel risk

All travellers to rabies affected countries, especially in Asia and Africa, should avoid contact with dogs, cats and other animals whenever possible, and seek advice on the need for rabies vaccination prior to travel.
Any individual who has been bitten, scratched or licked by an animal in a country where rabies is endemic, or has had direct contact with a bat in those countries, should take immediate action by washing the wound or site of exposure abundantly with soap and water, and seek local medical advice without delay, even if they have been previously vaccinated [1].
When administered promptly after exposure, a course of rabies vaccine is extremely effective in preventing the disease. If such exposure occurs abroad, travellers should also consult their doctor or the travel medicine specialist of their Local Health unit on return, in order to complete the course of rabies treatment. If they cannot receive medical advice abroad, travellers should contact their doctor promptly upon return, in order to be assessed [71].
In Europe, most human rabies cases involve travellers bitten by dogs or other animals in rabies-enzootic countries. Therefore, European travellers visiting rabies-enzootic countries should be aware of the risk of being infected with the rabies virus if they come into physical contact with mammals. They should also consider pre-exposure vaccination according to the criteria recommended by the WHO.
In this regard, travel clinics and public health authorities in the EU/EEA should reinforce their prevention campaigns and advise travellers visiting countries with a moderate or high risk of rabies (i) to be aware of the possibility of acquiring rabies infection through physical contact with mammals, (ii) to undergo PrEP vacci-

nation in accordance with the criteria recommended by the WHO, and (iii) to immediately seek medical attention in the event of being bitten or scratched by mammals [72]. Dedicated communication campaigns should be developed to target different groups of travellers and levels of awareness, and the use of social media to reach these subjects should be explored. In addition, travellers should be reminded to follow veterinary rules and regulations when travelling with pets. Finally, EU/EEA citizens should only acquire pets through authorised channels. Several practical guidelines from different countries are available and are useful tools for healthcare workers [72-77].

Rabies as an occupational risk

Workers in certain occupations may face a higher risk of exposure to rabies. Such individuals include those who work with rabies in laboratory settings, veterinarians, veterinary students, animal handlers, animal control and wildlife officers, those involved in outdoor recreational activities, forestry workers, and wildlife guides in at-risk areas, missionary workers traveling to certain countries, and recipients of transplants, particularly corneas [78, 79]. However, the at-risk population could well be wider, but it is not easy to identify all risk groups in the general population.

Several factors can increase a person's risk of contracting rabies. These include living in an environment where wild animals abound, living in areas with poor sanitation or far from vaccination services, traveling to or living in countries where rabies is more common, and engaging in activities that carry a risk of contact with wild animals, such as camping, hiking or caving [80].

For workers in occupations that are at high risk of rabies infection, PrEP is recommended, followed by a booster dose in the event of exposure [78].

For healthcare workers, routine precautions, including wearing gowns, goggles, masks and gloves, are recommended when providing care for persons suspected of having clinical rabies. In the event of exposure, public health officials should adopt specific criteria to identify high-risk contacts and provide immunization.

Transmission of the virus to healthcare workers caring for a patient infected by rabies has never been documented. However, the admission of a human rabies case to hospital often creates great anxiety among staff, who fear contamination. Theoretically, transmission could occur through direct contact the broken skin or mucosa, saliva, tears, oropharyngeal secretions, cerebrospinal fluid or neural tissue of an infected individual. The care of a rabies patient requires only standard precautions against infection, which consist of the basic preventive measures applied in many other common diseases. These should be sufficient to prevent transmission to staff. Preventing anxiety among healthcare workers should therefore be an achievable goal.

Discussion and Conclusions

Carnivores, especially of the *canidae* family, constitute the principal reservoir of the rabies virus, and are responsible for maintaining the infectious cycle, and hence for the persistence of rabies disease. Canine rabies accounts for 99% of the human death toll, causing more than 60,000 human deaths annually. However, bat species and other wildlife mammals are also a major reservoir of the virus and a threat for human health.

Countries in Asia and Africa carry the heaviest disease burden, and the available data are underestimated due to several reasons: i) inadequate surveillance systems not able to keep track of the number of rabies cases diagnosed and the number of people who have been treated for the disease, ii) PrEP and PEP shortages, and iii) lack of the necessary staff and infrastructure to conduct patient management. In this context, the Global alliance for vaccine immunization (GAVI) recently announced intentions to resume investment in human rabies vaccines, which was halted by the COVID-19 pandemic [81].

The majority of the EU/EEA countries are free from rabies in mammals, as elimination of the disease (no enzootic circulation of the virus and low number of imported cases) had been achieved by 2020. However, the international travels and illegal importation of potentially infected animals, mainly dogs, poses a risk to public health.

The WHO regards rabies as a neglected disease and promotes efforts to establish wider access to appropriate treatment for humans.

The "One Health" approach is the most promising strategy for achieving the global goal of eliminating canine-mediated human rabies by 2030. The 'Zero by 30' framework is a global strategy to effect pragmatic changes in approximately 100 countries over the decade. It advocates a unified surveillance mechanism and a collaborative alliance between human and animal healthcare, thereby enabling better financial and resource management by participating countries [82, 83].

Rabies is entirely preventable. Significantly raising the perception of this disease as a global health challenge demands international attention and active support in order to save lives. There is a need for rabies education and initiatives to raise awareness, including information on wound treatment (first aid) and PEP. Each of the many thousands of deaths that occur annually is a universal health system failure, in that victims of rabid bites have not accessed post-exposure vaccines, *i.e.*, in practice, universal health coverage remains an unavailable model.

Rabipur® is one of the available anti-rabies vaccines, and is indicated for active immunization in individuals of all ages. Its efficacy and safety have been amply demonstrated.

As regard as PrEP, in clinical trials carried out in unimmunised subjects almost all subjects achieved an adequate immune response 3 to 4 weeks after the end of a primary series of three injections.

About prophylaxis in humans living in rabies-free countries, PrEP is indicated for individuals who face occupational and/or travel-related exposure to the rabies virus in specific settings or over an extended period.
Considering PEP, in clinical trials Rabipur® elicited adequate neutralising antibodies in almost all subjects by day 14 or 30, when administered according to the 5- dose (day 0, 3, 7, 14, 28; 1.0 mL each, intramuscular) Essen regimen or 4-dose (day 0 [2 doses], 7, 21; 1.0 mL each, intramuscular) Zagreb regimen.
The good safety profile of the vaccine observed in clinical trials is confirmed by the post-licensure surveillance.
Wider use of human rabies vaccination for PrEPand PEP in conjunction with programs to eradicate rabies from animal populations would be the right direction in reducing the burden of disease.

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Conflicts of Interest statement

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Author's contribution

All authors equally contributed to this manuscript.

References

[1] WHO Rabies. Available at: https://www.who.int/news-room/fact-sheets/detail/rabies (Accessed on: 3/04/2024).

[2] Noah DL, Drenzek CL, Smith JS, Krebs JW, Orciari L, Shaddock J, Sanderlin D, Whitfield S, Fekadu M, Olson JG, Rupprecht CE, Childs JE. Epidemiology of human rabies in the United States, 1980 to 1996. Ann Intern Med 1998;128:922-30. https://doi.org/10.7326/0003-4819-128-11-199806010-00012.

[3] Giesen A, Gniel D, Malerczyk C. Correction to: 30 years of rabies vaccination with Rabipur: a summary of clinical data and global experience. Expert Rev Vaccines 2015;1:775. https://doi.org/10.1586/14760584.2015.1027863.

[4] Coulon P, Derbin C, Kucera P, Lafay F, Prehaud C, Flamand A. Invasion of the peripheral nervous systems of adult mice by the CVS strain of rabies virus and its avirulent derivative AvO1. J Virol 1989;63:3550-4. https://doi.org/10.1128/JVI.63.8.3550-3554.1989.

[5] Jackson AC, Phelan CC, Rossiter JP. Infection of Bergmann glia in the cerebellum of a skunk experimentally infected with street rabies virus. Can J Vet Res 2000;64:226-8.

[6] Lippi G, Cervellin G. Updates on Rabies virus disease: is evolution toward "Zombie virus" a tangible threat? Acta Biomed 2021;92:e2021045. https://doi.org/10.23750/abm.v92i1.9153.

[7] World Health Organization. WHO Expert Consultation on Rabies: third report. Geneva: World Health Organization 2018. Available at: https://www.who.int/publications/i/item/WHO-TRS-1012 (Accessed on: 20/06/2024).

[8] Scott TP, Nel LH. Lyssaviruses and the Fatal Encephalitic Disease Rabies. Front Immunol 2021;12:786953. https://doi.org/10.3389/fimmu.2021.786953.

[9] Marston DA, Banyard AC, McElhinney LM, Freuling CM, Finke S, de Lamballerie X, Müller T, Fooks AR. The lyssavirus host-specificity conundrum-rabies virus-the exception not the rule. Curr Opin Virol 2018;28:68-73. https://doi.org/10.1016/j.coviro.2017.11.007.

[10] Ness A, Aiken J, McKenzie D. Sheep scrapie and deer rabies in England prior to 1800. Prion 2023;17:7-15. https://doi.org/10.1080/19336896.2023.2166749.

[11] Wiktor TJ, György E, Schlumberger D, Sokol F, Koprowski H. Antigenic properties of rabies virus components. J Immunol 1973;110:269-76.

[12] Gaudin Y, Ruigrok RW, Tuffereau C, Knossow M, Flamand A. Rabies virus glycoprotein is a trimer. Virology 1992;187:627-32. https://doi.org/10.1016/0042-6822(92)90465-2.

[13] Lian M, Hueffer K, Weltzin MM. Interactions between the rabies virus and nicotinic acetylcholine receptors: A potential role in rabies virus induced behavior modifications. Heliyon 2022;8:e10434. https://doi.org/10.1016/j.heliyon.2022.e10434.

[14] Hemachudha T, Laothamatas J, Rupprecht CE. Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges. Lancet Neurol 2002;1:101-9. https://doi.org/10.1016/s1474-4422(02)00041-8.

[15] Ray NB, Ewalt LC, Lodmell DL. Rabies virus replication in primary murine bone marrow macrophages and in human and murine macrophage-like cell lines: implications for viral persistence. J Virol 1995;69:764-72. https://doi.org/10.1128/JVI.69.2.764-772.1995.

[16] Mitrabhakdi E, Shuangshoti S, Wannakrairot P, Lewis RA, Susuki K, Laothamatas J, Hemachudha T. Difference in neuropathogenetic mechanisms in human furious and paralytic rabies. J Neurol Sci 2005;238:3-10. https://doi.org/10.1016/j.jns.2005.05.004.

[17] Mader EC Jr, Maury JS, Santana-Gould L, Craver RD, El-Abassi R, Segura-Palacios E, Sumner AJ. Human Rabies with Initial Manifestations that Mimic Acute Brachial Neuritis and Guillain-Barré Syndrome. Clin Med Insights Case Rep 2012;5:49-55. https://doi.org/10.4137/CCRep.S9318.

[18] Hemachudha T, Phuapradit P. Rabies. Curr Opin Neurol 1997;10:260-7. https://doi.org/10.1097/00019052-199706000-00016.

[19] Hemachudha T, Wacharapluesadee S, Laothamatas J, Wilde H. Rabies. Curr Neurol Neurosci Rep 2006;6:460-8. https://doi.org/10.1007/s11910-006-0047-2.

[20] Centers for Disease Control and Prevention (CDC). Human rabies--Minnesota, 2007. MMWR Morb Mortal Wkly Rep 2008;57:460-2.

[21] Shantavasinkul P, Tantawichien T, Wacharapluesadee S, Jeamanukoolkit A, Udomchaisakul P, Chattranukulchai P, Wongsaroj P, Khawplod P, Wilde H, Hemachudha T. Failure of rabies postexposure prophylaxis in patients presenting with unusual manifestations. Clin Infect Dis 2010;50:77-9. https://doi.org/10.1086/649873.

[22] Smreczak M, Orłowska A, Trębas P, Stolarek A, Freuling C, Müller T. Re-emergence of rabies in Mazowieckie Voivodeship, Poland, 2021. Zoonoses Public Health 2023 Feb;70:111-6. https://doi.org/10.1111/zph.13005.

[23] Knobel DL, Cleaveland S, Coleman PG, Fèvre EM, Meltzer MI, Miranda ME, Shaw A, Zinsstag J, Meslin FX. Re-evaluating the burden of rabies in Africa and Asia. Bull World Health Organ 2005;83:360-8.

[24] Taylor LH, Hampson K, Fahrion A, Abela-Ridder B, Nel LH. Difficulties in estimating the human burden of canine rabies. Acta Trop 2017;165:133-40. https://doi.org/10.1016/j.actatropica.2015.12.007.

[25] Ma X, Bonaparte S, Toro M, Orciari LA, Gigante CM, Kirby JD, Chipman RB, Fehlner-Gardiner C, Cedillo VG, Aréchiga-Ceballos N, Rao AK, Petersen BW, Wallace RM. Rabies surveillance in the United States during 2020. J Am Vet Med Assoc 2022;260:1157-65. https://doi.org/10.2460/javma.22.03.0112.

[26] Subedi D, Chandran D, Subedi S, Acharya KP. Ecological and Socioeconomic Factors in the Occurrence of Rabies: A Forgotten Scenario. Infect Dis Rep 2022;14:979-86. https://doi.org/10.3390/idr14060097.

[27] CDC. Rabies. CDC Yellow Book 2024. Available at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/rabies (Accessed on: 24/07/2024).

[28] Velasco-Villa A, Mauldin MR, Shi M, Escobar LE, Gallardo-Romero NF, Damon I, Olson VA, Streicker DG, Emerson G. The history of rabies in the Western Hemisphere. Antiviral Res 2017;146:221-32. https://doi.org/10.1016/j.antiviral.2017.03.013.

[29] WHO's Strategic Advisory Group of Experts (SAGE) on Immunization, meeting of October 2017. Rabies session. Available at: https://www.who.int/news-room/events/detail/2017/10/17/default-calendar/strategic-advisory-group-of-experts-on-immunization-(sage)---october-2017 (Accessed on : 24/07/2024).

[30] Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, Barrat J, Blanton JD, Briggs DJ, Cleaveland S, Costa P, Freuling CM, Hiby E, Knopf L, Leanes F, Meslin FX, Metlin A, Miranda ME, Müller T, Nel LH, Recuenco S, Rupprecht CE, Schumacher C, Taylor L, Vigilato MA, Zinsstag J, Dushoff J. Global Alliance for Rabies Control Partners for Rabies Prevention. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis 2015;9:e0003709. https://doi.org/10.1371/journal.pntd.0003709. Erratum in: PLoS Negl Trop Dis 2015;9:e0003786. https://doi.org/10.1371/journal.pntd.0003786.

[31] Arief RA, Hampson K, Jatikusumah A, Widyastuti MD, Sunandar, Basri C, Putra AA, Willyanto I, Estoepangestie AT, Mardiana IW, Kesuma IK, Sumantra IP, Doherty PF Jr, Salman MD, Gilbert J, Unger F. Determinants of Vaccination Coverage and Consequences for Rabies Control in Bali, Indonesia. Front Vet Sci 2017;3:123. https://doi.org/10.3389/fvets.2016.00123. Erratum in: Front Vet Sci 2017;4:20. https://doi.org/10.3389/fvets.2017.00020.

[32] Tan J, Wang R, Ji S, Nanjing Agricultural University research group of The Challenge Cup Rabies Research Group, Su S, Zhou J. One Health strategies for rabies control in rural areas of China. Lancet Infect Dis 2017;17:365-7. https://doi.org/10.1016/S1473-3099(17)30116-0.

[33] Fang LX, Ping F, Ping du Y, Hui BG, Yan YX. Socioeconomic status is a critical risk factor for human rabies post-exposure prophylaxis. Vaccine 2010;28:6847-51. https://doi.org/10.1016/j.vaccine.2010.08.034.

[34] Arias-Orozco P, Bástida-González F, Cruz L, Villatoro J, Espinoza E, Zárate-Segura PB, Recuenco S. Spatiotemporal analysis of canine rabies in El Salvador: Violence and poverty as social factors of canine rabies. PLoS One 2018;13:e0201305. https://doi.org/10.1371/journal.pone.0201305.

[35] Fisher CR, Streicker DG, Schnell MJ. The spread and evolution of rabies virus: conquering new frontiers. Nat Rev Microbiol 2018;16:241-55. https://doi.org/10.1038/nrmicro.2018.11.

[36] Kunkel A, Jeon S, Joseph HC, Dilius P, Crowdis K, Meltzer MI, Wallace R. The urgency of resuming disrupted dog rabies vaccination campaigns: a modeling and cost-effectiveness analysis. Sci Rep 2021;11:12476. https://doi.org/10.1038/s41598-021-92067-5.

[37] Fehlner-Gardiner C. Rabies control in North America – past, present and future. Rev Sci Tech 2018;37:421-37. https://doi.org/10.20506/rst.37.2.2812.

[38] Brunt S, Solomon H, Brown K, Davis A. Feline and Canine Rabies in New York State, USA. Viruses 2021;13:450. https://doi.org/10.3390/v13030450.

[39] Moore SM. Rabies: Current Preventive Strategies. Vet Clin North Am Small Anim Pract 2019;49:629-41. https://doi.org/10.1016/j.cvsm.2019.02.014.

[40] WHO Rabies epidemiology. Available at: https://www.who.int/teams/control-of-neglected-tropical-diseases/rabies/epidemiology-and-burden#:~:text=Rabies%20is%20estimated%20to%20cause,the%20true%20burden%20of%20disease (Accessed on: 20/06/2024).

[41] Rupprecht CE, Hanlon CA, Hemachudha T. Rabies re-examined. Lancet Infect Dis 2002;2:327-43. https://doi.org/10.1016/s1473-3099(02)00287-6.

[42] Marston DA, Horton DL, Nunez J, Ellis RJ, Orton RJ, Johnson N, Banyard AC, McElhinney LM, Freuling CM, Fırat M, Ünal N, Müller T, de Lamballerie X, Fooks AR. Genetic analysis of a rabies virus host shift event reveals within-host viral dynamics in a new host. Virus Evol 2017;3:vex038. https://doi.org/10.1093/ve/vex038.

[43] GBD Results. Available at: https://vizhub.healthdata.org/gbd-results/. (Accessed on: 20/06/2024).

[44] Gan H, Hou X, Wang Y, Xu G, Huang Z, Zhang T, Lin R, Xue M, Hu H, Liu M, Cheng ZJ, Zhu Z, Sun B. Global burden of rabies in 204 countries and territories, from 1990 to 2019: results from the Global Burden of Disease Study 2019. Int J Infect Dis 2023;126:136-44. https://doi.org/10.1016/j.ijid.2022.10.046.

[45] Qin X, Liu K, Fu T, Song S, Zhao C, Li Z, Lu X, Shao Z. Global burden, trends, and predictions of rabies: an analysis from the Global Burden of Disease Study 1990–2019 and projections for 2030. J Public Health 2023. https://doi.org/10.1007/s10389- 023-01971-9

[46] WHO Rabies Modelling Consortium. Zero human deaths from dog-mediated rabies by 2030: perspectives from quantitative and mathematical modelling. Gates Open Res 2020;3:1564. https://doi.org/10.12688/gatesopenres.13074.2.

[47] WHO. African Region. Rabies preventable human death. Analytical Fact Sheet 2023. Available at: https://files.aho.afro.who.int/afahobckpcontainer/production/files/Regional_Rabies_fact_sheet_Nov23.pdf (Accessed on 15/07/2024).

[48] PAHO. PAN American Health Organization. World Rabies Day: Latin America and the Caribbean on the cusp of eliminating rabies deaths. Available at: https://www.paho.org/en/news/25-9-2018-world-rabies-day-latin-america-and-caribbean-cusp-eliminating-rabies-deaths (Accessed on: 15/07/2024).

[49] ECDC. The European Union One Health Zoonoses Report 2022. EFSA J 2023;21:e8442. https://doi.org/10.2903/j.efsa.2023.8442.

[50] Rabipur. Sumary of product. Available at: https://medicinali.aifa.gov.it/it/#/it/dettaglio/0000036335 (Accessed on: 15/07/2024).

[51] CDC ACIP. ACIP Evidence to Recommendations for Rabies Pre-exposure prophylaxis with a 2-dose Schedule. Available at: https://www.cdc.gov/vaccines/acip/recs/grade/rabies-2-dose-etr.html (Accessed on: 15/07/2024).

[52] Vodopija I, Sureau P, Lafon M, Baklaic Z, Ljubicić M, Svjetlicić M, Smerdel S. An evaluation of second generation tissue culture rabies vaccines for use in man: a four-vaccine comparative immunogenicity study using a pre-exposure vaccination schedule and an abbreviated 2-1-1 postexposure schedule. Vaccine 1986;4:245-8. https://doi.org/10.1016/0264-410x(86)90138-6.

[53] Nicholson KG, Farrow PR, Bijok U, Barth R. Pre-exposure studies with purified chick embryo cell culture rabies vaccine and human diploid cell vaccine: serological and clinical responses in man. Vaccine 1987;5:208-10. https://doi.org/10.1016/0264-410x(87)90102-2.

[54] Dreesen DW, Fishbein DB, Kemp DT, Brown J. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine 1989;7:397-400. https://doi.org/10.1016/0264-410x(89)90152-7.

[55] Jaijaroensup W, Limusanno S, Khawplod P, Serikul K, Chomchay P, Kaewchomphoo W, Tantawichien T, Wilde H. Immunogenicity of rabies postexposure booster injections in subjects who had previously received intradermal preexposure vaccination. J Travel Med 1999;6:234-7. https://doi.org/10.1111/j.1708-8305.1999.tb00524.x.

[56] Cramer JP, Jelinek T, Paulke-Korinek M, Reisinger EC, Dieckmann S, Alberer M, Bühler S, Bosse D, Meyer S, Fragapane E, Costantini M, Pellegrini M, Lattanzi M, Dovali C. One-year immunogenicity kinetics and safety of a purified chick embryo cell rabies vaccine and an inactivated Vero cell-derived Japanese encephalitis vaccine administered concomitantly according to a new, 1-week, accelerated primary series. J Travel Med 2016;23:taw011. https://doi.org/10.1093/jtm/taw011.

[57] Overduin LA, Koopman JPR, Prins C, Verbeek-Menken PH, De Pijper CA, Eblé PL, Heerink F, van Genderen PJJ, Grobusch MP, Visser LG. Boostability after single-visit pre-exposure prophylaxis with rabies vaccine: a randomised controlled non-inferiority trial. Lancet Infect Dis 2024;24:206-16. https://doi.org/10.1016/S1473-3099(23)00452-8.

[58] Garcia Garrido HM, van Put B, Terryn S, de Pijper CA, Stijnis C, D'Haens GR, Spuls PI, van de Sande MG, van Gucht S, Grobusch MP, Goorhuis A. Immunogenicity and 1-year boostability of a three-dose intramuscular rabies pre-exposure prophylaxis schedule in adults receiving immunosuppressive monotherapy: a prospective single-centre clinical trial. J Travel Med 2023 5;30:taac148. https://doi.org/10.1093/jtm/taac148.

[59] Lumbiganon P, Chaiprasithikul P, Sookpranee T, et al. Pre-exposure vaccination with purified chick embryo cell rabies vaccines in children. Asian Pac J Allergy Immunol 1989;7:99-101.

[60] Pengsaa K, Limkittikul K, Sabchareon A, Ariyasriwatana C, Chanthavanich P, Attanath P, Malerczyk C. A three-year clinical study on immunogenicity, safety, and booster response of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12- to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine. Pediatr Infect Dis J 2009;28:335-7. https://doi.org/10.1097/INF.0b013e3181906351.

[61] Sehgal S, Bhardwaj M, Bhattacharya D. Immunogenicity and feasibility of purified chick embryo cell vaccine. Indian Pediatr 1994;31:133-7.

[62] Lumbiganon P, Wasi C. Survival after rabies immunisation in newborn infant of affected mother. Lancet 1990;336:319. https://doi.org/10.1016/0140-6736(90)91861-4.

[63] Sudarshan MK, Giri MS, Mahendra BJ, Venkatesh GM, Sanjay TV, Narayana DH, Ravish HS. Assessing the safety of post-exposure rabies immunization in pregnancy. Hum Vaccin 2007;3:87-9. https://doi.org/10.4161/hv.3.3.4010.

[64] Quiambao BP, Dimaano EM, Ambas C, Davis R, Banzhoff A, Malerczyk C. Reducing the cost of post-exposure rabies prophylaxis: efficacy of 0.1 mL PCEC rabies vaccine administered intradermally using the Thai Red Cross post-exposure regimen in patients severely exposed to laboratory-confirmed rabid animals. Vaccine 2005;23:1709-14. https://doi.org/10.1016/j.vaccine.2004.09.027.

[65] Dobardzic A, Izurieta H, Woo EJ, Iskander J, Shadomy S, Rupprecht C, Ball R, Braun MM. Safety review of the purified chick embryo cell rabies vaccine: Data from the Vaccine Adverse Event Reporting System (VAERS), 1997-2005. Vaccine 2007;25:4244-51. https://doi.org/10.1016/j.vaccine.2007.02.075.

[66] Scheiermann N, Baer J, Hilfenhaus J, Marcus I, Zoulek G. Reactogenicity and immunogenicity of the newly developed purified chick embryo cell (PCEC)-rabies vaccine in man. Zentralbl Bakteriol Mikrobiol Hyg A 1987;265:439-50. https://doi.org/ 10.1016/s0176-6724(87)80263-8.

[67] Madhusudana SN, Tripathi KK. Post exposure studies with human diploid cell rabies vaccine and purified chick embryo cell vaccine: comparative serological responses in man. Zentralbl Bakteriol 1989;271:345-50. https://doi.org/10.1016/s0934-8840(89)80033-7.

[68] Briggs DJ, Dreesen DW, Nicolay U, Chin JE, Davis R, Gordon C, Banzhoff A. Purified Chick Embryo Cell Culture Rabies Vaccine: interchangeability with Human Diploid Cell Culture Rabies Vaccine and comparison of one versus two-dose post-exposure booster regimen for previously immunized persons. Vaccine 2000;19:1055-60. https://doi.org/10.1016/s0264-410x(00)00342-x.

[69] Bijok U, Vodopija I, Smerdel S, Thongcharoen P, Nicholson K, Dietrich M, Gonzalez de Cosio A. Purified chick embryo cell (PCEC) rabies vaccine for human use: clinical trials. Behring Inst Mitt 1984;(76):155-64.

[70] Sehgal S, Bhattacharya D, Bhardwaj M. Ten year longitudinal study of efficacy and safety of purified chick embryo cell vaccine for pre- and post-exposure prophylaxis of rabies in Indian population. J Commun Dis 1995;27:36-43.

[71] WHO. WHO Expert Consultation on Rabies Available at: https://iris.who.int/bitstream/handle/10665/272364/9789241210218-eng.pdf (Accessed on: 20/06/2024).

[72] NITAG. Available at: https://www.nitag-resource.org/sites/default/files/0cd83c26cce042fc02a514aa7c31e9616f281f46_1.pdf (Accessed on: 20/06/2024).

[73] GOV.UK. Rabies post-exposure treatment: management guidelines. Available at: https://www.gov.uk/government/publications/rabies-post-exposure-prophylaxis-management-guidelines (Accessed on: 21/06/2024).

[74] CDC. Rabies Post-exposure Prophylaxis. Available at: https://www.cdc.gov/rabies/hcp/prevention-recommendations/post-exposure-prophylaxis.html (Accessed on: 15/07/2024).

[75] Canada. Rabies Vaccinee: Canadian Immunization Guide. Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-18-rabies-vaccine.html (Accessed on: 15/07/2024).

[76] Hampson K. Good news for travellers, but what do rabies vaccines say about global health? Lancet Infect Dis 2024;24:119-21. https://doi.org/10.1016/S1473-3099(23)00499-1.

[77] Gossner CM, Mailles A, Aznar I, Dimina E, Echevarría JE, Feruglio SL, Lange H, Maraglino FP, Parodi P, Perevoscikovs J, Van der Stede Y, Bakonyi T. Prevention of human rabies: a challenge for the European Union and the European Economic Area. Euro Surveill 2020;25:2000158. https://doi.org/10.2807/1560-7917.ES.2020.25.38.2000158.

[78] Kan VL, Joyce P, Benator D, Agnes K, Gill J, Irmler M, Clark A, Giannakos G, Gabourel A, Gordin FM. Risk assessment for healthcare workers after a sentinel case of rabies and review of the literature. Clin Infect Dis 2015;60:341-8. https://doi.org/10.1093/cid/ciu850.

[79] Khairullah AR, Kurniawan SC, Hasib A, Silaen OSM, Widodo A, Effendi MH, Ramandinianto SC, Moses IB, Riwu KHP, Yanestria SM. Tracking lethal threat: in-depth review of rabies. Open Vet J 2023;13:1385-99. https://doi.org/10.5455/OVJ.2023.v13.i11.1.

[80] Chikanya E, Macherera M, Maviza A. An assessment of risk factors for contracting rabies among dog bite cases recorded in Ward 30, Murewa district, Zimbabwe. PLoS Negl Trop Dis 2021;15:e0009305. https://doi.org/10.1371/journal.pntd.0009305.

[81] GAVI. Gavi to boost access to life-saving human rabies vaccines in over 50 countries. Available at: https://www.gavi.org/news/media-room/gavi-boost-access-life-saving-human-rabies-vaccines-over-50-countries (Accessed on: 15/07/2024).

[82] WHO. New global strategic plan to eliminate dog-mediated rabies by 2030. Available at: https://www.who.int/news-room/commentaries/detail/new-global-strategic-plan-to-eliminate-dog-mediated-rabies-by-2030 (Accesesed on: 21/06/2024).

[83] Shafaati M, Akbarpour S, Priyanka, Saied AA, Choudhary OP. Tackling rabies by one health approach: Pitfalls on the road to global eradication. New Microbes New Infect 2023;52:101098. https://doi.org/10.1016/j.nmni.2023.101098.

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Non-comunicable disease

Awareness of Lung Cancer Among the Lebanese General Population: a Cross-Sectional Study

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Keywords

Lung • Cancer Awareness Measurement Tool • Lebanese Population • Lung cancer • Warning signs • Risk factors

Summary

Background. *Lung cancer is a significant contributor to mortality worldwide. The aim of this study was to assess the level of lung cancer awareness among the Lebanese general population.*
Methods. *An online-based questionnaire was completed by 410 participants all over Lebanon. A validated Lung Cancer Awareness Measurement tool was used. Multivariate analysis using Generalized Linear model and post-hoc analysis were performed after assessing validity and reliability of the scale.*
Results. *Only 13.7% correctly identified age-related lung cancer risk, while 60.7% thought age was unrelated. Warning signs were poorly recalled, with persistent cough being the most remembered (58%), and coughing up blood being highly recognized (87.8%). Participants struggled to recognize persistent shoulder pain (28.7%) and finger/nail changes (29.51%) as possible warning signs of lung cancer. Multivariate analysis showed that governorates, educational level, and occupation significantly affected warning sign-scores. Post-hoc analysis revealed that people residing in Bekaa scored lower warning sign recognition scales compared with participants residing in Beirut, Mount Lebanon, and North. Postgraduates and medical field workers showed higher symptom recognition, with the latter scoring higher recall scales as well. Smoking was the most recalled and recognized risk factor (82% and 95.6%). Females, postgraduates, and medical workers showed higher risk factor recognition. While 75% were willing to seek medical attention for lung cancer suspicion, 58% lacked confidence in identifying warning signs.*
Conclusion. *Extensive awareness campaigns focusing on age-related misconceptions, warning signs, and risk factors hold immense promise for improved therapeutic outcomes.*

Introduction

Despite ongoing research advancements in the field of oncology worldwide, the cancer burden remains high. According to the International Agency for Research on Cancer (IARC), the global incidence of cancer increased to 19.3 million new cases and resulted in 10 million deaths by the year 2020 [1].
As for specific cancer types, lung cancer ranked second after breast cancer in terms of worldwide incidence and accounted for 11.4% of total new cancers in 2020 [1]. It is also the leading cause of mortality among all types of cancer worldwide in men and ranks second after breast cancer in women (18% of the total cancer deaths), highlighting the substantial impact of lung cancer incidence on the healthcare system [1].
Additionally, a descriptive study assessing the expected global burden of lung cancer between the years 2020 and 2040 anticipated a further increase in its incidence, particularly in low and middle-income countries, thus potentially posing an additional burden on the healthcare systems and resources, especially in such regions [2].
In Lebanon, a recent epidemiological study also showed that lung cancer incidence comes right after breast cancer, accounting for approximately 9.2% of all reported cancer cases during the period from 2005 to 2015 [3]. The majority of patients are aged 50 years or older, with approximately 89.2% of cases occurring within this age group [3].
High rates of mortality and morbidity caused by lung cancer were linked to several barriers in a systematic review conducted in 2021, all of which can result in delayed diagnosis and hence poorer treatment outcomes [4]. The barriers include lack of symptom awareness, underestimation or misinterpretation of warning signs, poor doctor-patient relationships, and limited access to healthcare services, including financial hindrance, geographic distance, and inadequate access to specialized healthcare professionals [4].
The American Cancer Society categorizes lung cancer risk factors as modifiable or non-modifiable [5]. Modifiable risk factors include smoking, both direct and indirect as well as exposure to cancer-causing chemicals such as radon and asbestos. Non-modifiable risk factors encompass past chest radiation for treating different cancers, especially breast cancer, along with air pollution and a family history of lung cancer [5].
In that regard, assessing awareness levels among the Lebanese population regarding lung cancer is considered crucial to identify gaps in knowledge

and attitudes within the general population. Using validated and effective measurement tools can aid in the fulfillment of the targeted outcome. The Cancer Awareness Measurement Tool (CAM) was developed by University College London and Cancer Research UK. It is based on a generic CAM developed by Cancer Research UK, University College London, Kings College London, and Oxford University in 2007-08. The CAM tool was initially validated in 2008 [6] and has undergone continuous updates, including adaptations to incorporate the impact of the COVID-19 pandemic. As for lung cancer awareness measurement, scale validation was fulfilled in the UK in 2012 [7]. The most recent version of the CAM tool was available online in February 2023.

Despite the lack of updated validation, embracing the use of this scale still holds importance for knowledge assessment. Given the limited number of cancer research studies in the Arab World, including Lebanon, which accounted for only 1.52% of total cancer publications between 2005 and 2019 [8], the lack of epidemiological studies in Lebanon that have assessed the general population's awareness of lung cancer using a validated scale, combined with the increasing burden of lung cancer, makes conducting an awareness assessment among the Lebanese population critical. CAM was used in several observational studies aiming to assess knowledge in the general population, including Colombia, Australia, and Gaza [9-11]. As for Lebanon, CAM was not used for assessing lung cancer awareness, yet it was applied to colorectal cancer [12].

Therefore, the aim of this study is to assess the level of lung cancer awareness among the Lebanese general population using the Lung Cancer Awareness Measurement (LCAM) tool. The importance of this study is to gain insights into the level of knowledge, attitudes, and perceptions related to lung cancer in Lebanon.

Materials and methods

Study design

A cross-sectional study was conducted over a one-month period to assess the knowledge and awareness of the Lebanese general population towards lung cancer.

Population and sampling

Lebanese individuals aged 18 years or older, speaking either Arabic or English (no need to be bilingual), were eligible to take part in the study after providing their agreement to participate through an informed consent form. Participants need to have access to the internet or be able to receive delegate assistance to fill out the survey. Patients with a personal or family history of lung cancer will not be excluded from the study; they will be identified throughout the socio-demographic section after being questioned about the presence of a personal or family history of lung cancer. The study participants were approached randomly in different community settings such as restaurants, universities, pharmacies, and online groups all over Lebanon to ensure that the sample was representative of the Lebanese general population. This approach helped increase the likelihood of obtaining a diverse sample that reflects the population's characteristics.

Ethical Consideration

Prior to conducting the study, ethical approval was obtained for the study protocol. The protocol, which outlined the study design, procedures, and objectives, was submitted to the Research and Ethics Committee (REC) at the Institut National de Santé Publique d'Epidémiologie Clinique et de Toxicologie-Liban (INSPECT-LB) and was granted approval (IRB ID: 2023REC-011-INSPECT-07-11).

Sample size Calculation

The sample size calculation was performed using Epi Info 7. Because no comparable studies have been done on the Lebanese population, the sample size was calculated using the single population proportion formula by considering 50% proportion, a 95% CI (Confidence Interval), and a 5% margin of error.

$$N = \frac{Z\alpha^2 \times P\ (1-P)}{d^2} = \frac{1.96^2 \times 0.05(1-0.05)}{0.05^2} = 384.16$$

The minimum final sample size required was 384.16.

Data collection methods

An online-based questionnaire preceded by informed consent approval was utilized as the assessment tool to collect data from the participants. Before being able to access the survey, participants were informed about the nature of the study and were required to provide agreement to take part in it. The questionnaire was composed of two sections: the first section included sociodemographic questions, which aim to gather information about the participants' demographic characteristics, such as age, sex, governorate, marital status, educational level, living arrangement, medical coverage, regular physical check-ups, occupation, personal or family history of lung cancer, and smoking habits (yes/no, frequency). The second section of the questionnaire focused on the participants' knowledge and awareness of lung cancer using the LCAM (Lung CAM). The LCAM questions were designed and used to assess the knowledge of general populations regarding lung cancer via recall and recognition questions. Detailed questionnaire is presented in the supplementary section (Appendix 1).

To ensure the appropriateness of the questionnaire, questions were translated into Arabic, back-translated into English, and validated before being used in our study. The validation process demonstrated a high overall percent agreement between the Arabic and English CAM questionnaires as per 95% Kappa agreement, thus confirming the reliability of the translated questions. Refer to the supplementary section (Appendix 2) for validation test results.

The LCAM questions consisted of a set of open-ended

and closed-ended questions targeting different aspects of awareness. For the lung cancer warning signs awareness assessment, participants were asked to answer an open-ended question at first, followed by a closed-ended question comprising a set of 14 questions related to lung cancer warning signs to compare the difference between participants' ability to recall and recognize lung cancer warning signs. Participants were asked to choose between "yes," "no," and "I don't know" for each warning sign. A total score of 14 was granted to participants who answered all questions correctly, with 1 point for each correct answer (yes being the correct answer). Similarly, awareness of lung cancer risk factors included an open-ended question followed by a closed-ended one. Answers were "strongly disagree," "disagree," "not sure," "agree," or "strongly agree." Each correct question grants the participant 1 point, for a total score of 9 (strongly agree and agree being the correct answers). The remaining parts covered health seeking behavior, age-related risk of lung cancer development, and self-rated confidence level of noticing lung cancer (4 Likert score: not at all confident to very confident). Correct answers were identified as per LCAM Toolkit version 2.1 [13].

Statistical Analysis

The data were analysed using SPSS version 26. Descriptive statistics were used to describe the socio-demographic characteristics of the study participants, age at risk, health-seeking behavior, and confidence levels in terms of percentages and frequencies. A cumulative knowledge score for warning signs of lung cancer (range 0-14) was obtained by summing up the total correct answers to the 14-item questionnaire. The same applies to the knowledge score for the risk factors (range 0-9). Afterwards, mean recognition scores were obtained to assess the extent of awareness regarding warning signs and risk factors. An average warning sign recognition score of 11 and above was considered an indication of awareness, whereas a score below 11 was considered unaware. Similarly, a mean score of 7 or higher on the risk factor recognition scale signified awareness, while a score below 7 indicated unawareness. To ensure construct validity of the recognition scales, factor analysis was conducted for both warning signs and risk factor-recognition scales. Cronbach alpha was obtained to ensure the reliability of the scales mentioned. Moreover, to determine the association between the different covariates and the level of awareness, multivariate analysis using a generalized linear model was conducted to handle varying types of error distributions. The covariates considered in our study were age, sex, district, marital status, educational level, living arrangement, medical coverage, regular physician check-ups, occupation, personal/family history of lung cancer, and smoking (yes/no, frequency). A p-value of < 0.05 is considered statistically significant. Further Post-Hoc analysis was performed using Bonferroni correction for the significant categorical variables.

Results

Descriptive Analysis

Socio-Demographics of Study Participants

A sample comprising 410 Lebanese individuals was collected during the month of August from various governorates across Lebanon. The majority of the study participants were female (66.1%), with a mean age of 38 years (SD ± 15) for the entire study population. The socio-demographic attributes of the study population are presented in Table I. Approximately 53% of participants were bachelor degree holders and currently employed, with nearly equal distribution between medical (40.5%) and non-medical (42.7%) fields. Forty-one percent of participants lacked medical insurance coverage, and a significant portion did not undergo regular physician check-ups, accounting for 66.3% of the total sample size. Furthermore, a notable 78.5% reported no known personal or family history of lung cancer, while the majority abstained from both cigarette and waterpipe smoking (73.2 and 74.9%, respectively).

Awareness of age-related risk of developing lung cancer

As per the LCAM, participants were asked to identify the age at risk for developing lung cancer. Options included: a 30-year-old, 50-year-old, 70-year-old (correct answer), and lung cancer was unrelated to age. Results showed that only 13.7% of the study population were able to identify an age-related risk of developing lung cancer, whereas the majority of the population assumed no relationship between age and the risk of developing lung cancer (60.7%). The remaining participants chose 30-year-old (6.3%), and 50-year-old (19.3%) as ages at risk for lung cancer development.

Health Seeking Behavior

Seventy-five percent of the study population stated their immediate willingness to seek medical attention when having concerns regarding lung cancer development, suggesting a positive proactive attitude of the study population. The remaining 25% of answers were divided between either waiting weeks before seeking medical attention (9%), months (4%), or won't consider medical attention at all or when symptoms become very severe and disabling (12%).

Knowledge of warning signs of Lung Cancer

Study participants displayed a mean average recall of two symptoms, with a standard deviation of 1.68, ranging from 0-9 recalled symptoms. However, symptom recognition yielded a higher mean of 8.9 (SD ± 3.54, range 0-14), indicating unawareness. Among the recalled symptoms, persistent cough and shortness of breath were the most commonly reported (58 and 54.65%), respectively. In terms of symptom recognition, coughing blood and shortness of breath emerged as the most widely recognized warning signs, acknowledged by 87.8% and 81.7%, respectively. Study

Tab. I. Socio-Demographic Characteristics of Study Participants.

Characteristics	N = 410	%
Sex		
Male	139	33.9
Female	271	66.1
Age		
18-24	100	24.4
25-34	113	27.6
35-44	60	14.6
45-54	57	13.9
55-64	59	14.4
65 and over	21	5.1
Governorate		
Mount Lebanon	130	31.7
North	80	19.5
South	74	18
Bekaa	56	13.7
Beirut	44	10.7
Nabatieh	26	6.3
Living Arrangement		
Urban	219	53.4
Rural	191	46.6
Educational level		
Not educated	19	4.6
School Degree	68	16.6
Bachelor Degree	218	53.2
Post-graduate Degree	105	25.6
Marital Status		
Single	189	46.1
Married	199	48.5
Divorced	11	2.7
Widowed	11	2.7
Medical Coverage		
NSSF	85	20.7
Insurance	120	29.3
COOP	31	7.6
None	167	40.7
Others	7	1.7
Occupation		
Medical	166	40.5
Non-medical	175	42.7
Unemployed/ Retired	69	16.8
Regular Physician Check-Ups		
No	272	66.3
Yes	138	33.7
Personal or Family History of Lung Cancer		
No	322	78.5
Yes	88	21.5
Cigarette Smoker		
No	300	73.2
Yes	110	26.8
Waterpipe Smoker		
No	307	74.9
Yes	103	25.1

NSSF: National Social Security Fund; COOP: Co-operative insurance companies.

participants showed lower recall percentages for the remaining warning signs, whereas the majority were not able to recognize persistent shoulder pain (28.7%) and changes in the shape of a finger or nails (29.51%) as possible warning signs of lung cancer. Table II provides a comparative summary of recall and recognition-warning sign knowledge.

Knowledge of Lung Cancer Risk Factors

On average, participants were able to recall one risk factor (mean = 1.59, SD ± 0.94, range 0-6). As expected, participants demonstrated a higher ability to recognize risk factors, with an average of 7.1 recognized risk factors per participant (SD ± 1.9, range 0-9) implying risk factor awareness. Among the recalled risk factors, smoking was the most commonly identified (82%), while other risk factors received lower recall percentages. Similarly, smoking was the most recognized lung cancer risk factor (95.60%). Additionally, both air pollution and exposure to chemicals showed high recognition percentages (94.63 and 89.75%, respectively). Overall, more than half of the study participants were able to recognize all lung cancer risk factors. Details are presented in Table III.

Self-rated confidence level of noticing Lung cancer

Forty-eight percent of study participants were identified as not very confident when it comes to noticing lung cancer, according to the self-rating question, and 10% were not at all confident, which gives a total of 58% of the Lebanese population lacked confidence in identifying lung cancer warning signs. Thirty-six percent reported being fairly confident, while a lower percentage reported being very confident (6%).

Reliability and Validation of the Scale

For the warning signs recognition scale, factor analysis suggested that variables were able to explain 52% of total variances of the hidden variable, the Kaiser-Meyer-Olkin measure was 0.87, and Bartlett's test of sphericity was significant ($p < 0.001$), suggesting sample adequacy. The Cronbach alpha of all scale items was equal to 0.84. The same was applied to risk factor recognition scales, where the variables were able to explain 56.5% of the hidden variable, the Kaiser-Meyer-Olkin measure was 0.81, and Bartlett's test of sphericity was significant ($p < 0.001$), suggesting sample adequacy. The Cronbach alpha of all scale items was equal to 0.8.

Multivariate Analysis of Warning Signs knowledge scores

Multivariate Analysis Results

Multivariate associations between socio-demographics and total symptom awareness scores are presented in Table IV. For each level of socio-demographic predictors, means and a 95% CI are found. There was no difference in symptom awareness by age, sex, living arrangement, marital status, medical coverage, regular physician checkups, cigarette or waterpipe smoking, or familiarity with cancer. However, there was a significant difference when it came to the governorate for recognition scale only (recognition: $F(5,404) = 3.270$,

Tab. II. Knowledge of warning signs of lung cancer.

Symptom	Recall (Open-ended)		Recognition (closed-ended)	
	N = 410	%	N = 410	%
Unexplained weight loss	52	12.7	241	58.7
Persistent chest infection	11	2.7	276	67.3
Persistent cough	238	58	286	69.75
Shortness of breath	224	54.6	335	81.7
Persistent tiredness or lack of energy	50	12.2	250	60.97
Persistent chest pain	117	28.5	298	72.68
Persistent shoulder pain	0	--	118	28.7
Coughing blood	120	29.3	360	87.8
Ache or pain when breathing	3	0.7	303	73.9
Loss of appetite	9	2.2	206	50.24
Painful cough	0	--	332	80.97
Changes in shape of fingers or nails	2	0.5	121	29.51
Developing unexplained loud, high pitched sound when breathing	23	5.6	251	61.21
Worsening or change in existing cough	4	1	319	77.80

Tab. III. Knowledge of risk factors of Lung Cancer.

Risk Factors	Recall (Open-ended)		Recognition (closed-ended)	
	N = 410	%	N = 410	%
Exposure to Radon	3	0.7	329	80.24
Exposure to another persons' cigarette smoke	18	4.4	334	81.46
Previous cancer treatment	6	1.5	233	56.82
Having close relative with Lung Cancer	105	25.5	295	71.90
Exposure to chemicals such as Asbestos	27	6.6	368	89.75
Personal history of cancer such as head and neck cancer	4	1	271	66.09
Air Pollution	139	33.8	388	94.63
Being a smoker	338	82	392	95.60
Previous history of Lung disease such as COPD	13	3.2	311	75.85

COPD: Chronic Obstructive Pulmonary Disease.

$p = 0.007$, $\eta_p^2 = 0.041$). Similarly, education showed a significant effect on the recognition scale but not recall (recognition: $F(3,406) = 5.543$, $p = 0.001$, $\eta_p^2 = 0.041$). As for occupation, results showed significant differences for both recall and recognition scales (recall: $F(2,407) = 12.808$, $p < 0.001$, $\eta_p^2 = 0.073$; recognition: $F(2,407) = 15.147$, $p < 0.001$, $\eta_p^2 = 0.062$).

Post-hoc Analysis Results

Further Post Hoc analysis was conducted using Bonferroni correction to examine pairwise group differences among significant variables. Results showed that people residing in Bekaa scored approximately two times lower warning sign recognition scales compared with participants residing in Beirut, Mount Lebanon, and North Lebanon. As for education, participants with postgraduate degrees showed higher recognition scales compared to others, while less educated individuals showed the lowest level of awareness. Finally, medical-field workers were able to both recall and recognize a higher average of warning signs when compared to other field workers or their unemployed or retired counterparts. Non-medical field workers and retired/unemployed individuals showed 30% lower recall compared to medical field workers, where the latter were able to recognize warning signs two times higher. Details of the Hoc pairwise comparison are presented in Table V.

Multivariate Analysis of risk Factors Results

Multivariate Analysis Results

There was a significant difference in recognition of risk factors total scores by sex for the recognition scale only (recognition: $F(1,408) = 11.411$, $p = 0.001$, $\eta_p^2 = 0.029$) (Tab. IV). Educational level was associated with higher risk factor recognition scores (recognition: $F(3,406) = 21.85$, $p < 0.001$, $\eta_p^2 = 0.058$), but there was no significant difference by level of education in recall. Additionally, occupation showed no significant difference for recall but for recognition scale only (recognition: $F(2,407) = 30.52$, $p < 0.001$, $\eta_p^2 = 0.054$). Females scored higher when it came to risk factor recognition compared to males.

Tab. IV. Multivariate associations between socio-demographic factors and awareness of Lung Cancer performed on total study participants (N=410).

	Symptom Awareness		Risk Factor Awareness	
	Recall (open)	Recognition (closed)	Recall (open)	Recognition (closed)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Sex				
Male	1.69 (1.42 to 1.97)	8.00 (7.42 to 8.58)	1.51 (1.36 to 1.67)	6.35 (6.04 to 6.65)
Female	2.28 (2.08 to 2.47)	9.49 (9.08 to 9.91)	1.63 (1.51 to 1.74)	7.52* (7.30 to 7.73)
Age				
Under 40	2.44 (2.23 to 2.64)	9.48 (9.04 to 9.92)	1.72 (1.60 to 1.84)	7.48 (7.24 to 7.71)
40 and above	1.55 (1.30 to 1.80)	8.25 (7.71 to 8.79)	1.39 (1.25 to 1.53)	6.59 (6.31 to 6.87)
Governorate				
Beirut	2.43 (1.93 to 2.93)	9.79 (8.75 to 10.83)	1.65 (1.37 to 1.94)	7.61 (7.05 to 8.17)
Mount Lebanon	2.07 (1.78 to 2.36)	9.32 (8.71 to 9.92)	1.52 (1.36 to 1.68)	7.19 (6.86 to 7.51)
South Lebanon	2.25 (1.87 to 2.64)	8.82 (8.02 to 9.62)	1.67 (1.45 to 1.89)	7.31 (6.88 to 7.74)
North Lebanon	2.12 (1.75 to 2.49)	9.32 (8.55 to 10.09)	1.71 (1.50 to 1.92)	6.88 (6.47 to 7.30)
Bekaa	1.55 (1.11 to 1.99)	7.41* (6.49 to 8.33)	1.35 (1.10 to 1.60)	6.48 (5.98 to 6.97)
Nabatieh	2.03 (1.39 to 2.68)	8.80 (7.45 to 10.15)	1.73 (1.36 to 2.09)	7.53 (6.81 to 8.26)
Living Arrangement				
Urban	2.25 (2.03 to 2.47)	9.27 (8.80 to 9.74)	1.63 (1.50 to 1.76)	7.27 (7.02 to 7.52)
Rural	1.88 (1.64 to 2.12)	8.66 (8.15 to 9.16)	1.54 (1.40 to 1.68)	6.95 (6.68 to 7.22)
Education				
Not Educated	1.26 (0.53 to 1.99)	6.42 (4.87 to 7.96)	1.31 (0.89 to 1.73)	4.05 (3.26 to 4.84)
School Degree	1.17 (0.79 to 1.56)	8.82 (8.00 to 9.64)	1.23 (1.01 to 1.45)	6.73 (6.31 to 7.15)
Bachelor Degree	2.22 (2.00 to 2.44)	8.56 (8.10 to 9.02)	1.61 (1.48 to 1.73)	7.16 (6.92 to 7.39)
Post-grad Degree	2.52 (2.21 to 2.83)	10.44* (9.79 to 11.10)	1.83 (1.65 to 2.01)	7.85* (7.52 to 8.19)
Marital Status				
Single	2.56 (2.32 to 2.79)	9.39 (8.89 to 9.90)	1.76 (1.62 to 1.89)	7.45 (7.18 to 7.72)
Married	1.66 (1.44 to 1.89)	8.72 (8.23 to 9.22)	1.46 (1.33 to 1.59)	6.91 (6.64 to 7.17)
Divorced	1.81 (0.85 to 2.78)	9.00 (6.91 to 11.09)	1.36 (0.80 to 1.92)	7.00 (5.89 to 8.10)
Widowed	1.63 (0.66 to 2.60)	6.72 (4.63 to 8.81)	1.18 (0.62 to 1.73)	5.45 (4.35 to 6.56)
Medical Coverage				
NSSF	2.23 (1.87 to 2.59)	8.95 (8.19 to 9.70)	1.61 (1.40 to 1.81)	7.31 (6.91 to 7.72)
Insurance	2.10 (1.79 to 2.40)	9.44 (8.80 to 10.07)	1.60 (1.42 to 1.77)	7.30 (6.96 to 7.64)
COOP	1.74 (1.14 to 2.33)	8.03 (6.78 to 9.28)	1.61 (1.27 to 1.94)	6.96 (6.29 to 7.63)
None	2.03 (1.77 to 2.29)	8.85 (8.31 to 9.39)	1.55 (1.41 to 1.70)	6.87 (6.58 to 7.16)
Others	2.57 (1.31 to 3.82)	9.28 (6.65 to 11.92)	2.00 (1.29 to 2.70)	8.42 (7.02 to 9.83)
Occupation				
Medical	2.87* (2.63 to 3.11)	10.39* (9.88 to 10.91)	1.83 (1.68 to 1.97)	7.94* (7.67 to 8.21)
Non-medical	1.54 (1.31 to 1.77)	8.00 (7.50 to 8.49)	1.46 (1.32 to 1.60)	6.63 (6.37 to 6.89)
Unemployed-retired	1.55 (1.18 to 1.92)	8.11 (7.32 to 8.91)	1.34 (1.12 to 1.56)	6.39 (5.97 to 6.81)
Regular physician check-ups				
No	2.02 (1.82 to 2.22)	8.63 (8.21 to 9.05)	1.56 (1.44 to 1.67)	6.98 (6.75 to 7.20)
Yes	2.20 (1.92 to 2.48	9.68 (9.10 to 10.27)	1.65 (1.49 to 1.81)	7.40 (7.08 to 7.72)
Personal or Family History of Lung Cancer				
No	2.11 (1.93 to 2.30)	8.92 (8.54 to 9.31)	1.58 (1.48 to 1.69)	7.18 (6.98 to 7.39)
Yes	1.96 (1.61 to 2.32)	9.21 (8.47 to 9.96)	1.61 (1.41 to 1.81)	6.88 (6.48 to 7.28)
Smoker				
No	2.25 (2.06 to 2.44)	9.24 (8.84 to 9.64)	1.68 (1.58 to 1.79)	7.38 (7.17 to 7.59)
Yes	1.60 (1.29 to 1.92)	8.30 (7.63 to 8.96)	1.33 (1.16 to 1.51)	6.40 (6.06 to 6.75)
Waterpipe				
No	2.16 (1.98 to 2.35)	9.17 (8.78 to 9.57)	1.64 (1.53 to 1.74)	7.20 (6.99 to 7.41)
Yes	1.82 (1.49 to 2.15)	8.42 (7.74 to 9.11)	1.44 (1.26 to 1.63)	6.88 (6.51 to 7.25)

* P-value < 0.05.

Post-hoc Analysis Results

In conformity with warning signs results, Post hoc analysis showed that not-educated participants were able to recognize risk factors three times lower compared to other levels of education. Postgraduates showed the highest level of awareness. Additionally, non-medical field workers and unemployed or retired individuals showed lower level of risk factor recognition compared to medical field workers (31 and 55%, respectively). Detailed results are presented in Table V.

Tab. V. Post-Hoc Analysis using Bonferroni correction.

Dependent Variable	Independent Variable		Mean	P-value	95% CI (Upper and Lower Bounds)
Warning Signs-Recognition Scale	Governorate				
	Bekaa	Beirut	-2.38	0.004	-4.30 to -0.46
		Mount Lebanon	-1.91	0.004	-3.43 to -0.39
		South Lebanon	-1.41	0.205	-3.09 to 0.27
		North Lebanon	-1.91	0.011	-3.57 to -0.25
		Nabatieh	-1.39	1.00	-3.65 to 0.86
Warning Signs-Recognition Scale	Education				
	Not Educated	School Degree	-2.40	0.021	-4.56 to -0.23
		Bachelor Degree	-2.12	0.028	-4.13 to -0.14
		Post-Graduate Degree	-4.02	< 0.001	-6.10 to -1.94
	School Degree	Post-Graduate	-1.62	0.006	-2.92 to -0.32
	Bachelor Degree	Post-Graduate	-1.88	< 0.001	-2.87 to -0.89
Warning Signs-Recall Scale	Occupation				
	Unemployed/Retired	Medical	-1.32	< 0.001	-1.85 to -0.787
		Non-medical	0.0079	1.00	-0.52 to 0.53
	Non-medical	Medical	-1.33	< 0.001	-1.73 to -0.92
Warning Signs-Recognition Scale	Occupation				
	Medical	Non-medical	2.39	< 0.001	1.57 to 3.21
		Unemployed/Retired	2.28	< 0.001	1.19 to 3.36
Risk Factor-Recognition Scale	Education				
	Not Educated	School Degree	-2.68	< 0.001	-3.88 to -1.47
		Bachelor Degree	-3.10	< 0.001	-4.21 to -1.99
		Post-Graduate Degree	-3.80	< 0.001	-4.96 to -2.64
	School Degree	Post-Graduate	-1.12	< 0.001	-1.84 to -0.39
	Bachelor Degree	Post-Graduate	-0.69	0.005	-1.24 to -0.11
Risk Factor-Recognition Scale	Occupation				
	Non-Medical	Medical	-1.31	< 0.001	-1.76 to -0.85
	Unemployed/Retired	Medical	-1.55	< 0.001	-2.15 to -0.95

Discussion

For the purpose of identifying levels of awareness in the Lebanese general population towards lung cancer warning signs and risk factors, the Lung Cancer Awareness Measurement Tool (LCAM) was used. The survey revealed that a significant portion of the Lebanese population exhibited unawareness regarding lung cancer warning signs. More specifically, the majority of the respondents held the belief that there is no correlation between age and the likelihood of developing lung cancer.

In parallel, the findings from this study were mirrored in another study conducted in Gaza [11]. The study was employed to assess cancer awareness among the general population in Gaza using the CAM Tool, and its results uncovered similar beliefs when it comes to the relationship between age and the development of different types of cancer, including lung cancer [11]. Additionally, a separate Lebanese study on awareness related to colorectal cancer using the Bowel Cancer Awareness Measurement (Bowel CAM) displayed similar findings [12]. Just as with lung cancer, awareness of the relationship between age and colorectal cancer risk was inadequate among the Lebanese population [12]. Such consistency across different studies focusing on different types of cancer indicates the presence of misconceptions regarding the role of age in the development of lung cancer.

For risk factor awareness, participants showed an average recall of only one risk factor and two possible warning signs of lung cancer. A very low percentage of the study population managed to identify persistent shoulder pain and changes in the shape of fingers or nails as possible warning signs of lung cancer development. Similarly, nearly half of the study population couldn't link loss of appetite and unexplained weight loss to the possibility of lung cancer development. As for lung cancer risk factors, as expected, the Lebanese population was alert about smoking being one of the major risk factors for lung cancer development, as shown in both recall and recognition risk factor awareness questions. In contrast, awareness of the relationship between previous cancer treatment or personal history of cancer, such as head and neck cancer, and lung cancer development was low. The above-mentioned results come in conformity with a population-based study on the people of the UK using the LCAM tool [7], along with a study assessing

knowledge of Lebanese populations' knowledge of cancer-related environmental risk factors a using literature-based questionnaire that has highlighted both smoking and air pollution as the most recognized factors [14].

The study findings highlight differences in awareness of lung cancer warning signs across various socio-demographic backgrounds. This suggests that factors such as location, education, and occupation play a crucial role in shaping the level of awareness among the population. One striking observation is the regional variation in awareness. People residing in Bekaa governorate displayed lower levels of risk factor awareness compared to Beirut, Mount Lebanon, and North Lebanon, guiding stakeholders towards the main regions of interest while developing educational campaigns. Education, on the other hand, appears to be a key determinant of awareness. Postgraduates showed higher levels of awareness, as expected in parallel to Chinese study findings aiming to assess knowledge of lung cancer in community residents and medical field workers [15]. This positive correlation can be justified by the fact that individuals with higher levels of education often have access to more resources and are likely to engage in more health-related information-seeking behavior. Moreover, and as anticipated, individuals working in the medical field demonstrated a deeper understanding of lung cancer warning signs. This heightened awareness among medical professionals is likely attributed to their daily exposure to healthcare-related information and patients, resulting in more comprehensive disease-related knowledge.

When it comes to risk factor awareness in relation to socio-demographic factors, there was no significant difference in risk factor recall among the whole population. However, females, postgraduates, and medical field workers demonstrated a higher level of risk-factor recognition compared to the rest of the population. The sex-related difference in the level of risk factor awareness could be attributed to various factors, including greater health awareness and more proactive health-seeking behavior. Those results come in parallel with a study conducted in Australia using a convergent parallel mixed-method design [10]. The higher level of awareness among educated individuals and medical professionals is justified by their educational background [15], along with their daily scientific and disease-related learning and experience.

There was no difference in symptom or risk factor awareness among smoking categories (cigarette or waterpipe). Although a population-based study conducted in the UK using the LCAM tool [7] and a survey-based cross-sectional study assessing knowledge differences in lung cancer knowledge and prevention across different ethnic and socioeconomic statuses conducted in the USA [16] studies demonstrated lower recall, studies in Australia and a cross-sectional study in Nepal using a structured questionnaire to assess lung cancer risk factor awareness demonstrated no difference in awareness among smoking groups [10, 17]. Such a result can be justified by the fact that smokers could be aware of the harmful and devastating effects of smoking and still choose to smoke. This knowledge could stem from the extensive presence of awareness campaigns that extensively highlight the health-related consequences of smoking. The concept of cognitive dissonance may provide insight into this result. Cognitive dissonance refers to the psychological discomfort that arises when an individual holds conflicting beliefs or engages in actions that are contrary to their beliefs [18]. In the context of smoking, individuals may be fully aware of the health risks, such as the development of lung cancer or heart diseases associated with smoking. However, the addictive nature and other factors may lead them to continue their smoking habit despite this knowledge.

Moreover, the majority of the study population expressed their intent to seek medical attention directly when having concerns about the development of lung cancer. This initial willingness is a positive indication of a proactive approach to health care. However, this seemingly positive indication is countered by the study findings regarding the low level of awareness among the participants. Specifically, their response to the question addressing their confidence in identifying lung cancer warning signs revealed that they had low to fair levels of confidence. This implies that, despite their willingness to consult a healthcare professional, their ability to recognize early signs might be limited. Meanwhile, such findings come in parallel to an international benchmarking partnership study conducted in different countries using Awareness and Beliefs about Cancer Measures (ABC) [19]. The combination of the low level of awareness and limited confidence in identifying warning signs of lung cancer suggests that individuals might delay seeking medical attention until the emergence of more severe symptoms, such as coughing up blood, which might lead to a delayed surgical resection procedure. Notably, these findings align with a study conducted in Australia [10] along with a meta-analysis performed examining delay in seeking medical attention [20], suggesting that this phenomenon might not be unique to the Lebanese population. Public health campaigns and awareness initiatives can play a crucial role in addressing such issues by disseminating information about lung cancer warning signs and encouraging individuals to seek medical attention as soon as they have concerns. These initiatives can help promote earlier detection of lung cancer and, hence, earlier resection when needed, especially in cases of non-small-cell lung cancer, potentially saving more lives, as shown by a cohort study investigating opportunities to reduce lung cancer mortality [21].

This study was the first to assess the level of awareness of the Lebanese general population using an LCAM-validated tool. The tool was properly translated and validated in a pilot study ahead of the study and was representative of the Lebanese population as per

governorates, along with an appropriate sample size. Factorial and reliability analyses confirmed the validity of the used tool (the Cronbach alpha of all scale items was equal to 0.84 and 0.81 for the warning signs and recognition scales, respectively). Using such a tool allowed us to highlight the most frequently recalled warning signs and risk factors for lung cancer in comparison to guided questions, as the latter showed a higher level of awareness. The results will enable the development of educational campaigns targeting misconceptions for the purpose of increasing the likelihood of early diagnosis and thus better treatment outcomes, as shown by a population-based study using Awareness and Beliefs about Cancer Measure (ABC) in the UK [22]. Moreover, similar findings were stated by comparative studies assessing cancer educational campaign impacts in England [23, 24], a systematic review examining the association between time to diagnosis and treatment outcomes [25], in addition to a study assessing the 5-year impact of the National Awareness and Early Diagnosis Initiative in England [26]. Our findings highlight the importance of developing a multidisciplinary lung cancer program for the sake of reducing the delay in seeking medical attention, as such programs have proven efficacy, as shown in a retrospective study assessing the impact of a multidisciplinary lung cancer program in reducing the delay between diagnosis and treatment in the USA [27], as well as in India assessing the impact of an educational campaign in increasing awareness and adopting safer practices [28].

The limitation of this study is that the LCAM survey was conducted online. Such a method for data collection allowed study participants to access the internet or other sources to aid their responses, which might lead to misclassification bias. Although participants were able to navigate backward and forward during the survey, it didn't affect the expected pattern of answers when comparing recalled and recognition questions. The difference between those questions was significantly high, suggesting that such biases were non-differential. To minimize the effects of such limitations, a face-to-face survey will ensure that the responses are representative of the real level of knowledge of the study participants. Additionally, older people were less likely to participate in the study, resulting in selection bias. However, the study protocol allowed elderly participants who received proper aid in filling out the survey to be included in the study so that we could enhance the representativeness of the study results. Moreover, although multivariate analyses were conducted to decrease the chance of false-positive results, there is always a risk of residual confounding. Further studies are recommended to overcome such limitations.

Conclusions

Employing the LCAM survey tool played a crucial role in obtaining a comprehensive insight into the level of awareness among the Lebanese population concerning various facets of lung cancer. One of the most significant takeaways from this study is the identification of specific areas that require attention and improvement. By pinpointing the weak links in public awareness, this research has paved the way for a targeted approach. Properly targeted campaigns hold importance in enhancing public knowledge and consequently fostering early diagnosis and more effective therapeutic outcomes in the context of lung cancer, and hence can make a substantial difference in the health and well-being of the Lebanese population.

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Ethics approval and informed consent to participate

Ethical approval was granted by Research and Ethics Committee (REC) at Institut National de Santé Publique d'Epidémiologie Clinique et de Toxicologie-Liban (INSPECTLB) ethical review board (IRB ID: 2023REC-011-INSPECT-07-11). Prior to accessing the survey, participants agreed to participate through an informed consent form.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that they have no competing interests.

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Authors' contributions

Concept and design aspects were led by MH and RA. Data acquisition and statistical analysis were conducted by MH under supervision of RA. Analysis and interpretation of the data were performed collectively by MH, PS, SA, and RA. MH was responsible for drafting the manuscript, which was critically revised for

important intellectual content by PS, SA, and RA. All authors reviewed and approved the final manuscript.

References

[1] 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.

[2] Wéber A, Morgan E, Vignat J, Laversanne M, Pizzato M, Rumgay H, Singh D, Nagy P, Kenessey I, Soerjomataram I, Bray F. Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040. BMJ Open 2023;13:e065303. https://doi.org/10.1136/bmjopen-2022-065303.

[3] Lakkis NA, Musharafieh UM, Issa HG, Osman MH. Lung Cancer and Risk Factors in Lebanon: Epidemiology, Temporal Trends, and Comparison to Countries From Different Regions in the World. Cancer Control 2023;30:10732748231169596. https://doi.org/10.1177/10732748231169596.

[4] Saab MM, FitzGerald S, Noonan B, Kilty C, Collins A, Lyng Á, Kennedy U, O'Brien M, Hegarty J. Promoting lung cancer awareness, help-seeking and early detection: a systematic review of interventions. Health Promot Int 2021;36:1656-71. https://doi.org/10.1093/heapro/daab016.

[5] American Cancer Society. Lung Cancer Causes, Risk Factors, and Prevention. Available at: https://www.cancer.org/cancer/types/lung-cancer/causes-risks-prevention/risk-factors.html. (Accessed on: 8/01/2023).

[6] Stubbings S, Robb K, Waller J, Ramirez A, Austoker J, Macleod U, Hiom S, Wardle J. Development of a measurement tool to assess public awareness of cancer. Br J Cancer 2009;101:S13-7. https://doi.org/10.1038/sj.bjc.6605385.

[7] Simon AE, Juszczyk D, Smyth N, Power E, Hiom S, Peake MD, Wardle J. Knowledge of lung cancer symptoms and risk factors in the U.K.: development of a measure and results from a population-based survey. Thorax 2012;67:426-32. https://doi.org/10.1136/thoraxjnl-2011-200898.

[8] Machaalani M, El Masri J, El Ayoubi LM, Matar B. Cancer research activity in the Arab world: a 15-year bibliometric analysis. J Egypt Public Health Assoc 2022;97:26. https://doi.org/10.1186/s42506-022-00120-6.

[9] Meneses-Echávez JF, Alba-Ramírez PA, Correa-Bautista JE. Raising Awareness for Lung Cancer Prevention and Healthy Lifestyles in Female Scholars from a Low-Income Area in Bogota, Colombia: Evaluation of a National Framework. J Cancer Educ 2018;33:1294-300. https://doi.org/10.1007/s13187-017-1246-z.

[10] Crane M, Scott N, O'Hara BJ, Aranda S, Lafontaine M, Stacey I, Varlow M, Currow D. Knowledge of the signs and symptoms and risk factors of lung cancer in Australia: mixed methods study. BMC Public Health 2016;16:508. https://doi.org/10.1186/s12889-016-3051-8.

[11] Elshami M, Elshami A, Alshorbassi N, Alkhatib M, Ismail I, Abu-Nemer K, Hana M, Qandeel A, Abdelwahed A, Yazji H, Abuamro H, Matar G, Alsahhar A, Abolamzi A, Baraka O, Elblbessy M, Samra T, Bottcher B. Knowledge level of cancer symptoms and risk factors in the Gaza Strip: a cross-sectional study. BMC Public Health 2020;20:414. https://doi.org/10.1186/s12889-020-08553-4.

[12] Tfaily MA, Naamani D, Kassir A, Sleiman S, Ouattara M, Moacdieh MP, Jaffa MA. Awareness of Colorectal Cancer and Attitudes Towards Its Screening Guidelines in Lebanon. Ann Glob Health 2019;85:75. https://doi.org/10.5334/aogh.2437.

[13] Cancer Research UK, University College of London Lung Cancer Awareness Measure (Lung CAM) Toolkit Version 2.1. Available at: https://www.cancerresearchuk.org/sites/default/files/health_professional_lung_cam_toolkit_version_2.1_09.02.11.pdf. (Accessed on: 8/01/2023).

[14] Kabalan M, El-Hajj M, Khachman D, Awada S, Rachidi S, Al-Hajje A, Ajrouche R. Public awareness of environmental risk factors of cancer and attitude towards its prevention among the Lebanese general population. J Prev Med Hyg 2021;62:E466-78. https://doi.org/10.15167/2421-4248/jpmh2021.62.2.1974.

[15] Ren G, Ye J, Fan Y, Wang J, Sun Z, Jia H, Du X, Hou C, Wang Y, Zhao Y, Zhou Q. [Survey and analysis of awareness of lung cancer prevention and control in a LDCT lung cancer screening project in Tianjin Dagang Oilfield of China]. Zhongguo Fei Ai Za Zhi 2014;17:163-70. https://doi.org/10.3779/j.issn.1009-3419.2014.02.16.

[16] Wilkinson AV, Vasudevan V, Honn SE, Spitz MR, Chamberlain RM. Sociodemographic characteristics, health beliefs, and the accuracy of cancer knowledge. J Cancer Educ 2009;24:58-64. https://doi.org/10.1080/08858190802664834.

[17] Chawla R, Sathian B, Mehra A, Kiyawat V, Garg A, Sharma K. Awareness and assessment of risk factors for lung cancer in residents of Pokhara Valley, Nepal. Asian Pac J Cancer Prev 2010;11:1789-93.

[18] Bran A, Vaidis DC. On the Characteristics of the Cognitive Dissonance State: Exploration Within the Pleasure Arousal Dominance Model. Psychol Belg. 2020;60:86-102. https://doi.org/10.5334/pb.517.

[19] Pedersen AF, Forbes L, Brain K, Hvidberg L, Wulff CN, Lagerlund M, Hajdarevic S, Quaife SL, Vedsted P. Negative cancer beliefs, recognition of cancer symptoms and anticipated time to help-seeking: an international cancer benchmarking partnership (ICBP) study. BMC Cancer 2018;18:363. https://doi.org/10.1186/s12885-018-4287-8.

[20] Smith LK, Pope C, Botha JL. Patients' help-seeking experiences and delay in cancer presentation: a qualitative synthesis. Lancet 2005;366:825-31. https://doi.org/10.1016/S0140-6736(05)67030-4.

[21] Currow DC, You H, Aranda S, McCaughan BC, Morrell S, Baker DF, Walton R, Roder DM. What factors are predictive of surgical resection and survival from localised non-small cell lung cancer? Med J Aust 2014;201:475-80. https://doi.org/10.5694/mja14.00365.

[22] Quaife SL, Forbes LJ, Ramirez AJ, Brain KE, Donnelly C, Simon AE, Wardle J. Recognition of cancer warning signs and anticipated delay in help-seeking in a population sample of adults in the UK. Br J Cancer 2014;110:12-8. https://doi.org/10.1038/bjc.2013.684.

[23] Ball S, Hyde C, Hamilton W, Bright CJ, Gildea C, Wong KF, Paley L, Hill HL, Mak V, Moffat J, Elliss-Brookes L. An evaluation of a national mass media campaign to raise public awareness of possible lung cancer symptoms in England in 2016 and 2017. Br J Cancer 2022;126:187-95. https://doi.org/10.1038/s41416-021-01573-w.

[24] Ironmonger L, Ohuma E, Ormiston-Smith N, Gildea C, Thomson CS, Peake MD. An evaluation of the impact of large-scale interventions to raise public awareness of a lung cancer symptom. Br J Cancer 2015;112:207-16. https://doi.org/10.1038/bjc.2014.596.

[25] Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, Hamilton W, Hendry A, Hendry M, Lewis R, Macleod U, Mitchell ED, Pickett M, Rai T, Shaw K, Stuart N, Tørring ML, Wilkinson C, Williams B, Williams N, Emery J. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer 2015;112:S92-107. https://doi.org/10.1038/bjc.2015.48.

[26] Hiom SC. Diagnosing cancer earlier: reviewing the evidence for improving cancer survival. Br J Cancer 2015;112:S1-5. https://doi.org/10.1038/bjc.2015.23.

[27] Albano D, Bilfinger T, Feraca M, Kuperberg S, Nemesure B. A Multidisciplinary Lung Cancer Program: Does It Reduce Delay

Between Diagnosis and Treatment? Lung 2020;198:967-972. https://doi.org/10.1007/s00408-020-00404-8.

[28] Shankar A, Roy S, Bhandari R, Malik A, Rath GK, Julka PK, Barnwal K, Upadhyaya S, Singh R, Srivastava V. Level of awareness of lung cancer risk factors, signs, symptoms and safe practices among college teachers of different states in India: Do awareness programmes have an impact on adoption of safe practices? Gulf J Oncolog 2015;1:57-62.

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Appendix 1: Questionnaire

Lung Cancer Awareness among the Lebanese General Population: a cross-sectional study

You are Kindly Invited to take part in this study conducted by Master Candidate at Lebanese University. This study aims to determine knowledge of general Lebanese population regarding Lung Cancer risk factors and warning signs in which the results can identify gaps of knowledge.

You are eligible to participate if you are:
Lebanese Living in Lebanon
Age 18 years or above.
Speaks English/ Arabic.

Your participation is voluntary with the right to withdraw at any time is reserved. It won't take more than 5 minutes and all the information will be handled confidentially throughout the study and used for research purpose only.

Thank You

أنت مدعو إلى المشاركة في استطلاع لطالب ماجيستير في الجامعة اللبنانية.

تهدف هذه الدراسة إلى تحديد معرفة اللبنانيين عامة فيما يتعلق بعوامل خطر الإصابة بسرطان الرئة وعلامات التحذير التي يمكن أن تحدد النتائج من خلالها ثغرات المعرفة.

أنت مؤهل للمشاركة إذا كنت:

لبناني الجنسية ومقيم في لبنان.

18 سنة وما فوق.

تتحدث اللغة العربية أو الإنكليزية.

أدعوكم للمشاركة في الاستبيان، والمشاركة طوعية، والحق في الانسحاب في أي وقت محفوظ. لن يستغرق الأمر أكثر من خمسة دقائق وسيتم التعامل مع جميع المعلومات بسرية طوال فترة الدراسة واستخدامها لأغراض البحث فقط.

شكرا لك

Please check all the boxes below to proceed to the survey/ يرجى تعبئة جميع المربعات أدناه لمتابعة الاستبيان:

- ☐ I have read and understood the above information/لقد قرأت وفهمت المعلومات الواردة أعلاه
- ☐ I understand that my participation is voluntary/ أفهم أن مشاركتي تطوعية
- ☐ I understand that my data will be kept confidential/ أفهم أن بياناتي ستبقى سرية
- ☐ I agree to participate in the study/ أوافق على المشاركة في الدراسة

Part 1: Sociodemographic Characteristics/ الخصائص الاجتماعية والديموغرافية:

- Sex/ الجنس:

- ☐ Male/ ذكر
- ☐ Female/ أنثى

- Age (years)/ (بالسنوات) العمر: _____
- Governorate/ المحافظة:
  - ☐ Beirut / بيروت
  - ☐ Mount Lebanon / جبل لبنان
  - ☐ Bekaa / البقاع
  - ☐ North Lebanon / الشمال
  - ☐ South Lebanon/ الجنوب
  - ☐ Nabatieh / النبطية
- Living Arrangement/ السكن:
  - ☐ Urban / مدينة
  - ☐ Rural / قرية
- Educational level/ مرحلة التعلم:
  - ☐ Not educated/ غير متعلم
  - ☐ School degree / درجة مدرسية
  - ☐ Bachelor's degree/ درجة جامعية
  - ☐ Post grad degree / دراسات عليا
- Marital Status/الوضع العائلي :
  - ☐ Single /أعزب
  - ☐ Married / متزوج
  - ☐ Divorced / مطلق
  - ☐ Widowed / أرمل
- Medical Coverage/ تغطية طبية
  - ☐ None/ لا يوجد
  - ☐ NSSF / الصندوق الوطني للضمان الاجتماعي
  - ☐ Insurance/ تأمين
  - ☐ COOP / تعاونية موظفي الدولة
  - ☐ Others / غير ذلك
- Occupation/المهنة
  - ☐ Medical / في المجال الطبي
  - ☐ Non-medical / خارج الجال الطبي
  - ☐ Unemployed/ retired / متقاعد لا أعمل
- Regular Physician checkups/هل تخضع لفحص طبي منتظم
  - ☐ No/ كلا
  - ☐ Yes / نعم
- Personal or Family History of Lung Cancer/وجود سابقة شخصية أو عائلية للإصابة بسرطان الرئة
  - ☐ No / كلا
  - ☐ Yes / نعم
- Do you smoke cigarette/ ?هل تدخن السجائر
  - ☐ No / كلا
  - ☐ Yes / نعم
- Do you smoke waterpipe/?هل تدخن الأركيلة
  - ☐ No/ كلا
  - ☐ Yes / نعم

Part 2: LCAM Questionnaire:

- There are many warning signs and symptoms of lung cancer. Please name as many as you can think of/ هنالك العديد من العلامات والأعراض التحذيرية لسرطان الرئة، أذكر حسب رأيك الشخصي العدد الأكبر منها:
- The following may or may not be signs for lung cancer. We are interested in your opinion/ قد تكون العلامات التالية علامات تحذيرية لسرطان الرئة و قد لا تكون كذلك, و نحن مهتمون برأيك

	Yes/ نعم	No/ لا	I don't know/ لا أعرف
Do you think that unexplained weight loss could be a sign of lung cancer/ هل تعتقد أن فقدان الوزن غير المبرر علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that a persistent (3 weeks or longer) chest infection could be a sign of lung cancer/ هل تعتقد أن التهابات أوعدوى الصدر المستمرة لمدة 3 أسابيع أو أكثر قد تكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that a cough that does not go away for two or three weeks could be a sign of lung cancer/ هل تعتقد أن السعال الذي يستمر لمدة أسبوعين أو ثلاثة أسابيع قد يكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that persistent shortness of breath could be a sign of lung cancer/ هل تعتقد أن ضيق التنفس المستمر قد يكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that persistent tiredness or lack of energy could be a sign of lung cancer/ هل تعتقد أن التعب المستمر أو نقص الطاقة يمكن أن يكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that persistent chest pain could be a sign of lung cancer/ هل تعتقد أن ألم الصدر المستمر قد يكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that persistent shoulder pain could be a sign of lung cancer/ هل تعتقد أن آلام الكتف المستمرة قد تكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that coughing up blood could be a sign of lung cancer/ هل تعتقد أن خروج الدم عند السعال قد يكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that an ache or pain when breathing could be a sign of lung cancer/ هل تعتقد أن الألم عند التنفس يمكن أن يكون علامة على سرطان الرئة	□	□	□
Do you think that loss of appetite could be a sign of lung cancer/ هل تعتقد أن فقدان الشهية يمكن أن يكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that a painful cough could be a sign of lung cancer/ هل تعتقد أن السعال المؤلم يمكن أن يكون علامة على سرطان الرئة	□	□	□
Do you think that changes in the shape of your fingers or nails could be a sign of lung cancer/ هل تعتقد أن التغييرات في شكل أصابعك أو أظافرك يمكن أن تكون علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that developing an unexplained loud, high pitched sound when breathing could be a sign of lung cancer/ هل تعتقد أن صدور صوت غير مفسّر أو الصوت العالي النبرة عند التنفس علامة على الإصابة بسرطان الرئة	□	□	□
Do you think that worsening or change in an existing cough could be a sign of lung cancer/ هل تعتقد أن تفاقم أو تغيير السعال الموجود يمكن أن يكون علامة على سرطان الرئة	□	□	□

- If you had a symptom that you thought might be a sign of lung cancer how soon would you contact your doctor to make an appointment to discuss it/ إذا كانت لديك أعراض تعتقد أنها قد تكون علامة على الإصابة بسرطان الرئة ، فمتى ستتصل بطبيبك لتحديد موعد لمناقشتها

- In the next Year, who is more likely to develop Lung Cancer/ في العام المقبل ، من هو الأكثر عرضة للإصابة بسرطان الرئة

- □ A 30-year-old/ شخص يبلغ من العمر 30 سنة
- □ A 50-Year-old/ شخص يبلغ من العمر 50 سنة
- □ A 70-year-old/ شخص يبلغ من العمر 70 سنة
- □ Lung Cancer is unrelated to age/ لا يوجد علاقة بين العمر وخطر الإصابة بسرطان الرئة

- What things do you think affect a person's chance of developing lung cancer/ ما هي الأشياء التي تعتقد أنها تؤثر على فرصة إصابة الشخص بسرطان الرئة
- The following may or may not increase a person's chance of developing lung cancer. How much do you agree that each of these can increase a person's chance of developing lung cancer/ ما يلي قد يزيد أو لا يزيد من فرصة إصابة الشخص بسرطان الرئة. إلى أي مدى توافق على أن كل واحدة من هذه يمكن أن تزيد من فرصة إصابة الشخص بسرطان الرئة

	Strongly Agree / أوافق بشدة	**Agree / أوافق**	**Not sure / لا أعلم**	**Disagree / لا أوافق**	**Strongly Disagree / لا أوافق بشدة**
Exposure to radon gas (a naturally occurring radioactive gas)/ التعرض لغاز الرادون (غاز مشع طبيعي)	□	□	□	□	□
Exposure to another person's cigarette smoke/ التعرض لدخان سجائر شخص آخر	□	□	□	□	□
Having had treatment for any cancer in the past/ تلقي علاجًا من أي سرطان في الماضي	□	□	□	□	□
Having a close relative with lung cancer/ وجود قريب مصاب بسرطان الرئة	□	□	□	□	□
Exposure to chemicals (such as asbestos)/ التعرض للمواد الكيميائية (مثل الأسبستوس)	□	□	□	□	□
Having a previous history of cancer such as head and neck cancer/ التعرّض سابقاً للإصابة بالسرطان مثل سرطان الرأس والعنق	□	□	□	□	□
Air pollution/ تلوث الهواء	□	□	□	□	□
Being a smoker/ أن تكون مدخنا	□	□	□	□	□
Having a previous history of lung disease, such as, Chronic Obstructive Pulmonary Disease (COPD)/ التعرّض سابقاً لأمراض الرئة، مثل مرض الانسداد الرئوي المزمن	□	□	□	□	□

- How Confident are you that you would notice a symptom of Lung Cancer/ ما مدى ثقتك في أنك ستلاحظ أحد أعراض سرطان الرئة

Not at all confident/ غير واثق على الإطلاق	**Not very confident/ لست واثقا جدا**	**Fairly confident/ واثق**	**Very Confident/ واثق جدا**
□	□	□	□

Appendix 2: Scale Validation Results

Tab. S1. Proportion of answer per categories of warning signs awareness variables and Kappa agreement with 95% confidence interval between the Arabic and English reference questionnaires.

Warning signs	English questionnaire (reference)		Arabic questionnaire		Kappa Agreement	95% CI of Kappa Agreement	p-value
	N	%	N	%			
Unexplained weight loss					0.879	(0.66,1.00)	< 0.001
Yes	16	76.19	16	76.19			
No	2	9.52	3	14.28			
Don't Know	3	14.28	2	9.52			
Persistent (3 weeks or longer) chest infection					1	--	< 0.001
Yes	16	76.19	16	76.19			
No	3	14.28	3	14.28			
Don't Know	2	9.52	2	9.52			
Cough that doesn't go away for two to three weeks					1	--	< 0.001
Yes	20	95.23	20	95.23			
No	1	4.76	1	4.76			
Don't Know	0	0.00	0	0.00			
Persistent shortness of breath					1	--	< 0.001
Yes	20	95.23	20	95.23			
No	0	0.00	0	0.00			
Don't Know	1	4.76	1	4.76			
Persistent tiredness or lack of energy					0.790	(0.51,1.00)	< 0.001
Yes	16	76.19	15	66.66			
No	2	9.52	3	14.28			
Don't Know	3	14.28	3	14.28			
Persistent chest pain					1	--	< 0.001
Yes	21	100	21	100			
No	0	0.00	0	0.00			
Don't Know	0	0.00	0	0.00			
Persistent shoulder pain					0.921	(0.771,1.00)	< 0.001
Yes	7	33.33	8	38.09			
No	11	52.38	10	47.61			
Don't Know	3	14.28	3	14.28			
Coughing up blood					1	--	< 0.001
Yes	20	95.23	20	95.23			
No	0	0.00	0	0.00			
Don't Know	1	4.76	1	4.76			
Ache or pain when breathing					1	--	< 0.001
Yes	20	100	20	95.23			
No	0	0.00	0	0.00			
Don't Know	1	0.00	1	4.76			
Loss of appetite					0.913	(0.75,1.00)	< 0.001
Yes	13	61.90	13	61.90			
No	3	14.28	4	19.04			
Don't Know	5	23.80	4	19.04			
Painful Cough					1	--	< 0.001
Yes	20	90.47	20	90.47			
No	1	4.76	1	4.76			
Don't Know	0	0.00	0	0.00			
Changes in the shape of fingers or nails					0.927	(0.797,1.00)	< 0.001
Yes	8	38.09	9	42.85			
No	8	38.09	7	33.33			
Don't Know	5	23.80	5	23.80			

Tab. S1 *(follows).* Proportion of answer per categories of warning signs awareness variables and Kappa agreement with 95% confidence interval between the Arabic and English reference questionnaires.

Warning signs	English questionnaire (reference)		Arabic questionnaire		Kappa Agreement	95% CI of Kappa Agreement	p-value
	N	%	N	%			
Developing unexplained loud, high pitched sound when breathing					0.877	(0.687, 1.00)	<0.001
Yes	16	76.19	16	76.19			
No	3	14.28	4	19.04			
Don't Know	2	9.52	1	4.76			
Worsening or change in an existing cough					1	--	<0.001
Yes	20	95.23	20	95.23			
No	1	4.76	1	4.76			
Don't Know	0	0.00	0	0.00			

Tab. S2 *(follows).* Proportion of answers per categories of age at risk variable and Kappa agreement with 95% confidence interval between Arabic and English reference questionnaire

Risk factors	English questionnaire (reference)		Arabic questionnaire		Kappa Agreement	95% CI of Kappa Agreement	p-value
	N	%	N	%			
Age					1	--	< 0.001
1,058	0	0.00	0	0.00			
50-year-old	1	4.76	1	4.76			
70-year-old	11	52.38	11	52.38			
Unrelated to age	9	42.85	9	42.85			

Tab. S3. Proportion of answer per categories of risk factors awareness variables and Kappa agreement with 95% confidence interval between the Arabic and English reference questionnaires.

Risk factors	English questionnaire (reference)		Arabic questionnaire		Kappa Agreement	95% CI of Kappa Agreement	p-value
	N	%	N	%			
Exposure to radon gas					0.913	(0.753,1.00)	< 0.001
Strongly agree	13	61.90	13	61.90			
Agree	4	19.04	5	23.80			
Not sure	4	19.04	3	14.28			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			
Exposure to another persons' cigarette smoke					0.90	(0.73,1.00)	< 0.001
Strongly agree	13	61.90	14	66.66			
Agree	6	28.57	5	23.80			
Not sure	2	9.52	2	9.52			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			
Having had treatment for any cancer in the past					1	--	< 0.001
Strongly agree	11	52.38	11	52.38			
Agree	6	28.56	6	28.56			
Not sure	3	14.28	3	14.28			
Disagree	1	4.76	1	4.76			
Strongly Disagree	0	0.00	0	0.00			

▶

Tab. S3 *(follows)*. Proportion of answer per categories of risk factors awareness variables and Kappa agreement with 95% confidence interval between the Arabic and English reference questionnaires.

Risk factors	English questionnaire (reference)		Arabic questionnaire		Kappa Agreement	95% CI of Kappa Agreement	p-value
	N	%	N	%			
Having a close relative with lung cancer					0.911	(0.75,1.00)	<0.001
Strongly agree	13	61.90	13	61.90			
Agree	6	28.56	5	23.80			
Not sure	2	9.52	3	14.28			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			
Exposure to chemicals such as asbestos					0.892	(0.7,1.00)	<0.001
Strongly agree	15	71.42	15	71.42			
Agree	4	19.04	5	23.80			
Not sure	2	9.52	1	4.76			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			
Having previous history of cancer such as head and neck cancer					1	--	<0.001
Strongly agree	11	52.38	11	52.38			
Agree	4	19.04	4	19.04			
Not sure	5	23.80	5	23.80			
Disagree	1	4.76	1	4.76			
Strongly Disagree	0	0.00	0	0.00			
Air pollution					1	--	<0.001
Strongly agree	18	85.71	18	85.71			
Agree	3	14.28	3	14.28			
Not sure	0	0.00	0	0.00			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			
Being a smoker					1	--	<0.001
Strongly agree	19	90.47	19	90.47			
Agree	2	9.52	2	9.52			
Not sure	0	0.00	0	0.00			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			
Having a previous history of lung disease, such as Chronic Obstructive Pulmonary Disease (COPD)					1	--	<0.001
Strongly agree	18	85.71	18	85.71			
Agree	2	9.52	2	9.52			
Not sure	1	4.76	1	4.76			
Disagree	0	0.00	0	0.00			
Strongly Disagree	0	0.00	0	0.00			

Tab. S4. Proportion of answers per categories of confidence variable and Kappa agreement with 95% confidence interval between Arabic and English reference questionnaire

Risk factors	English questionnaire (reference)		Arabic questionnaire		Kappa Agreement	95% CI of Kappa Agreement	p-value
	N	%	N	%			
Confidence					1	--	< 0.001
Not at all confident	0	0.00	0	0.00			
Not very confident	7	33.33	7	33.33			
Fairly confident	9	42.9	9	42.9			
Very confident	5	23.8	5	23.8			

Reference: Handbook of Parametric and Nonparametric Statistical Procedures, Third Edition-2004.

Non-comunicable disease

Eosinophil count and clinical outcome in patients with acute exacerbation of Chronic obstructive pulmonary disease

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Keywords

Eosinophil count • Clinical outcome • Acute exacerbation • COPD

Summary

Introduction. *We examined the association of blood eosinophil counts at the time of AECOPD hospitalization with the risk of ICU admission as well as the hospital lengths of stay and mortality.*

Methods. *In the current retrospective study, the association between blood eosinophil counts in COPD patients at the time of AECOPD hospitalization and the risk of subsequent ICU admission as well as mortality was assessed. The chi-squared test and t-test were used to compare categorical and continuous variables. The statistical significance level was set at 0.05. Kaplan-Meier curves for mortality as well as ICU admission up to 40 days after discharge from the index hospitalization were constructed using the determined optimal eosinophil threshold derived above and for the predetermined ≥ 300 vs < 300 cells/μL threshold. All analyses were performed using SPSS version 19.*

Results. *Antibiotic prescription was significantly associated with increased ICU admission (OR = 1.57; confidence interval [95% CI] = 1.02-2.42. Patients with higher FEV1 had decreased ICU admission (OR = 0.98, 95% CI = 0.97-1.01, p = 0.1) as well as all-cause mortality compared (OR = 0.98, 95% CI= 0.92-1.04, p = 0.58). There were significantly greater mortality rates for patients with higher ESR (OR = 1.02, CI =1.01-1.03, p = 0.01) and CRP (OR = 1.02, 95% CI = 1.01-1.03, p = 0.01). There were significantly lower ICU admission rates for patients with higher FVC (OR = 0.97, 95% CI = 0.95-0.98, p = 0.002).*

Conclusions. *Blood eosinophil count could help determine the risk of ICU admission as well as mortality in COPD patients at the time of hospitalization.*

Introduction

Chronic obstructive pulmonary disease (COPD) has different phenotypes and prognoses (1). Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the most common respiratory problems, which is associated with serious complications and consequences such as reduced quality of life and high attenuation. It defined as the sudden worsening in airway function and respiratory symptoms in patients with COPD [2]. It is crucial to diagnose patients with a severe prognosis to treat and prevent disease from exacerbating as well as their deaths [3, 4]. Blood eosinophil counts have been used as a biomarker of airway inflammation [5]. There are conflicting reports on whether elevated blood eosinophil counts predict an increased risk of intensive care unit (ICU) admission [5-9]. There is also evidence of the relationship between the number of eosinophils and the possibility of hospitalization, hospital mortality, and the length of stay in the hospital [10, 11]. Nevertheless, using a single cut-off of blood eosinophil level to predict clinical outcome has been challenged [12, 13]. Studies reported that the within-subject variation of hourly blood eosinophil counts was more than 20%. Between-subject variation was even greater [14]. In COPD patients, blood eosinophil counts are associated with severe AECOPD [8]. Exacerbations associated with blood eosinophil counts >2% (approximately >150 cells/mL) are associated with shorter hospitalization in severe AECOPD [5, 15]. We hypothesized that monitoring blood eosinophils could be helpful in managing treatment. The current study aimed to assess the association of blood eosinophil count at the time of AECOPD hospitalization with subsequent risk of ICU admission, as well as increased length of stay and in-hospital mortality.

Materials and methods

This was a retrospective study on COPD patients during AECOPD hospitalization in Imam Khomeini Hospital between January 1, 2017, and Dec 31, 2019. The data source was the electronic medical records. Age, gender,

and comorbidity status were determined. Based on Hegewald et al study, the highest blood eosinophil count was measured 7 days before the index admission until 24 hours after the index admission (The first AECOPD-related hospitalization in the study period) [16] and before the administration of systemic corticosteroids (oral or intravenous). Laboratory variables including WBC count, FEV1 (%), FVC (%), ESR, and CRP were measured.

Study Patients

The hospitalized AECOPD patients aged >40 years with a secondary diagnosis related to asthma were included. All patients who were included in the study met the inclusion criteria. Overall, 1196 AECOPD hospitalizations were recognized; after excluding ineligible patients, 477 AECOPD patients were identified. Only subjects with a confirmed diagnosis of exacerbation of COPD were studied. An exacerbation of COPD was defined by a new onset of two or more events of dyspnea, coughing, increased sputum production or chest tightness that led to a change in treatment with systemic glucocorticoids or antibiotics for at least 3 days Diagnoses of COPD, chronic asthma, bronchiectasis, or interstitial lung disease were made based on previously confirmed spirometry or imaging by a physician. The first AECOPD-related hospitalization in the study period was selected as the index admission. Patients who died during the index admission, patients without blood eosinophil counts, pregnant cases, patients who had a known malignancy, and hospitalizations occurring after the index hospitalization were excluded.

Statistical Analyses

The primary outcomes were ICU admission as well as death due to all causes. For the primary outcomes, a blood eosinophil count ≥ 300 cells/μL was used to stratify patient groups. Multiple logistic regression analyses adjusted for age, sex comorbidities, and corticosteroid use were performed. The statistical significance level was set at 0.05. Kaplan-Meier curves for mortality as well as ICU admission up to 40 days after discharge from the index hospitalization. All analyses were performed using SPSS version 16.

Results

The mean and standard deviation of blood eosinophil count at the time of admission for understudied patients was 319.77 ± 200.78 cells/μL. Overall, the blood eosinophil count in 45 (9.4%) of patients was < 100 cells/μL. Also, the blood eosinophil counts in 198 (41.5%) and 234 (49.1%) cases were 100-300 cells/μL and counts ≥ 300 cells/μL (eosinophilic) respectively. Compared to patients with eosinophil counts ≥ 300 cells/μL, Cases who had eosinophil counts < 300 cells/μL were generally older (P: 0.22) with a higher rate of male patients (P: 0.03) and higher forced expiratory volume in one second (FEV1) value (P: 0.007) (Tab. I).

Regarding comorbidities, there were not statistical significant differences in the prevalence of diabetes (P: 0.82), hypertension (P: 0.40), cerebrovascular disease (P: 0.28), and apnea-hypopnea syndrome (OSAHS) (P: 0.70). More than thirty-four percent of patients had hypertension, with a non-significant difference between the high and low eosinophil groups (P: 0.40). A history of bronchodilator use was 74.2% with no -significant difference between the eosinophil groups (P:0.84). The

Tab. I. Comparison Different factors by eosinophil count.

Variable	Total (n = 477)	EOS < 100 cells/μjnL (n = 45)	EOS = 100-300 cells/μL (n = 198)	EOS ≥ 300 cells/μL (n = 234)	P
Age	66.16 ± 11.18	68.42 ± 10.21	66.50 ± 11.90	65.44 ± 10.70	0.22
Male Gender	329 (69)	25 (55.6)	132 (66.7)	172 (73.5)	0.03
Hypertension	163 (34.2)	18 (40.0)	71 (35.9)	74 (31.6)	0.4
Diabetes	89 (18.7)	10 (22.2)	36 (18.2)	43 (18.4)	0.82
Cerebrovascular disease	52 (10.9)	2 (4.4)	25 (12.6)	25 (10.7)	0.28
Pulmonary disease	25 (5.2)	5 (11.1)	6 (3.0)	14 (6.0)	0.07
OSAHS	6 (1.3)	0(0.0)	3 (1.5)	3 (1.3)	0.7
Bronchodilator	354 (74.2)	35 (77.8)	146 (73.7)	173 (73.9)	0.84
Antibiotic	149 (31.2)	16 (35.6)	71 (35.9)	62 (26.5)	0.09
ICU Admission	147 (30.8)	12 (26.7)	55 (27.8)	80 (34.2)	0.30
Death	28 (5.9)	3 (6.7)	11 (5.6)	14 (6.0)	0.95
Hospital Stay(Day)	8.05 ± 4.35	8.20 ± 4.49	8.07 ± 4.36	8.02 ± 4.25	0.96
WBC count	9539.97 ± 3823.69	7654.44 ± 3721.18	8433.38 ± 2922.98	10838.93 ± 4075.33	0.001
FEV1(%)	51.31 ± 19.31	55.52 ± 16.02	55.07 ± 19.85	47.49 ± 18.85	0.007
FVC(%)	68.00 ± 19.87	69.41 ± 19.58	71.21 ± 19.92	65.17 ± 19.63	0.07
ESR	22.53 ± 26.61	27.02 ± 23.34	24.57 ± 29.50	19.94 ± 24.37	0.09
CRP	27.98 ± 34.67	25.91 ± 33.89	24.93 ± 28.62	27.50 ± 36.66	0.72

* Those with P value < 0.05 were highlighted using the bold font. Data are presented as the number of patients (%), mean ± SD. FEV1% predicted from the stable stage of the patients.

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; EOS: eosinophils; SD: standard deviation; BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; OSAHS: obstructive sleep apnea-hypopnea syndrome.

mean and standard deviation of hospital length of stay was 8.05 ± 4.35 days, with a non-significant difference between the eosinophil group (P:0.40). A total of 147 patients (30.8%) were admitted to ICU and the admission rate was not significantly different between eosinophil groups. Mortality during hospitalization for all cases was 5.9% (28 of 477 patients). Mortality was not significantly different between the eosinophil groups (6.7, 5.6, and 6.0%). Kaplan-Meier curves for mortality, as well as ICU admission based on eosinophil value of ≥ 300 cells/μL, are shown in figure 1. There was no significant difference in the of hospital length of stay between eosinophil groups using a threshold of 300 cells/μL. In terms of laboratory tests, the white blood cells (WBC), were significantly higher in the patients with eosinophilic AECOPD (P: 0.001) and conversely, erythrocyte sedimentation rate (ESR) was lower in the patients with eosinophilic AECOPD; the differences between the groups was not statistically significant (Tab. I).

In addition, Antibiotic prescription was significantly associated with increased ICU admission (OR = 1.57; confidence interval [95% CI] = 1.02-2.42) (Tab. II). There was no significant difference in the primary outcome of ICU admission between the high eosinophil and low eosinophil groups using a threshold of 300 cells/μL, Odds ratio [OR] =1.45, 95% confidence interval [95% CI] = 0.98-2.17) (Tab. II).

However, patients with higher FEV1 had decreased ICU admission (OR = 0.98, 95% CI = 0.97-1.01, P: 0.10) as well as all-cause mortality compared (OR = 0.98, 95% CI = 0.92-1.04, P: 0.58). There were significantly greater mortality rates for patients with higher ESR (OR = 1.02, CI = 1.01-1.03, P: 0.01) and CRP (OR = 1.02, 95% CI = 1.01-1.03, P:0.01). There were significantly lower ICU admission rates for patients with higher FVC (OR = 0.97, 95% CI = 0.95-0.98, P: 0.002).

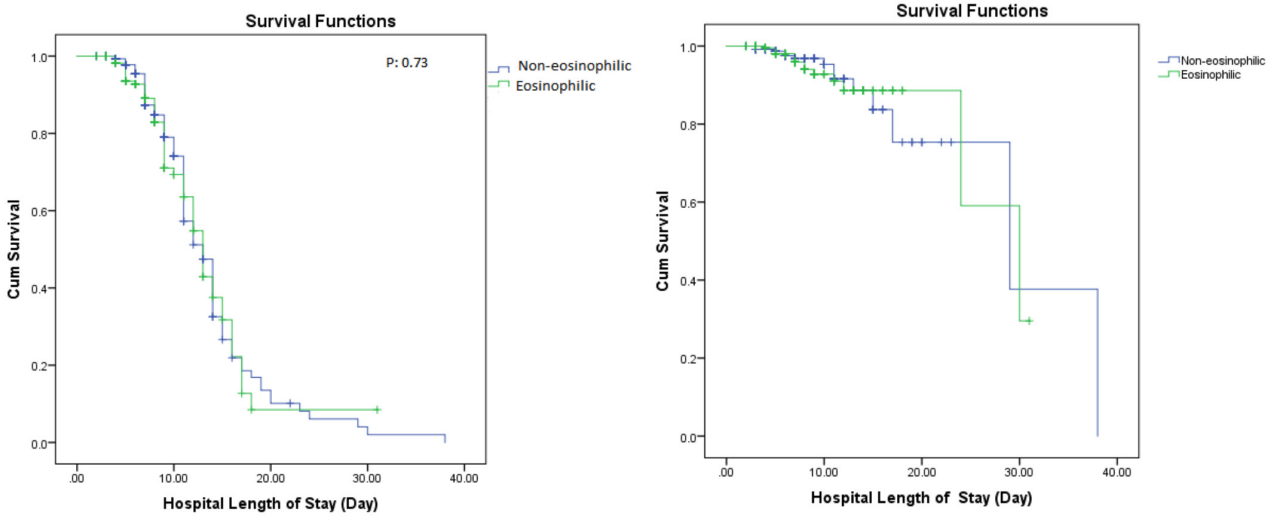
Discussion

The available evidence indicates the importance of blood eosinophil levels in predicting the severity of COPD disease, the response rate of patients to treatment, and the proper management of these patients [17-19]. However, there is still not much agreement on the threshold used to define the eosinophilic phenotype [16]. Although studies have used varying thresholds to define eosinophilic phenotype [5, 20], thresholds used to define the eosinophilic phenotype are not yet standardized. We found that blood eosinophil counts of ≥300 cells/μL are common, occurs in 49% of patients.

There was no statistically significant association between eosinophilic AECOPD and ICU admission. Various studies have evaluated blood eosinophils in AECOPD. However, results in different populations with AECOPD are inconsistent [5, 8, 16, 20]. Some studies have shown an increased risk of readmission with increased eosinophils [6, 21]. A study [6] showed that high eosinophilia was associated with COPD-related readmission [9]. Other studies showed a negative association [5], or even no association [7] between blood eosinophils and re-admission. One of the possible reasons for the different results is the use of corticosteroids before eosinophil measurement in some studies [5, 6] may play a role in the different results. Eosinophils play an important role in the type 2 immune response pathway and are also associated with allergic, rheumatological, infectious, and rare idiopathic disorders [22]. Also, the relationship between high blood eosinophils and readmission in patients with COPD may be partially explained by the presence of comorbidities [16].

Our results showed that higher eosinophil is not significantly associated with mortality. Many studies have shown that eosinopenia is associated with mortality in AECOPD patients [15, 23-27]. This discrepancy

Fig.1. Comparison of Hospital lengths of stay by eosinophil status.



Tab. II. Effective factors on Mortality and ICU admission of understudied cases.

Variables	Mortality	P	ICU admission	P
	OR (95% CI)		OR (95% CI)	
Age	1.04 (1-1.08)	0.06	1.01 (99-1.03)	0.22
Sex(males)	1.45 (0.60-3.47)	0.41	1.06 (0.69-1.65)	0.78
Antibiotics	1.28 (0.57-2.89)	0.55	**1.57 (1.02-2.42)**	**0.04**
Bronchodilators	1.23 (0.44-3.46)	0.69	0.78 (0.49-1.25)	0.31
EOS < 300 cells/μL	1.08 (0.49-2.35)	0.85	1.45 (0.98-2.17)	0.07
Comorbidity	1.71 (0.66-4.44)	0.27	0.88 (0.57-1.36)	0.57
WBC count	1.03 (1.01-1.09)	0.03	1.0 (0.99-1.01)	0.1
FEV1(%)	0.98 (0.92-1.04)	0.58	0.98 (0.97-1.01)	0.1
FVC(%)	1.02 (0.86-1.20)	0.45	**0.97 (0.95-0.98)**	0.002
ESR	**1.02 (1.01-1.03)**	0.01	0.99 (0.98-1.01)	0.07
CRP	**1.02 (1.01-1.03)**	0.01	1.0 (0.99-1.01)	0.25

may be due to patient selection. On the contrary, some studies have shown that the number of blood eosinophils is not related to in-hospital mortality in AECOPD patients [28, 29], For example, Chen et al concluded that the number of eosinophils on admission in patients with AECOPD is not related to mortality in patients requiring hospitalization in the intensive care unit [10].

The possibility of an association between eosinophil count and risk of death is still unclear [30]. In the present study, AECOPD patients with lower eosinophils tended to have increased ESR levels, which may indicate that they are more susceptible to infection [30]. Some studies have shown a correlation between low eosinophils and infection [31, 32]. We also observed that non-eosinophilic patients were older, which suggested that they may be more prone to infection. Therefore, the relationship between mortality in patients with eosinopenia may be due to severe infection. Eosinophil count was associated with ICU admission, and length of stay, which was in agreement with previous reports [29, 33, 34].

The use of bronchodilators for AECOPD has also been evaluated in various studies. The results of these studies indicate that the use of bronchodilators, especially in patients with a history of frequent exacerbations and an increase in the number of eosinophils, has been associated with a reduction in AECOPD [35-37].

High blood eosinophil counts were not associated significantly with mortality. Similarly, a clinical study involving COPD patients found that elevated blood eosinophil counts (≥200, 300, 400 cells/μL) were not associated with mortality when compared with patients with decreased eosinophil counts [38]. This observation is not consistent with other studies. Discrepancies between study results may be due to differences in COPD severity. Some beneficial factors such as better FEV1, fewer symptoms, less dyspnea, and less emphysema [35], may be present in patients with high eosinophil counts [39]. In addition, higher eosinophil counts may influence mortality because there is an association between improved response to corticosteroids and eosinophil counts [36, 40, 41]. Another point to consider when interpreting study results is that, eosinophil cutoff may influence the results.

The present study had limitations. First, the present study was an observational study and its results do not imply causal relationships. Second, the lack of follow-up of patients prevented further evaluation of long-term outcomes. Another limitation was related to the uncertainty regarding the diagnosis of COPD. Finally, there is an increasing body of evidence linking eosinophil counts to clinical outcomes in COPD patients. As such, further evaluation in future studies is essential.

Conclusions

The current study presents evidence of the association between blood eosinophils and clinical outcomes of AECOPD. Our data further support the use of blood eosinophils levels on admission as a prognostic biomarker for hospitalized COPD patients. Blood eosinophil count could help determine the risk of ICU admission as well as mortality of COPD cases, although further studies are necessary to identify the prognostic value of blood eosinophils in COPD patients.

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Data availability statement

The data presented in this study are available on request from the corresponding author.

Informed consent statement

Not applicable.

Ethical consideration

This study approved by ethics' committee of Tehran university of medical sciences with ID: IR.TUMS.IKHC.REC.1400.427.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' Contributions

NF, FM: conceptualization, Methodology, validation, project administration, supervision. IHB: data curation, formal analysis, investigation. HH, HK, MA and AN: writingoriginal draft preparation and editing. All authors have read and agreed to the published version of the manuscript.

References

[1] Segal LN, Martinez FJ. Chronic obstructive pulmonary disease subpopulations and phenotyping. J Allergy Clin Immunol 2018;141:1961-71. https://doi.org/10.1016/j.jaci.2018.02.035.

[2] MacIntyre N, Huang YC. Acute exacerbations and respiratory failure in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008;5:530-5. https://doi.org/10.1513/pats.200707-088ET.

[3] Pu J, Yi Q, Luo Y, Wei H, Ge H, Liu H, Li X, Zhang J, Pan P, Zhou H, Zhou C, Yi M, Cheng L, Liu L, Zhang J, Peng L, Aili A, Liu Y, Zhou H; MAGNET AECOPD Registry Investigators. Blood Eosinophils and Clinical Outcomes in Inpatients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study. Int J Chron Obstruct Pulmon Dis 2023;18:169-79. https://doi.org/10.2147/COPD.S396311.

[4] Agusti A, Vogelmeier C, de Oca M. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 Report).

[5] Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K, Patel H, Rugman P, Dodson P, Jenkins M, Saunders M, Newbold P, Green RH, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662-71. https://doi.org/10.1164/rccm.201104-0597OC.

[6] Couillard S, Larivée P, Courteau J, Vanasse A. Eosinophils in COPD Exacerbations Are Associated With Increased Readmissions. Chest 2017;151:366-373. https://doi.org/10.1016/j.chest.2016.10.003.

[7] Duman D, Aksoy E, Agca MC, Kocak ND, Ozmen I, Akturk UA, Gungor S, Tepetam FM, Eroglu SA, Oztas S, Karakurt Z. The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. Int J Chron Obstruct Pulmon Dis 2015;10:2469-78. https://doi.org/10.2147/COPD.S90330.

[8] Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med 2016;193:965-74. https://doi.org/10.1164/rccm.201509-1869OC.

[9] Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2015;192:523-5. https://doi.org/10.1164/rccm.201502-0235LE.

[10] Chen PK, Hsiao YH, Pan SW, Su KC, Perng DW, Ko HK. Independent factors associate with hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease requiring intensive care unit admission: Focusing on the eosinophil-to-neutrophil ratio. PLoS One 2019;14:e0218932. https://doi.org/10.1371/journal.pone.0218932.

[11] Greulich T, Tüffers J, Mager S, Eder A, Maxheim M, Alter P, Schmeck B, Vogelmeier CF. High eosinophil blood counts are associated with a shorter length of hospital stay in exacerbated COPD patients-a retrospective analysis. Respir Res 2020;21:106. https://doi.org/10.1186/s12931-020-01365-5.

[12] Schumann DM, Tamm M, Kostikas K, Stolz D. Stability of the Blood Eosinophilic Phenotype in Stable and Exacerbated COPD. Chest 2019;156:456-65. https://doi.org/10.1016/j.chest.2019.04.012.

[13] Vogelmeier CF, Kostikas K, Fang J, Tian H, Jones B, Morgan CL, Fogel R, Gutzwiller FS, Cao H. Evaluation of exacerbations and blood eosinophils in UK and US COPD populations. Respir Res 2019;20:178. https://doi.org/10.1186/s12931-019-1130-y.

[14] Spector SL, Tan RA. Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?". J Asthma 2012;49:807-10. https://doi.org/10.3109/02770903.2012.713428.

[15] Saltürk C, Karakurt Z, Adiguzel N, Kargin F, Sari R, Celik ME, Takir HB, Tuncay E, Sogukpinar O, Ciftaslan N, Mocin O, Gungor G, Oztas S. Does eosinophilic COPD exacerbation have a better patient outcome than non-eosinophilic in the intensive care unit? Int J Chron Obstruct Pulmon Dis 2015;10:1837-46. https://doi.org/10.2147/COPD.S88058.

[16] Hegewald MJ, Horne BD, Trudo F, Kreindler JL, Chung Y, Rea S, Blagev DP. Blood Eosinophil Count and Hospital Readmission in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis 2020;15:2629-41. https://doi.org/10.2147/COPD.S251115.

[17] Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? Lancet Respir Med 2017;5:747-59. https://doi.org/10.1016/S2213-2600(17)30217-5. Erratum in: Lancet Respir Med 2017;5:e28. https://doi.org/ 10.1016/S2213-2600(17)30260-6.

[18] Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, Maitland-van der Zee AH, de Vries F, Franssen FME. Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. Am J Respir Crit Care Med 2017;195:1402-4. https://doi.org/10.1164/rccm.201701-0009LE.

[19] Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, Barnes N, Hilton E. Blood eosinophil levels as a biomarker in COPD. Respir Med 2018;138:21-31. https://doi.org/10.1016/j.rmed.2018.03.016.

[20] Yun JH, Lamb A, Chase R, Singh D, Parker MM, Saferali A, Vestbo J, Tal-Singer R, Castaldi PJ, Silverman EK, Hersh CP; COPDGene and ECLIPSE Investigators. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2018;141:2037-47.e10. https://doi.org/10.1016/j.jaci.2018.04.010.

[21] Bélanger M, Couillard S, Courteau J, Larivée P, Poder TG, Carrier N, Girard K, Vézina FA, Vanasse A. Eosinophil counts in first COPD hospitalizations: a comparison of health service

utilization. Int J Chron Obstruct Pulmon Dis 2018;13:3045-54. https://doi.org/10.2147/COPD.S170743.

[22] Klion AD. Eosinophilia: a pragmatic approach to diagnosis and treatment. Hematology Am Soc Hematol Educ Program 2015;2015:92-7. https://doi.org/10.1182/asheducation-2015.1.92.

[23] Mao Y, Qian Y, Sun X, Li N, Huang H. Eosinopenia Predicting Long-term Mortality in Hospitalized Acute Exacerbation of COPD Patients with Community-acquired Pneumonia-A Retrospective Analysis. Int J Chron Obstruct Pulmon Dis 2021 Dec 30;16:3551-9. https://doi.org/10.2147/COPD.S347948.

[24] Yang J, Yang J. Association Between Blood Eosinophils and Mortality in Critically Ill Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study. Int J Chron Obstruct Pulmon Dis 2021;16:281-8. https://doi.org/10.2147/COPD.S289920.

[25] Håkansson KEJ, Ulrik CS, Godtfredsen NS, Kallemose T, Andersen O, Eugen-Olsen J, Marsaa K, Rasmussen LJH. High suPAR and Low Blood Eosinophil Count are Risk Factors for Hospital Readmission and Mortality in Patients with COPD. Int J Chron Obstruct Pulmon Dis 2020;15:733-43.https://doi.org/10.2147/COPD.S229904.

[26] Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax 2012;67:970-6. https://doi.org/10.1136/thoraxjnl-2012-202103.

[27] Zhang Y, Liang LR, Zhang S, Lu Y, Chen YY, Shi HZ, Lin YX. Blood Eosinophilia and Its Stability in Hospitalized COPD Exacerbations are Associated with Lower Risk of All-Cause Mortality. Int J Chron Obstruct Pulmon Dis 2020;15:1123-34. https://doi.org/10.2147/COPD.S245056.

[28] Martínez-Gestoso S, García-Sanz MT, Calvo-Álvarez U, Doval-Oubiña L, Camba-Matos S, Salgado FJ, Muñoz X, Perez-Lopez-Corona P, González-Barcala FJ. Variability of blood eosinophil count and prognosis of COPD exacerbations. Ann Med 2021;53:1152-8. https://doi.org/10.1080/07853890.2021.1949489.

[29] Yu S, Zhang J, Fang Q, Tong Z. Blood Eosinophil Levels and Prognosis of Hospitalized Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Am J Med Sci 2021;362:56-62. https://doi.org/10.1016/j.amjms.2021.02.013.

[30] Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JE, Morgan MD, Brightling CE, Hussain SF, Pavord ID, Singh SJ, Steiner MC. Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. Chest 2016;150:320-8. https://doi.org/10.1016/j.chest.2016.01.026.

[31] Abidi K, Khoudri I, Belayachi J, Madani N, Zekraoui A, Zeggwagh AA, Abouqal R. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units. Crit Care 2008;12:R59. https://doi.org/10.1186/cc6883.

[32] Shaaban H, Daniel S, Sison R, Slim J, Perez G. Eosinopenia: Is it a good marker of sepsis in comparison to procalcitonin and C-reactive protein levels for patients admitted to a critical care unit in an urban hospital? J Crit Care 2010;25:570-5. https://doi.org/10.1016/j.jcrc.2010.03.002.

[33] Wu HX, Zhuo KQ, Cheng DY. Peripheral Blood Eosinophil as a Biomarker in Outcomes of Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis 2019;14:3003-15.https://doi.org/10.2147/COPD.S226783.

[34] Ko FWS, Chan KP, Ngai J, Ng SS, Yip WH, Ip A, Chan TO, Hui DSC. Blood eosinophil count as a predictor of hospital length of stay in COPD exacerbations. Respirology 2020;25:259-66. https://doi.org/10.1111/resp.13660.

[35] Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, Vogelmeier C, Fabbri LM, Chanez P, Dahl R, Disse B, Finnigan H, Calverley PM. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med 2016;4:390-8. https://doi.org/10.1016/S2213-2600(16)00100-4.

[36] Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med 2015;3:435-42. https://doi.org/10.1016/S2213-2600(15)00106-X. Erratum in: Lancet Respir Med 2015;3:e19. https://doi.org/10.1016/S2213-2600(15)00154-X.

[37] Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ; IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378:1671-80. https://doi.org/10.1056/NEJMoa1713901.

[38] Trigo JMM, Martinez M, Cubero P, Forner M, Saetta M, Cosio MG. Blood eosinophils and outcomes in COPD. Eur Respiratory Soc 2016;48:4624. https://doi.org/10.1183/13993003.congress-2016.PA4624

[39] Turato G, Semenzato U, Bazzan E, Biondini D, Tinè M, Torrecilla N, Forner M, Marin JM, Cosio MG, Saetta M. Blood Eosinophilia Neither Reflects Tissue Eosinophils nor Worsens Clinical Outcomes in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2018;197:1216-19. https://doi.org/10.1164/rccm.201708-1684LE.

[40] Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R; ECLIPSE investigators. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014;44:1697-700. https://doi.org/10.1183/09031936.00162414.

[41] Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD. Thorax 2016;71:118-25. https://doi.org/10.1136/thoraxjnl-2015-207021.

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Non-comunicable disease

Comparison of the effect of Sacubitril/Valsartan with Losartan and Captopril in improving right ventricular function in patients with right heart failure, a randomized clinical controlled trial

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Keywords

Sacubitril/valsartan • Right ventricle • Right heart failure

Summary

Background. *There is evidence supporting the efficacy of Sacubitril /Valsartan for improving left heart failure, but few studies have examined its effects on right ventricular (RV) dysfunction. The current study aimed to investigate the effects of Sacubitril / Valsartan on RV dysfunction in patients with right heart failure.*
Methods. *The current study was a randomized and parallel clinical trial study. Patients over 18 years with any degree of right heart failure regardless of Left ventricular ejection fraction (LVEF) were included. The included patients were assigned randomly to three study arms using simple random allocation, i.e. the intervention group (Sacubitril Valsartan recipients) and the control groups (Losartan and Captopril recipients). The SPSS software version 19 was used for data analysis.*
Results. *The changes in LVEF, RV FAC, RV diameter, DOE grade, and TAPSE in the Sacubitril/Valsartan group were significantly higher than the other two groups. The severity of RV dysfunction, as well as TR (Tricuspid Regurgitation) severity, decreased significantly three months after the intervention compared to the beginning of the intervention in all groups especially in the Sacubitril/Valsartan group (p: 0.006). The mortality rate in the Sacubitril/Valsartan, Losartan, and Captopril groups, were 2 (6.7%), 2 (11.2%), and 1 (7.7%) respectively (p: 0.83). Also, 27.6, 62.5, and 7.7% of cases in the Sacubitril/Valsartan, Losartan, and Captopril reached to optimum dose (p: 0.006).*
Conclusions. *Considering the results, it seems that Sacubitril/Valsartan has a positive effect on improving RV dysfunction in patients with right heart disorders.*

Introduction

During the last decade, cardiovascular diseases have become the most important cause of death all over the world; and at least one death out of three deaths is due to cardiovascular diseases [1]. One of the important cardiovascular complications in patients with heart failure with reduced ejection fraction (HFrEF) is right ventricular (RV) dysfunction [2]. During the treatment of HFrEF, right heart dysfunction and improvement of its function should be considered. This disorder is associated with high mortality, especially in patients with congenital heart diseases, valvular diseases, coronary artery diseases, and patients with pulmonary hypertension [3-5].
Losartan potassium, an angiotensin II receptor antagonist, and captopril, an angiotensin-converting enzyme (ACE) inhibitor, have been used in the treatment of heart failure for many years. However, their use often has side effects such as angioedema and hyperkalemia [6]. Sacubitril and valsartan are combination drugs for patients with chronic heart failure. Sacubitril causes vasodilation by inhibiting the degradation of BNP (brain natriuretic peptide) [7]. Valsartan prevents the contraction of blood vessels, which reduces blood pressure and improves blood flow. It was shown that Sacubitril/Valsartan has positive effects in reducing mortality and hospital admission, as well as reducing the hospital lengths of stay in patients with heart failure [8]. Also, this drug is related to improving the quality of life (QoL) and reversing heart reconstruction [9]. The beneficial effects of this drug have been described as improving the systolic function of the right ventricle and reducing its disorders [10, 11]. The improvement of the right ventricular function is associated with the improvement of the patient's clinical outcome and the reduction of hospitalization [12]. Studies have shown that sacubitril/valsartan improves heart function by reducing peripheral vascular resistance, preventing the narrowing of arteries, and reducing cardiac load [13, 14]. Different studies assessed the effects of Sacubitril/Valsartan in cardiovascular patients, however, results about the efficacy have been reported inconsistently [15-17].
Previous studies showed improvements in right ventricular function such as tricuspid annular plane systolic excursion, pulmonary hypertension, and systolic pulmonary arterial pressure after Sacubitril/Valsartan initiation [10, 18]. However, some studies failed to show any beneficial effect of Sacubitril/

Valsartan on improving RV function. Therefore, the effects of Sacubitril/Valsartan on RV dysfunction remain a controversial issue [19]. Therefore, considering the importance of the topic, this study aimed to compare the effect of Sacubitril /Valsartan with Losartan and Captopril in improving biventricular function, including left ventricular ejection fraction, fractional area change, Pulmonary arterial systolic pressure, tricuspid annular plane systolic excursion, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and right ventricular–pulmonary artery coupling.

Materials and methods

The present study was an open-label randomized and parallel clinical trial study.

Inclusion criteria

Inclusion criteria included patients over 18 years of age with any degree of right heart failure regardless of the severity of LV dysfunction (mild, moderate, and severe). Informed consent was obtained from all participants.

Exclusion criteria

The patients with SBP < 100 mmHg, GFR < 30 or Cr > 2.5 or renal artery stenosis, ACEI/ARB intolerance, and history of angioedema, or acute pulmonary embolism were excluded. Sampling was done from patients with right-sided heart failure referring to Hazrat-e Rasoul Akram Hospital who need treatment with ACEi/ARB/ARNI.

Patient allocation

The included patients were assigned randomly to three study arms using simple random allocation, *i.e.* the intervention group (Sacubitril Valsartan recipients) and the control groups (Losartan and Captopril recipients). Graphpad random assignment software was used to generate random sequences. In this way, before using the software and generating the sequence, it was decided to receive the letter (E) of the studied drug, the letter (B) of losartan, and the letter (C) of captopril. Then, using the production sequence software, each letter was placed inside a sealed envelope. To maintain the created sequence, the number was recorded on the outer surface of the envelopes. The patients received the order of referral according to the method inside the envelope. After determining the sequence of patients and the type of intervention, at the beginning of the study, an echocardiography was performed by the fellowship of this field in groups and before the start of the treatments. Then, the intervention group was treated with sacubitril-valsartan drug at a dose of 24/26 mg twice a day, and in subsequent visits, if the patient tolerated this amount, the dose was increased to 97/103 mg twice a day. The control group also received Losartan with a starting dose of 25 mg daily prescribed to patients with any degree of RV dysfunction, and in subsequent visits, if the patient tolerated this amount, the dose was increased to 50mg daily and Captopril drug with the starting dose of 6.25 mg three times daily in patients with any degree of RV dysfunction and subsequent visits, if the patient tolerated this amount, the dose was increased to 50mg three times daily, according to the guidelines for heart failure patients. The intervention continued for three months and during the follow-up period, the patients of all groups were repeatedly evaluated for clinical symptoms. During this period, monthly visits monitored the patients or if they were unable to come to the clinic because of long distances, they were questioned about their functional status, dyspnea grade, daily dose of medication, and compliance by routine phone calls. At the end of the third month, the follow-up echo was repeated. The outcomes that were examined in two echocardiography sessions included: EF, LVESD, LVEDD, E/e', RV size, TAPSE, FAC, PAP, and RV-PA coupling. RV function was assessed by several parameters and each one has its prognostic value. Of the direct indicators of RV function is RVEF, which is the quality of RV muscle contraction and relaxation in apical 4chamber view by eyeball measurement and is classified as normal, mild, moderate, and severe RV dysfunction. The complementary index of RVEF is RV FAC. RV diameter is also important, and directly associated with RV dilation and dysfunction. TAPSE measures RV longitudinal movement by putting M mode on the lateral wall of the RV in an apical 4-chamber view. Tricuspid valve regurgitation (known as TR) is the result of both RV/annulus dilation and tricuspid valve incompetence. It is measured by the percent of the TR jet area occupying the right atrium. TR gradient which is measured by putting CW on TV in apical 4chamber view, is also helpful to define the amount of pressure on RV, and adding RA pressure (which is indirectly estimated by IVC size and collapse) to RVSP is called pulmonary artery systolic pressure (PASP). RA-PA coupling is the relationship between RV contractility and RV afterload. It can be estimated by echo using the ratio between TAPSE and PASP. Other indicators (LVEF, LVESD, LVEDD, E/e') are related to LV systolic and diastolic function and are assessed for considering the effect of drugs on both ventricles. All the data, including the baseline and the data related to the final results, were recorded in the checklist and then entered into SPSS software version 22 to be analyzed according to the objectives of the study (Fig. 1).

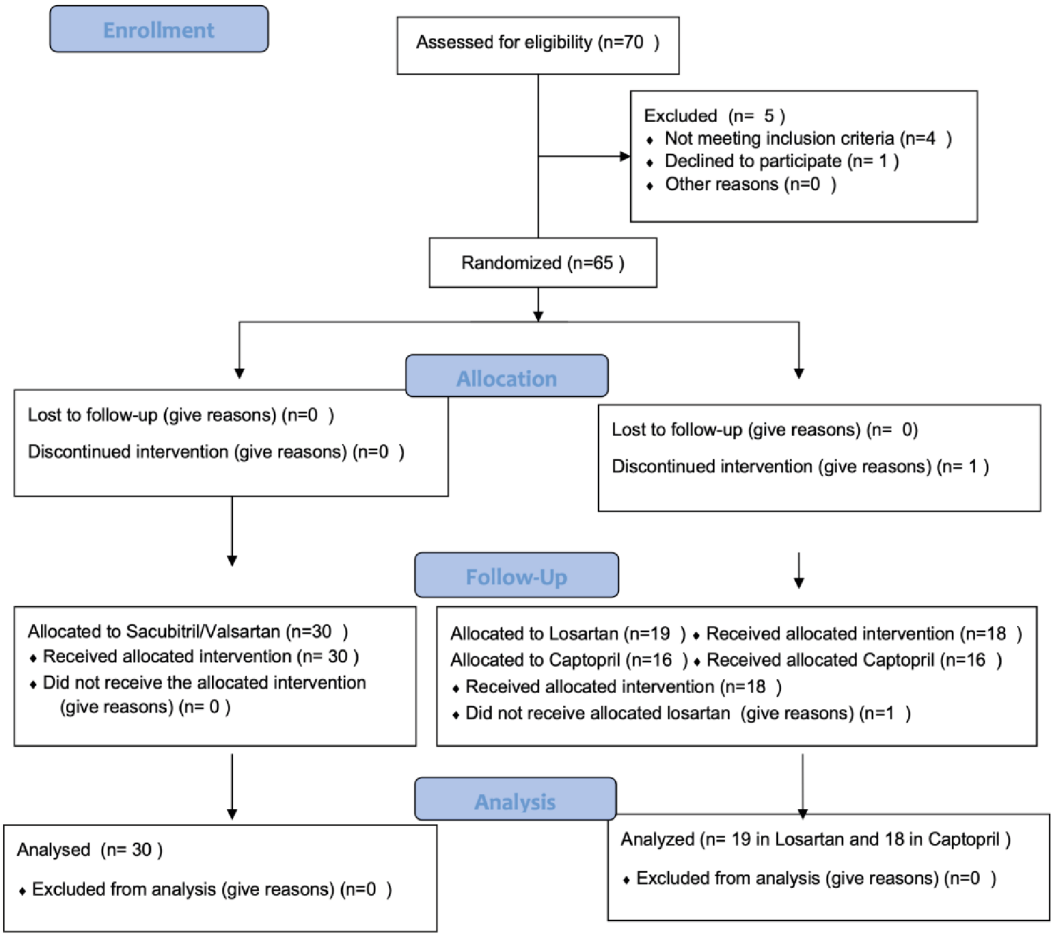
Sample size

All available patients who were willing to participate in the study were selected included in the study and randomly assigned to studied groups.

Data analysis

The results for quantitative variables were expressed as mean and standard deviation (mean ±SD) and for qualitative variables as frequency and percentages. The Chi-square or Fisher's exact tests were used to compare qualitative variables. The continuous variables were analyzed using a one-way ANOVA test. The Bonferroni

Fig. 1. Consort flow chart.



post hoc analysis was used for multiple comparisons. The 5% was considered as a statistically significant level. All analysis was conducted using SPSS software version 22.

Results

Baseline characteristic

Regarding gender, 22 (73.3%), 13 (72.2%) and 12 (75.0%) cases in Sacubitril/Valsartan, Losartan, and Captopril groups were men, respectively (p: 0.59). The mean Age in the Sacubitril/Valsartan, Losartan, and Captopril were 55.93 ± 12.95, 63.66 ± 12.09, and 64.40±13.53 respectively (P: 0.05). Also, the most common type of cardiac disorder in the three studied groups was Biventricular dysfunction (BiV) (p: 0.58). In terms of the history of underlying diseases, 16 (53.3%), 9 (50.0%) and 10 (66.7%) patients in Sacubitril/Valsartan, Losartan, and Captopril groups had a history of IHD (p: 0.44). Other important information is shown in Table I.

Main outcomes

In the Comparison of the mean of changes of different indices between the studied groups, the changes in LVEF, RV FAC, RV diameter, DOE grade, and TAPSE in the Sacubitril/Valsartan group were significantly higher than the other two groups (Tab. II). Regarding the RV dysfunction, most of the cases at the baseline in each group had moderate RV dysfunction (Sacubitril/Valsartan: 66.7%, Losartan: 50%, and Captopril: 75%) and there was no significant difference between the study groups (P: 0.60). But after three months, 68, 13.3 and 50% of cases in the Sacubitril/Valsartan, Losartan and Captopril had mild RV dysfunction respectively. This index had a significant difference between the studied groups three months after receiving the intervention (P: 0.04). Also, the severity of RV dysfunction decreased significantly three months after the intervention compared to the beginning of the intervention in all studied groups (p: 0.006) (Tab. III). The TR (Tricuspid Regurgitation) severity index at the beginning of the study had a significant difference between the studied groups so the most severe cases were in the losartan group (p: 0.03). While this index did not have a significant difference between the studied groups three months after receiving the intervention (p: 0.13). At the baseline, the TR gradient in 3.3, 33.3 and 14.3% of cases in the Sacubitril/Valsartan, Losartan, and Captopril was severe respectively but at the end of the study, 0, 14.3 and 16.7 % of cases in the mentioned groups showed severe TR gradient. These changes were statistically

Tab. I. Basic characteristics of the participants in the studied groups.

Variable	Subgroups		Group			p
			Sacubitril/Valsartan (n:30)	Losartan (n:18)	Captopril (n:16)	
Gender	Males	N	22	13	12	
		%	73.30%	72.20%	75.0%	0.59
Type of heart disorder	BiV	N	27	14	13	0.58
		%	90.00%	77.80%	81.30%	
	RV dysfunction	N	3	4	3	
		%	10.00%	22.20%	18.80%	
History of underlying disease	IHD	N	16	9	10	0.44
		%	53.30%	50.00%	62.5%	
	Other diseases	N	14	9	6	
		%	46.70%	50.00%	37. 5%	
Age		Mean ±SD	55.93±12.95	63.66±12.09	64.40±13.53	0.05

Tab. II. Comparison of the mean of changes of different indices between the studied groups.

Factor	Group	Mean	SD	P
LVEF	Sacubitril/Valsartan *	**0.05**	0.04	**0.001**
	Losartan*	-0.01	0.04	
	Captopril	0.01	0.04	
RV FAC	Sacubitril/Valsartan *	**0.07**	0.04	**0.001**
	Losartan	0.04	0.05	
	Captopril*	0.01	0.04	
PASP	Sacubitril/Valsartan	-6.04	7.68	0.47
	Losartan	-3.64	4.91	
	Captopril	-3.70	6.18	
RV diameter	Sacubitril/Valsartan *	**-0.31**	0.33	**0.007**
	Losartan	-0.13	0.20	
	Captopril*	0.02	0.32	
DOE grade	Sacubitril/Valsartan *	**-1.14**	0.45	**0.009**
	Losartan	-0.67	0.98	
	Captopril*	-0.50	0.52	
TAPSE	Sacubitril/Valsartan *$	**2.75**	2.14	**0.01**
	Losartan*	0.79	2.46	
	Captopril$	0.67	3.14	
LVESD	Sacubitril/Valsartan	-0.32	0.36	0. 15
	Losartan	-0.15	0.40	
	Captopril	-0.10	0.35	
LVEDD	Sacubitril/Valsartan	-0.14	0.28	0.83
	Losartan	-0.16	0.43	
	Captopril	-0.08	0.30	
E/e'	Sacubitril/Valsartan	-3.14	4.61	0.41
	Losartan	-3.03	5.57	
	Captopril	-1.08	3.26	
RV-PA coupling	Sacubitril/Valsartan	0.09	0.09	0.71
	Losartan	0.07	0.12	
	Captopril	0.06	0.15	

* indicates to significant difference according to post hoc test results. $ indicates to significant difference according to post hoc test results. LVEF: Left ventricular ejection fraction, FAC: fractional area change, PASP: Pulmonary arterial systolic TAPSE: pressure, tricuspid annular plane systolic excursion, LVESD: left ventricular end-systolic diameter, LVEDD: left ventricular end-diastolic diameter, RV-PA coupling: Right ventricular–pulmonary artery coupling,

Tab. III. Comparison of RV dysfunction and TR severity between the studied groups.

Group	Baseline				p	Three months later(follow-up)				p	P trend
	RV dysfunction					RV dysfunction					
RV dysfunction (based on RVEF)	Mild	Moderate	Severe	Normal		Mild	Moderate	Severe	Normal		
Sacubitril/Valsartan	6	**20**	4	-	0.60	17	8	0	3	**0.04**	**0.006**
	20.00%	**66.7%**	13.3%	-		68.00%	28.6%	0.00%	10.7%		
Losartan	4	**9**	5	-		2	11	1	1		
	22.2%	**50.0%**	27.8%	-		13.3%	73.3%	6.7%	6.7%		
Captopril	2	**12**	2	-		6	5	1	0		
	12.5%	**75.0%**	12.5%	-		50.0%	41.7%	8.3%	0.00%		
TR severity											
Sacubitril/Valsartan	11	18	1	-	**0.03**	17	11	0	-	0.13	**0.02**
	36.7%	60.0%	3.3%	-		60.70%	39.3%	0.00%	-		
Losartan	7	5	**6**	-		7	5	2	-		
	38.9%	27.8%	**33.3%**	-		25.00%	35.70%	14.3%	-		
Captopril	4	8	2	-		4	6	2	-		
	28.6%	57.1%	14.3%	-		33.30%	50.0%	16.7%	-		

Tab. IV. Comparison reaching to optimum dose between the studied groups.

Group	**Optimum dose**			**P**
	Yes	No	Total	
Sacubitril/Valsartan	8	21	29	**0.006**
	27.60%	72.40%	100.00%	
Losartan	10	6	16	
	62.50%	37.5%	100.00%	
Captopril	1	12	13	
	7.7	92.3%	100.00%	
Total	19	39	58	
	32.8%	67.2%	100.00%	
	50% Optimum dose			
Sacubitril/Valsartan	29	0	29	**0.001**
	100.0%	100.00%	100.00%	
Losartan	15	1	16	
	93.8%	6.30%	100.00%	
Captopril	8	5	13	
	61.5%	38.5%	100.00%	
Total	52	6	58	
	89.7%	10.3%	100	

significant (0.02) (Tab. III). In terms of mortality, 5 deaths occurred, and the incidence of deaths in the Sacubitril/Valsartan, Losartan, and Captopril groups, were 2 (6.7%), 2 (11.2%), and 1 (7.7%) respectively and this difference was not statistically significant (p:0.83). In the comparison of the percentage of reaching the optimum dose as well as 50% of the optimum dose at the end of the study, there was a significant difference between the studied groups. Regarding the reaching optimum dose, 27.6, 62.5, and 7.7% of cases in the Sacubitril/Valsartan, Losartan, and Captopril reached to optimum dose (p: 0.006). Also, 100, 93.8, and 61.5% of cases in the mentioned groups reached 50% optimum dose (p: 0.001) (Tab. IV).

Discussion

Right ventricular dysfunction is associated with increased mortality in patients with congenital heart diseases, valvular diseases, coronary artery diseases, increased pulmonary blood pressure, and patients with heart failure. Therefore, treatment of right ventricular dysfunction and the presence of an effective treatment regime is one of the main concerns. The improvement of the right ventricular function can lead to improving the patient's clinical outcomes as well as a decrease in mortality and hospital lengths of stay. Considering the importance of the subject, the present study aimed to assess the effectiveness of Sacubitril/Valsartan compared to Losartan and Captopril in patients with RV dysfunction.

Main findings

The results of the current study showed that the increase in LVEF, RV FAC, and TAPSE as well as a decrease in DOE grade and RV diameter in the Sacubitril/Valsartan group was significantly higher than in the Losartan and

Captopril groups. Regarding the RV dysfunction, this disorder in the Sacubitril/Valsartan group improved significantly compared to the Losartan and Captopril groups. Also, the TR gradient change in the Sacubitril/Valsartan group was significantly higher than control groups. Regarding the mortality rate, this amount in the Sacubitril/Valsartan group was lower than in the control groups. Regarding the reaching optimum dose, 27.6, 62.5, and 7.7% of cases in the Sacubitril/Valsartan, Losartan, and Captopril reached to optimum dose. Also, 100, 93.8, and 61.5% of cases in the mentioned groups reached 50% optimum dose.

Our results showed that Sacubitril/Valsartan improved the TAPSE index. This result is similar to other studies. A meta-analysis which conducted to evaluate the effects of Sacubitril/Valsartan on RV function and PH in patients with HFrEF (Heart Failure with Reduced Ejection Fraction), The results showed that Sacubitril/Valsartan significantly improves TAPSE and S' (functional state of the right ventricle) and reduces sPAP and mPAP (state of pulmonary circulation) (20). The studies conducted in this field indicate the positive effects of these drugs in improving TAPSE in patients with HFrEF with long-term improvement [10]. In another in Italy, the mean TAPSE increased significantly after one year of treatment [11]. In another study that assessed the effect of reversible abnormal TAPSE and patient survival on patients with chronic HFrEF, the results showed that in patients whose TAPSE values were abnormal at the beginning of the study, but these values improved during the treatment, the prognosis of the disease was much better than compared to patients with abnormal TAPSE values [21]. In another study, significant improvement in TAPSE, RVFAC, S', and PASP was observed in patients receiving Sacubitril/Valsartan regardless of NYHA classification, gender, hypertension status, diabetes status, history of MI, and length of follow-up [22]. TAPSE is one of the main indices reflecting RV systolic function [23]. A decrease in TAPSE is associated with a poor prognosis of the disease [24, 25]. The results of the present study showed that Sacubitril/Valsartan has a positive effect in increasing TAPSE and improving the prognosis of the disease.

Our results showed that Sacubitril/Valsartan improved the LVEF, RV FAC, RV diameter, and DOE grade, as well as a decrease in DOE grade and RV diameter. The beneficial therapeutic effects of Sacubitril/Valsartan on improving RV function have also been reported in other studies [26, 27]. A meta-analysis showed significant improvements in LVEF and a reduction in LVEDV in the Sacubitril/Valsartan users [28]. Other studies showed the important therapeutic value of Sacubitril/Valsartan for patients with HFrEF and RV systolic dysfunction [22]. Masarone et al showed that Sacubitril/Valsartan may improve RV-pulmonary artery coupling [10], Landolfo et al. reported a PAsP improvement after S/V therapy [29], and Yenerçağ et al. showed FAC and pulmonary artery stiffness improvement [30].

Right ventricular dysfunction can have three origins, including pressure overload, ischemic heart disease, and cardiomyopathy [31]. The exact mechanisms by which Sacubitril/Valsartan improves the RV function and PH is unknown. However, Sacubitril valsartan may prevent maladaptive RV remodeling in a pressure overload model via amelioration of RV pressure rise, hypertrophy, collagen, and myofiber reorientation, as well as tissue stiffening at both the tissue and myofiber level [31]. Sacubitril/valsartan has dual effects through which it improves right ventricular function. This dual function includes inhibiting neprilysin and inactivating the renin-angiotensin-aldosterone system. This drug leads to natriuresis, vasodilation, and anti-apoptosis by inactivating many neurohormones, such as angiotensin II, aldosterone, and endothelin-1, modulating gene expression, such as transforming growth factor-β1 and promoting re-endothelialization, anti-fibrotic, anti-inflammatory, and anti-thrombotic reactions, as well as reducing cardiac hypertrophy, and ultimately improving the compensation of cardiac damage.

According to the results of this study and other studies conducted in this field, it seems that the evidence supports the effect of Sacubitril/Valsartan as a treatment option for RV dysfunction. The current study had limitations, which include; first, this study was a single-center study that can affect the generalizability of the results. Because the patients included in this study may not be similar in terms of clinical characteristics to all patients with right ventricular disorders, therefore, caution should be used in generalizing the results. Second, the sample size was small and the follow-up period was short, a small sample size can affect the ability of statistical tests to detect differences and lead to non-significant results to be seen. So Further confirmation needs a larger group of patients with longer follow-up periods to have a better perspective of long-term outcomes.

Conclusions

According to the results, it seems that Sacubitril/Valsartan has a positive effect on improving the right ventricular dysfunction in patients with right heart disorders. This effect may be independent of left heart dysfunction. Therefore, this treatment method can be used as an alternative in the treatment of these patients. However, the confirmation of the above findings requires larger studies with more samples.

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Data availability statement

the data set is not publicly available. Requests to access these data sets should be directed to the corresponding author, elahezeinali93@gmail.com

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Iran University of Medical Sciences, Tehran with the ethics code "IR.IUMS.FMD.REC.1401.706."

Irct registration number

The study protocol was registered in the Iranian registry of clinical trials with ID: IRCT20230926059524N1

Transparency statement

The lead author Elahe Zeinali affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

MH and EZ: conceptualization, methodology, and formal analysis. PJ, MP: investigation, data curation. EZ, MH, AND MP: writing - original draft preparation, writing - review and editing. MH: visualization and supervision and project administration. All authors have read and agreed to the published version of the manuscript.

References

[1] Maleki Jamasbi M, Azami H, Samari B, Yousofvand V, Shourcheh E. Epidemiological Survey of Mortality and Morbidity Caused by Cardiovascular Diseases in Patients Admitted to the Cardiac Care Units of Hamadan Educational-medical Hospitals, Hamadan, Iran, in 2017. J Health Res Commun 2019;5:27-38.

[2] Iglesias-Garriz I, Olalla-Gómez C, Garrote C, López-Benito M, Martín J, Alonso D, Rodríguez MA. Contribution of right ventricular dysfunction to heart failure mortality: a meta-analysis. Rev Cardiovasc Med 2012;13:e62-9. https://doi.org/10.3909/ricm0602.

[3] Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol 2008;52:1683-92. https://doi.org/10.1016/j.jacc.2008.08.033.

[4] Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, Seward SB. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838-47. https://doi.org/10.1016/s0894-7317(96)90476-9.

[5] Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984;107:526-31. https://doi.org/10.1016/0002-8703(84)90095-4.

[6] Wang SJ, Sander GE. Nebivolol/valsartan combination for the treatment of hypertension: a review. Future Cardiol 2021;17:573-83. https://doi.org/10.2217/fca-2020-0079.

[7] Hubers SA, Brown NJ. Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition. Circulation 2016;133:1115-24. https://doi.org/10.1161/CIRCULATIONAHA.115.018622.

[8] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004. https://doi.org/10.1056/NEJMoa1409077.

[9] Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-Related Quality of Life Outcomes in PARADIGM-HF. Circ Heart Fail 2017;10:e003430. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003430.

[10] Masarone D, Errigo V, Melillo E, Valente F, Gravino R, Verrengia M, Ammendola E, Vastarella R, Pacileo G. Effects of Sacubitril/Valsartan on the Right Ventricular Arterial Coupling in Patients with Heart Failure with Reduced Ejection Fraction. J Clin Med 2020;9:3159. https://doi.org/10.3390/jcm9103159.

[11] Correale M, Mallardi A, Mazzeo P, Tricarico L, Diella C, Romano V, Ferraretti A, Leopizzi A, Merolla G, Di Biase M, Brunetti ND. Sacubitril/valsartan improves right ventricular function in a real-life population of patients with chronic heart failure: The Daunia Heart Failure Registry. Int J Cardiol Heart Vasc 2020;27:100486. https://doi.org/10.1016/j.ijcha.2020.100486.

[12] Moliner-Abós C, Rivas-Lasarte M, Pamies Besora J, Fluvià-Brugues P, Solé-González E, Mirabet S, López López L, Brossa V, Pirla MJ, Mesado N, Álvarez-García J, Roig E. Sacubitril/Valsartan in Real-Life Practice: Experience in Patients with Advanced Heart Failure and Systematic Review. Cardiovasc Drugs Ther 2019;33:307-14. https://doi.org/10.1007/s10557-019-06858-0.

[13] Triposkiadis F, Xanthopoulos A, Bargiota A, Kitai T, Katsiki N, Farmakis D, Skoularigis J, Starling RC, Iliodromitis E. Diabetes Mellitus and Heart Failure. J Clin Med 2021;10:3682. https://doi.org/10.3390/jcm10163682.

[14] Lee JW, Choi E, Son JW, Youn YJ, Ahn SG, Ahn MS, Kim JY, Lee SH, Yoon J, Ryu DR, Park SM, Hong KS, Yoo BS. Comparison of Blood Pressure Variability Between Losartan and Amlodipine in Essential Hypertension (COMPAS-BPV). Am J Hypertens 2020;33:748-55. https://doi.org/10.1093/ajh/hpaa060.

[15] Lluri G, Lin J, Reardon L, Miner P, Whalen K, Aboulhosn J. Early Experience With Sacubitril/Valsartan in Adult Patients With Congenital Heart Disease. World J Pediatr Congenit Heart Surg 2019;10:292-95. https://doi.org/10.1177/2150135119825599.

[16] Appadurai V, Thoreau J, Malpas T, Nicolae M. Sacubitril/Valsartan in Adult Congenital Heart Disease Patients With Chronic Heart Failure - A Single Centre Case Series and Call for an International Registry. Heart Lung Circ 2020;29:137-41. https://doi.org/10.1016/j.hlc.2018.12.003.

[17] Maurer SJ, Pujol Salvador C, Schiele S, Hager A, Ewert P, Tutarel O. Sacubitril/valsartan for heart failure in adults with complex congenital heart disease. Int J Cardiol 2020;300:137-40. https://doi.org/10.1016/j.ijcard.2019.06.031.

[18] Suematsu Y, Miura S, Goto M, Matsuo Y, Arimura T, Kuwano T, Imaizumi S, Iwata A, Yahiro E, Saku K. LCZ696, an angiotensin receptor-neprilysin inhibitor, improves cardiac function with

the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. Eur J Heart Fail 2016;18:386-93. https://doi.org/10.1002/ejhf.474.

[19] Bayard G, Da Costa A, Pierrard R, Roméyer-Bouchard C, Guichard JB, Isaaz K. Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation. Int J Cardiol Heart Vasc 2019;25:100418.https://doi.org/10.1016/j.ijcha.2019.100418.

[20] Zhang J, Du L, Qin X, Guo X. Effect of Sacubitril/Valsartan on the Right Ventricular Function and Pulmonary Hypertension in Patients With Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis of Observational Studies. J Am Heart Assoc 2022;11:e024449. https://doi.org/10.1161/JAHA.121.024449.

[21] Dini FL, Carluccio E, Simioniuc A, Biagioli P, Reboldi G, Galeotti GG, Raineri C, Gargani L, Scelsi L, Mandoli GE, Cannito A, Rossi A, Temporelli PL, Ghio S; Network Labs Ultrasound (NEBULA) in Heart Failure Study Group. Right ventricular recovery during follow-up is associated with improved survival in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail 2016;18:1462-71. https://doi.org/10.1002/ejhf.639.

[22] Yang Y, Shen C, Lu J, Fu G, Xiong C. Sacubitril/Valsartan in the Treatment of Right Ventricular Dysfunction in Patients With Heart Failure With Reduced Ejection Fraction: A Real-world Study. J Cardiovasc Pharmacol 2022;79:177-82. https://doi.org/10.1097/FJC.0000000000001162.

[23] Aloia E, Cameli M, D'Ascenzi F, Sciaccaluga C, Mondillo S. TAPSE: An old but useful tool in different diseases. Int J Cardiol 2016;225:177-83. https://doi.org/10.1016/j.ijcard.2016.10.009.

[24] Damy T, Kallvikbacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, Nikitin NP, Dubois-Randé JL, Hittinger L, Clark AL, Cleland JG. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. J Card Fail 2012;18:216-25. https://doi.org/10.1016/j.cardfail.2011.12.003.

[25] Kjaergaard J, Akkan D, Iversen KK, Køber L, Torp-Pedersen C, Hassager C. Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. Eur J Heart Fail 2007;9:610-6. https://doi.org/10.1016/j.ejheart.2007.03.001.

[26] Nederend M, Kiès P, Regeer MV, Vliegen HW, Mertens BJ, Robbers-Visser D, Bouma BJ, Tops LF, Schalij MJ, Jongbloed MRM, Egorova AD. Tolerability and beneficial effects of sacubitril/valsartan on systemic right ventricular failure. Heart 2023;109:1525-32. https://doi.org/10.1136/heartjnl-2022-322332.

[27] Nugara C, Giallauria F, Vitale G, Sarullo S, Gentile G, Clemenza F, Lo Voi A, Zarcone A, Venturini E, Iannuzzo G, Coats AJ, Sarullo FM. Effects of Sacubitril/Valsartan on Exercise Capacity in Patients with Heart Failure with Reduced Ejection Fraction and the Role of Percentage of Delayed Enhancement Measured by Cardiac Magnetic Resonance in Predicting Therapeutic Response: A Multicentre Study. Card Fail Rev 2023;9:e07. https://doi.org/10.15420/cfr.2022.13.

[28] Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. J Am Heart Assoc 2019;8:e012272. https://doi.org/10.1161/JAHA.119.012272.

[29] Landolfo M, Piani F, Esposti DD, Cosentino E, Bacchelli S, Dormi A, Borghi C. Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. Int J Cardiol Heart Vasc 2020;31:100656. https://doi.org/10.1016/j.ijcha.2020.100656.

[30] Yenerçağ M, Arslan U, Dereli S, Çoksevim M, Doğduş M, Kaya A. Effects of angiotensin receptor neprilysin inhibition on pulmonary arterial stiffness in heart failure with reduced ejection fraction. Int J Cardiovasc Imaging 2021;37:165-73. https://doi.org/10.1007/s10554-020-01973-8.

[31] Lyon RC, Zanella F, Omens JH, Sheikh F. Mechanotransduction in cardiac hypertrophy and failure. Circ Res 2015;116(8):1462-76. https://doi.org/10.1161/CIRCRESAHA.116.304937.

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Non-comunicable disease

Diagnostic delay among symptomatic breast cancer patients: a study in Sudanese women

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Key words

Breast cancer • Diagnosis, Delay • Prevalence

Summary

Background. *Early diagnosis of breast cancer is essential for effective treatment and improved survival rates. A longer gap between the appearance of symptoms and the initiation of therapy results in advanced disease and lower survival.*
Objectives: to assess factors associated with diagnosis delay among Sudanese women with breast cancer.
Methods. *A prospective, descriptive cross-sectional study conducted at Radiation and Isotope Centre of Khartoum (RICK) in Khartoum, Sudan. Relationship between the independent variables and the main outcome of the study was determined by multivariate regression analysis.*
Results. *A total number of 149 women participated in the study. A total of 58.4% of patients delayed seeking medical advice for more than three months after noticing symptoms. The delay was associated with patient's area of residence and age. Women coming from outside Khartoum had a higher odd of having delayed diagnosis of breast cancer (AOR = 3.283, 95% CI: 1.113 9.687, p = .031). Likewise, older age was another predictor of delayed diagnosis of breast cancer among the study participants (AOR = 101.664, 95% CI: 4.839 - 2135.883, p = .003).*
Conclusions. *The present study showed that more than half of the women who participated had experienced delays in seeking medical attention for their breast cancer symptoms. This finding highlighted the impact of limited access to healthcare services as a contributing factor to such delays. These findings show the need for collaborative approaches to address the challenges surrounding breast cancer in Sudan.*

Background

Breast cancer is the most prevalent cancer in women and one of the leading causes of cancer death among women, with nearly 2.26 million new cases of breast cancer diagnosed in women worldwide in 2020 [1-3]. Amongst women, breast cancer accounts for approximately one in four cancer diagnoses and one in six cancer- related deaths globally [4]. Regarding breast cancer survival, significant disparities exist across countries [3]. The sub Saharan Africa region faces a unique set of challenges related to managing breast cancer, largely due to socioeconomic factors and health systems. These include delays in starting standard treatments due to insufficient patient education, limited access to care, and high financial burdens, making it even more difficult to effectively combat the disease [2].
Early diagnosis of breast cancer is essential for effective treatment and improved survival rates as timely detection and treatment offer the best chance of improving breast cancer outcomes [4]. A longer gap between the appearance of symptoms and the initiation of therapy results in advanced disease and lower survival rates [5]. Higher mortality and late stage of the disease are seen with delay in diagnosis and treatment of breast cancer. However, prompt treatment within three months can significantly increase a woman's chances of surviving breast cancer [6, 7].
In developing countries, delayed presentation of breast cancer is a common problem. While more than 70% of breast cancer patients in high-income countries are diagnosed in stage 1 and 2, the corresponding proportion in low- and middle-income countries is about 20–50% [8,9]. Studies show that delayed presentation is significantly affected by the patients' health-seeking behaviour and several factors are related to delay in diagnosis including age, educational level, breast cancer awareness, economic status, and the nature of first symptoms noted by the patients [10].
While breast cancer rates are rising in Sudan, data about this problem in the country are scarce [11]. The rarity of such studies in this population highlights the existing knowledge gap. Moreover, conducting such a study could help identify the reasons for patients' delays and the factors associated with it, which will provide information for stakeholders to adapt strategies to shorten the time of delay. By studying this delay, researchers can identify areas for targeted improvement in the healthcare system and patient education to increase early detection rates, which can ultimately contribute to a reduction in breast cancer mortality rates. The aim of this study was to assess and investigate factors associated with the delayed presentation of breast cancer.

Methods

Study design and settings

A prospective, hospital based, descriptive cross-sectional study conducted at Radiation and Isotope Centre of Khartoum (RICK) in Khartoum, Sudan during the period between 1st January and 15th February 2018. The setting main referral hospital and one of the only two public centres in Sudan specialized in oncology services and cancer care [11]. The hospital provides a host of therapeutic and diagnostic services for a significant portion of the population in Khartoum state, as well as, to citizens coming from all other states of the country.

The inclusion criteria for this study were all female patients with breast cancer presented to the hospital during the study period, with the exclusion of those refusing to participate in the study. This represents a census of the eligible population within that timeframe. However, we performed sample size calculation based on a power analysis to ensure adequate statistical power and generalizability of the findings. The sample size was determined by the following formula ($n = z^2. p. q /d^2$); where n is the sample size, z is the standard deviation (1.96), p is the prevalence (89%), q is 1 minus the prevalence, and d is the margin of error. The sample size was estimated with 5 % margin of error and 95% confidence. Since no similar published study was available in Sudan at the time of this research, a study conducted in Uganda was referenced, where the prevalence of delaying presentation of breast cancer was 89% [12]. Therefore, this proportion was used to estimate the sample size for the current study. A total of twenty-five patients were excluded from the study because they refused to consent to participate.

Data collection

The data collection process was done by using a questionnaire during the interview with the participants. The questionnaire, which took approximately 10 minutes to complete, was designed based on the literature and study objectives to collect information about participants' demographics, their experiences with breast cancer diagnosis, and the factors that may have contributed to any delays in seeking medical consultation. Diagnosis time variable was calculated as the interval between the date of the first symptoms reported by the patient and the date of the medical consultation with a specialized breast cancer doctor (surgeon or oncologist). For further analysis, we categorized patients according to the presentation time into two groups: those diagnosed within three months of their first symptoms and those diagnosed after three months. We defined a "delay in diagnosis" as a situation where a patient took longer than three months from noticing symptoms to seeking medical attention and receiving a breast cancer diagnosis [13-16].

Several socio-demographic and health characteristics were considered potential determinants of diagnosis delay and were considered independent variables in this study. These factors included age; residence (Khartoum, outside Khartoum); educational level (illiterate, primary school, secondary school, university degree); monthly income in SDG (less than 1000, 1000-2000, more than 2000); occupation (employed, unemployed); marital status (married, single, widow, divorced); practicing breast self-examination (no, yes); first symptoms noticed (pain, paraesthesia, breast lump, skin changes and edema, ulcer); family history of breast cancer (no, yes); and stated reasons for delayed presentation after noticing the symptoms.

Data analysis

Sample baseline characteristics were presented with descriptive statistics in terms of the frequency and percentage of data. Because the continuous variables in our study showed a skewed distribution, as indicated by the results of Kolmogorov-Smirnov and Shapiro-Wilk tests, we presented continuous variables in form of median and interquartile range. In addition, linear correlation analysis, by using Spearman's rho correlation test, was done to show association between continuous variables. To investigate the potential associations between the postulated risk factors and the outcome, the analysis was done in two parts. In the first part, we performed the bivariate analyses for intergroup comparison to identify factors that have significant correlation with the outcome. Then, variables that showed a statistically significant relationship at the bivariate analyses level were further entered into the multivariate regression models. The results of regression analysis were reported as adjusted Odds Ratios (OR) along with their corresponding 95% Confidence Interval (95% CI). Data analysis was performed using the SPSS software version 20 (SPSS Inc., Chicago, IL, USA). The *p*-value of $< .05$ was set as the significance level for all analyses of the study.

Ethical consideration and consent

Before study initiation, permission for conducting this research was obtained from the institutional review board of Faculty of Medicine, University of Khartoum, as well as from the general director of RICK hospital. Additionally, ethical clearance was obtained from the State Ministry of Health in Khartoum state, Sudan. Each participant was provided with a thorough explanation of the study, and informed consent was obtained before their participation. Participants were also assured of their right to withdraw from the study at any time, even after giving consent. The confidentiality of all study participants was maintained. All data pertaining to patients and hospital staff were kept secure throughout the research process, ensuring the privacy and confidentiality of the collected information.

Results

Features of the study participants

A total number of 149 women participated in the study (response rate = 100%). The median and interquartile

range age of the participants was 49.9 ± 12.0 years. Most of the participants were unemployed (77.9%) and near half of them (49%) had a monthly income of less than 1000 SDG (with one SDG equivalent to 0.0278 US dollars at the time of data collection). Additionally, 41.6% of the women had attended secondary school. More than half of the participants (58.4%) lived outside Khartoum state (Tab. I).

A total of 25.5% of the participants reported having a family history of breast cancer. Regarding self-examination prior to the onset of symptoms, 16.1% indicated that they performed self-examinations, whereas 83.9% did not. The first symptom noticed by 58.4% of the patients was a breast lump, while 20.1% initially experienced pain. Additionally, 24.8% of the women reported a lack of social support from family and spouses upon the appearance of symptoms. The baseline characteristics of the participants are presented in table I. The median and IQR for time between noticing a symptom and consulting a medical doctor was 7.0 ± 17.0 months. A total of 58.4% of patients delayed seeking medical advice for more than 3 months. There were several reasons stated by the respondents that affect their decision to seek medical advice. Most of the patients (83.9%) reported delaying seeking medical attention because they either underestimated the significance of their breast symptoms or did not believe they could actually have breast cancer. The other common reasons stated were seeking traditional healing instead of formal medical consultation (14.1%), lack of financial support (11.4%), previous misdiagnosis (19.5%), fear of stigma (10.1%), fear of treatments side effect (19.5%) (Tab. II).

Presentation delay and its associated factors

Results of bivariate analysis showed a significant difference in proportion of delaying diagnosis between groups of residence outside Khartoum ($X^2 = 14.27$, $p < 0.001$), seeking traditional healing ($X^2 = 17.42$, $p < 0.001$), lack of financial support ($X^2 = 13.67$, $p < 0.001$), fear of stigma ($X^2 = 11.89$, $p < 0.001$), fear of embarrassment ($X^2 = 5.17$, $p = 0.026$), fear of

Tab. I. baseline characteristics of the respondents.

Variable		Number	Percent %
Age group	30-39 years	12	8.10
	40-49 years	64	43.0
	50-59 years	46	30.9
	> 60 years	27	18.1
Residence	Khartoum	62	41.6
	Outside Khartoum	87	58.4
Educational level	Illiterate	24	16.1
	Primary school	34	22.8
	Secondary school	62	41.6
	University	29	19.5
Monthly income	Less than 1000	73	49.0
	1000-2000	62	41.6
	More than 2000	14	9.4
Occupation	Employed	33	22.1
	Unemployed	116	77.9
Marital status	Married	86	57.7
	Single	8	5.4
	Widow	24	16.1
	Divorced	31	20.8
Practicing Breast self-examination	No	125	83.9
	Yes	24	16.1
First symptoms noticed	Pain	30	20.1
	Paraesthesia	8	5.4
	Breast lump	87	58.4
	Skin changes and edema	17	11.2
	Ulcer	7	4.7
Family history of breast cancer	No	111	74.5
	Yes	38	25.5

Tab. II. Reasons for delayed presentation of breast cancer among the participants.

Variable		Number	Percent %
Traditional healing was sought	No	128	85.9
	Yes	21	14.1
Lack of financial support	No	132	88.6
	Yes	17	11.4
Fear of stigma	No	134	89.9
	Yes	15	10.1
Fear of embarrassment	No	138	92.6
	Yes	11	7.4
Fear of treatments side effect	No	120	80.5
	Yes	29	19.5
Partner constrains	No	142	95.3
	Yes	7	4.7
Underestimating the condition	No	24	16.1
	Yes	125	83.9

treatment side effects ($X^2 = 25.66$, $p < 0.001$), previous misdiagnosis ($X^2 = 14.49$, $p < 0.001$), and family history of breast cancer ($X^2 = 16.99$, $p < 0.001$) (Tab. III). In addition, the correlation analysis showed a significant positive correlation between women age and time taken for presenting to the hospital with breast cancer ($r = 0.28$, $p = 0.001$), indicating that older people tend to have delaying diagnosis of breast cancer.

Results of multivariate regression analysis

The finding of this analysis revealed that delayed diagnosis of breast cancer was only significantly associated with women age and residence, The other factors examined did not demonstrate a significant relationship. Regarding the area of residence, women coming from outside Khartoum had a higher odd of having delayed diagnosis of breast cancer (AOR = 3.283, 95% CI: 1.113 9.687, $p = .031$). Likewise, older age was another predictor of delayed diagnosis of breast cancer among the study participants (AOR = 101.664, 95% CI: 4.839-2135.883, $p = .003$) (Tab. IV).

Discussion

The study shed light on the barriers Sudanese women face in relation to breast cancer presentation. The main finding of this study was the high proportion of women delaying seeking medical attention for breast cancer symptoms, exceeding three months for over half the participants, which is higher than those reported by studies from Ethiopia and Nigeria [16, 17]. The median time interval for presentation in this study was longer than those of studies conducted in Tunisia and Iran [7, 18]. This delay can have potential negative consequences and harmful impact on the clinical outcomes of breast cancer, including increased tumor size and stage at diagnosis, leading to more complex and aggressive treatments, and lower chances of successful treatment and survival.

Sudanese women face unique challenges in accessing healthcare, including financial barriers and cultural factors. The current study showed that residing outside the capital city of Khartoum was one of the factors associated with delayed presentation of breast cancer cases. This finding can be attributed to several potential contributing factors, such as the scarcity of public facilities that provide oncology services and cancer care [11]. Additionally, limited access to healthcare facilities and specialists in rural areas, financial constraints and difficulty accessing healthcare services, and the long travel times required to reach Khartoum for consultations due to transportation challenges in the country could contribute to the finding. Another factor related to rural residence is the populace of traditional healing practices. These cultural beliefs and practices related to health and illness can further limit access to evidence-based healthcare services [8].

Impact of the older age on the delayed presentation can be attributed to complex interplay of social, cultural, and personal factors. Stigma surrounding breast cancer can make women reluctant to discuss symptoms with family or friends and limited their access to support groups or counseling services. In addition, local cultural norms and expectations discourage open communication about health concerns of the women. Limited awareness and knowledge about breast cancer symptoms can lead to misinterpretation, with women dismissing symptoms as harmless or temporary, as shown by a previous study revealed lack of awareness of breast cancer among Sudanese women and clear ignorant attitude practiced by a significant proportion of them [19]. Lastly, old age could trigger fear and denial, making women hesitant to seek medical attention, particularly if they have witnessed the financial strain or treatment side effects experienced by relatives or family members.

Although routine mammography screening is recommended by the World Health Organization for early detection of symptoms to improve timely diagnosis and prognosis, the feasibility is significantly challenged by numerous factors related to limitation in resources and infrastructure, as well as, personal and socio-economic factors. A previous study assessed 110 Sudanese women showed poor practices regarding breast cancer screening and reveal that none of the participants ever did routine mammography screening [20].

There are implications that can be drawn from the study findings. From clinical perspective, knowledge and deeper understanding of the factors contributing to delayed breast cancer presentation in Sudanese women help the healthcare workers tailor their communication and interventions to address specific concerns and barriers. Since the emotional issues are significant factors for delaying presentation, healthcare providers need to prioritize clear and empathetic communication with patients, addressing their anxieties and concerns about breast cancer and its treatment.

Tab. III. Bivariate analysis of factors associated with delayed diagnosis of breast cancer.

Variable		Total No.	No. of patients with delayed diagnosis	X^2	p value
Age group	30-39 years	12	6	20.12	< .001
	40-49 years	64	34		
	50-59 years	46	21		
	> 60 years	27	26		
Residence	Khartoum	62	25	14.27	< .001
	Outside Khartoum	87	62		
Educational level	Illiterate	24	14	0.43	.94
	Primary school	34	19		
	Secondary school	62	38		
	University	29	16		
Monthly income	Less than 1000	73	37	3.51	.17
	1000-2000	62	41		
	More than 2000	14	9		
Occupation	Employed	33	17	0.82	.36
	Unemployed	116	70		
Marital status	Married	86	21	14.4	.02
	Single	8	1		
	Widow	24	20		
	Divorced	31	15		
Practicing Breast self-examination	No	125	77	3.29	.07
	Yes	24	10		
First symptoms noticed	Pain	30	22	4.97	.29
	Paraesthesia	8	6		
	Breast lump	87	46		
	Skin changes and edema	17	9		
	Ulcer	7	4		
Family history of breast cancer	No	111	45	16.99	< .001
	Yes	38	33		
Traditional healing was sought	No	128	66	17.42	< .001
	Yes	21	21		
Lack of financial support	No	132	70	13.67	< .001
	Yes	17	17		
Fear of stigma	No	134	72	11.89	< .001
	Yes	15	15		
Fear of embarrassment	No	138	77	5.17	.026
	Yes	11	10		
Fear of treatments side effect	No	150	58	25.66	< .001
	Yes	28	28		
Partner constrains	No	142	80	5.23	.042
	Yes	7	7		
Underestimating the condition	No	24	12	0.83	.369
	Yes	125	75		

The findings highlight the need for developing targeted screening programs and outreach initiatives to reach women, particularly those residing in underserved areas and allocation of resources to improve access to healthcare services in rural areas, including the establishment of more primary care clinics and specialized breast cancer centers. A previous program of implementing screening using local volunteers showed

Tab. IV. Multivariate regression results of factors associated with delayed diagnosis of breast cancer.

Variable		AOR	CI	p value
Age group	30-39 years	Ref.	-	-
	40-49 years	2.147	0.220-20.939	.511
	50-59 years	1.713	0.164- 17.947	.653
	> 60 years	101.664	4.839-2135.883	.003
Residence	Khartoum	Ref.	-	-
	Outside Khartoum	3.283	1.113-9.687	.031

promising results regarding detection of breast cancer in rural areas of Sudan, demonstrating the potential impact of community-based initiatives in improving healthcare outcomes [21]. In addition, the findings also highlight importance of investing in community-based health programs, particularly those focused on breast cancer awareness, screening, and education, to actively challenge cultural norms and perceptions that contribute to stigma can have a significant impact on early detection.

The findings of this study should be interpreted within the context of certain limitations. Due to the specific location of the study, generalizing the findings to the broader population may be restricted. While our multivariate logistic regression analysis identified two significant factors associated with the outcome, it is important to acknowledge that the study's relatively small sample size may have limited our ability to detect other potential associations. With a larger sample, we might have observed statistically significant relationships for additional factors that were not identified in this analysis. Delayed breast cancer presentation in Sudan is a substantial problem that warrants further research with a larger sample size to explore the influence of all potential factors and to confirm the findings of this study. Lastly, the self-reported nature of the data could raise potential for recall bias or inaccurate reporting.

Conclusions

The present study showed that more than half of the women who participated had experienced delays in seeking medical attention for their breast cancer symptoms. This finding highlighted the impact of limited access to healthcare services as a contributing factor to such delays. These findings indicate the role limited access to healthcare services in contributing to this delay. The study shows the need for a collaborative and comprehensive approaches to address the challenges surrounding breast cancer in Sudan.

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Availability of data and materials

The dataset generated during this study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Before study initiation, permission for conducting this research was obtained from the institutional review board of Faculty of Medicine, University of Khartoum, as well as from the general director of RICK hospital. Additionally, ethical clearance was obtained from the State Ministry of Health in Khartoum state, Sudan. Each participant was provided with a thorough explanation of the study, and informed consent was obtained before their participation. Participants were also assured of their right to withdraw from the study at any time, even after giving consent. The confidentiality of all study participants was maintained. All data pertaining to patients and hospital staff were kept secure throughout the research process, ensuring the privacy and confidentiality of the collected information.

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Conflicts of interest statement

The authors declare that they have no competing interests.

Authors' contributions

M.M.: conceptualized the research idea. M.M. and M.A.: made the study design and undertook data collection. M.M. and S.M.: undertook data analysis. M.M., M.A., K.A., I.E., H.M.S., D.M., A.A., A.H., and S.M.: interpreted the results and drafted the manuscript. All authors revised, read, and approved the final manuscript.

References

[1] Shinden Y, Kamimura K, Hayashi N, Nomoto Y, Nagata A, Eguchi Y, Yano H, Saho H, Nakajo A, Minami K, Hirashima

T, Sasaki K, Yoshinaka H, Owaki T, Tanimoto A, Nakamura M, Otsuka T. Relationship between Delayed Breast Cancer Diagnosis and Behavioral Economic Factors and Personality Characteristics. Asian Pac J Cancer Prev 2023;24:3437-40. https://doi.org/10.31557/APJCP.2023.24.10.3437.

[2] Twahir M, Oyesegun R, Yarney J, Gachii A, Edusa C, Nwogu C, Mangutha G, Anderson P, Benjamin E, Müller B, Ngoh C. Real-world challenges for patients with breast cancer in sub-Saharan Africa: a retrospective observational study of access to care in Ghana, Kenya and Nigeria. BMJ Open 2021;11:e041900. https://doi.org/ 10.1136/bmjopen-2020-041900.

[3] Lv L, Zhao B, Kang J, Li S, Wu H. Trend of disease burden and risk factors of breast cancer in developing countries and territories, from 1990 to 2019: results from the Global Burden of Disease Study 2019. Front Public Health 2023;10:1078191. https://doi.org/10.3389/fpubh.2022.1078191.

[4] Retell JD, Cameron JK, Aitken JF, Youl P, Pyke C, Dunn J, Chambers S, Baade PD. Individual and area level factors associated with the breast cancer diagnostic-treatment interval in Queensland, Australia. Breast Cancer Res Treat 2024;203:575-86. https://doi.org/10.1007/s10549-023-07134-4.

[5] An D, Choi J, Lee J, Kim JY, Kwon S, Kim J, Lee S, Jeon S, Lee C, Lee S, Woo H. Time to surgery and survival in breast cancer. BMC Surg 2022;22:388. https://doi.org/10.1186/s12893-022-01835-1.

[6] Ho PJ, Cook AR, Binte Mohamed Ri NK, Liu J, Li J, Hartman M. Impact of delayed treatment in women diagnosed with breast cancer: A population-based study. Cancer Med 2020;9:2435-44. https://doi.org/10.1002/cam4.2830.

[7] Dianatinasab M, Fararouei M, Mohammadianpanah M, Zare-Bandamiri M. Impact of social and clinical factors on diagnostic delay of breast cancer: A Cross-sectional Study. Medicine 2016;95:e4704. https://doi.org/10.1097/MD.0000000000004704.

[8] Foroozani E, Ghiasvand R, Mohammadianpanah M, Afrashteh S, Bastam D, Kashefi F, Shakarami S, Dianatinasab M. Determinants of delay in diagnosis and end stage at presentation among breast cancer patients in Iran: a multi-center study. Sci Rep 2020;10:21477. https://doi.org/10.1038/s41598-020-78517-6.

[9] Rai A, Sharda P, Aggarwal P, Ravi B. Study of Diagnostic Delay among Symptomatic Breast Cancer Patients in Northern India: A Mixed-Methods Analysis from a Dedicated Breast Cancer Centre. Asian Pac J Cancer Prev 2022;23:893-904. https://doi.org/10.31557/APJCP.2022.23.3.893.

[10] Sobri FB, Bachtiar A, Panigoro SS, Ayuningtyas D, Gustada H, Yuswar PW, Nur AA, Putri RCRA, Widihidayati AD. Factors Affecting Delayed Presentation and Diagnosis of Breast Cancer in Asian Developing Countries Women: A Systematic Review. Asian Pac J Cancer Prev 2021;22:3081-92. https://doi.org/10.31557/APJCP.2021.22.10.3081

[11] Abdalla Elhassan SI. The five-year survival rate of breast cancer at Radiation and Isotopes Centre Khartoum, Sudan. Heliyon 2020;6:e04615. https://doi.org/10.1016/j.heliyon.2020.e04615.

[12] Odongo J, Makumbi T, Kalungi S, Galukande M. Patient delay factors in women presenting with breast cancer in a low income country. BMC Res Notes 2015;8:467. https://doi.org/10.1186/s13104-015-1438-8.

[13] Montazeri A, Ebrahimi M, Mehrdad N, Ansari M, Sajadian A. Delayed presentation in breast cancer: a study in Iranian women. BMC Womens Health 2003;3:4. https://doi.org/10.1186/1472-6874-3-4.

[14] Tesfaw A, Demis S, Munye T, Ashuro Z. Patient Delay and Contributing Factors Among Breast Cancer Patients at Two Cancer Referral Centres in Ethiopia: a Cross-Sectional Study. J Multidiscip Healthc 2020;13:1391-401. https://doi.org/10.2147/JMDH.S275157.

[15] Soh JY, Yahya MM, Bachok N, Wan Zain WZ, Wong MP, Zakaria Z, Hashim Isa Merican SR, Md Hashim MN, Wan Mokhter WM, Ramely R, Zakaria AD, Mohamad IS. Factors associated with delay in seeking care for breast symptoms. BMC Womens Health 2022;22:316. https://doi.org/10.1186/s12905-022-01898-5.

[16] Olarewaju SO, Oyekunle EO, Bamiro AO. Effect of Sociodemographic Variables on Patient and Diagnostic Delay of Breast Cancer at the Foremost Health Care Institution in Nigeria. J Glob Oncol 2019;5:1-8. doi: 10.1200/JGO.19.00108.

[17] Gebremariam A, Addissie A, Worku A, Assefa M, Pace LE, Kantelhardt EJ, Jemal A. Time intervals experienced between first symptom recognition and pathologic diagnosis of breast cancer in Addis Ababa, Ethiopia: a cross-sectional study. BMJ Open 2019;9:e032228. https://doi.org/10.1136/bmjopen-2019-032228.

[18] Balhi S, Khiari H, Hsairi M. Factors Associated with Diagnostic Delays among Tunisian Breast Cancer Patients. Asian Pac J Cancer Prev 2023;24:471-7. https://doi.org/10.31557/APJCP.2023.24.2.471.

[19] Rafat Munir Lawis M, Sabir M. Breast cancer awareness among Sudanese females in Omdurman city: 2021. BMC Public Health 2023;23:1907.https://doi.org/10.1186/s12889-023-16833-y.

[20] Altirifi HI, Elsanousi OM, Bedri S. Very poor practices regarding breast cancer screening among Sudanese female workers at a secondary-level hospital: a cross-sectional study. Pan Afr Med J 2022;41:43. https://doi.org/10.11604/pamj.2022.41.43.30179.

[21] Abuidris DO, Elsheikh A, Ali M, Musa H, Elgaili E, Ahmed AO, Sulieman I, Mohammed SI. Breast-cancer screening with trained volunteers in a rural area of Sudan: a pilot study. Lancet Oncol 2013;14:363-70. https://doi.org/10.1016/S1470-2045(12)70583-1.

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HEALTHCARE MANAGMENT

Change management for services redesign in healthcare: a conceptual framework

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Keywords

Change management • Services redesign • Conceptual framework • Healthcare services

Summary

Introduction. *The introduction of process innovations in healthcare organizations faces challenges in knowledge sharing and incorporating best practices due to a strong professional autonomy, leading to resistance to change. The healthcare paradigm is shifting towards value-based organizations with a patient-centered approach, requiring multidisciplinary care. Change management is crucial, but current approaches are often limited. This study proposes a conceptual framework to support change management in healthcare services redesign.*
Methods. *The proposed conceptual framework was developed applying Jabareen's multidimensional and multi-method approach. The methodology involved 8 steps consisting in literature review, thematic and content analyses, concepts deconstruction and aggregation, graphical design of the framework, external validation and revision.*
Results. *The framework integrates 53 evidences from the literature, 3 macro areas of interest and 42 change management models applied to the healthcare context, through 244 implementation actions. Aggregation of concepts led to 15 macro topics applicable to all levels of change and composing the proposed framework. Interviews validated the framework, emphasizing the importance of people-focused approaches and addressing resistance to change. Moreover, steps most and less cited in the literature are highlighted and differences between developed countries and economies in transition or developing countries are explored.*
Conclusions. *The article proposes a 15-step framework for change in healthcare services redesign. It integrates evidence from literature and change management models, emphasizing stakeholder involvement. A case study in South Africa highlights the importance of awareness, planning, communication, training, and continuous review. Further validation and adaptation are recommended.*

Introduction

The introduction of process innovations has been more difficult for organizations operating in the healthcare sector compared with other sectors due to challenges in identifying effective ways to share their knowledge and incorporate best practices [1]. These organizations, defined as "professional bureaucracies", are characterized by a strong professional autonomy for medical operators, therefore, resistance to change is frequently observed due to fragmentation and siloing [2].
Worldwide the healthcare paradigm is shifting toward value-based organizations, focused on a patient-centred approach [3]. Furthermore, disease management is becoming increasingly complex, and beyond the need of technological innovations for treatment and diagnosis, it requires multidisciplinary care involving teams of professionals that collaborate in integrated processes [4].
Moreover, healthcare processes are frequently designed within multiprofessional stakeholders' teams involving actors outside the actual clinical activity such as social workers, outpatients' facilities, drugs and devices manufacturers, insurance providers, policy makers and patient representatives [5].
In this complex environment, change is increasingly rapid and continuous, and its management is progressively difficult [6]. Therefore, it is essential to understand how to manage change processes with a holistic approach [7, 8].
Change management can support these challenges being a structured approach to manage the transition from the current state to a desired one, considering human resources, materials, and processes [9].
A further issue is that relating to the success rate of the change initiatives which is estimated to be less than 30% and change management plays an important role for the success of change initiatives [10]. Moreover, scholars have often focused on tools that consider only parts of the change process or that focus on specific professionals [7].
Starting from these premises, the authors of this manuscript propose a conceptual framework that, by integrating methods already adopted in the healthcare context and considering its expanding and changing needs, will support change management in healthcare process innovations.
Specifically, this work seeks to address the following research question: how can change management support the implementation of services redesign in healthcare?
In detail, the objective of the analysis are:

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Primary: to develop a conceptual framework for the application of change management in the field of healthcare services redesign.
Secondary: to detect differences in the application of change management in healthcare in developed countries and economies in transition or developing countries.
The purpose of the analysis is, therefore, to propose a conceptual framework of change management, and identify and describe the different drivers of change management in the contexts of process innovation in healthcare, evaluating the differences related to its implementation in developed countries (*e.g.*, Italy) and economies in transition or developing countries (*e.g.*, South Africa), as defined by United Nations [11].

Methods

The development of the conceptual framework proposed is based on the multidimensional and multi-method eight-phase approach published by *Jabareen* (2009) [12].
The approach combines literature review with qualitative research, following eight phases.
Phase 1, "Mapping the selected data sources", involves a review of literature. The literature review was performed on June 21st, 2022, using the biomedical literature database PubMed. As suggested by Jabareen (2009) to ensure literature saturation, the search was performed on all fields and no restrictions have been imposed on the type of document, period of publication, area of interest, language, or country. To ensure validity of the results, only systematic reviews were included in the first literature analysis, while an additional search included also qualitative, quantitative, or mixed/multi methods analyses and case studies or experiments. The search string adopted is "change management". Two reviewers with economic/managerial and engineering/managerial backgrounds independently screened the titles, abstracts and full texts yielded by the search and any disagreement was solved through discussion. To obtain saturation of information, the reference lists of the articles included in the narrative synthesis was scanned to add any additional article of interest.
Phase 2, "Extensive reading and categorizing of the selected data", was performed through a qualitative analysis of the documents selected in the previous phase. Two reviewers analysed the documents and carried out a thematic analysis by grouping the information by topic/concept and "representative power", and any discrepancy was solved through discussion.
Phase 3, "Identifying and naming concepts", the content of each document was analysed to identify the themes reported. The themes were clustered through the re-reading of the documents.
Phase 4, "Deconstructing and categorizing the concepts", was performed by the researchers individually with a subsequent discussion performed in group to finalise the analysis of each concept to deconstruct it. The concepts, their characteristics, and their role were then assessed, along with their methodological assumptions and main references.
Phase 5, "Integrating concepts", was carried out grouping similar concepts to systematize the analysis.
Phase 6, "Synthesis, resynthesis, and making it all make sense", consists in a synthesis of the concepts through an iterative process performed in team. The results of the previous phases were analysed, and the researchers built a consumptive framework using a graphical format.
Phase 7, "Validating the conceptual framework", was performed through an external validation of the proposed framework. Data were retrieved through virtual audio-recorded semi-structured interviews (using MS Teams) and transcribed in a Microsoft Word document [13]. In detail, the guiding questions of the interview were related to the general perception of the interviewee towards the framework and its 15 steps in terms of completeness, deficiencies, and applicability of the framework, context peculiarities and more important steps in terms of change management application. The core concepts emerged through the interviews were synthesized using an extraction grid in Microsoft Excel. Moreover, a quantitative evaluation of completeness and applicability using a 7 levels Likert scale (*i.e.*, 1 = very uncomplete/very applicable, 2 = uncomplete/unapplicable, 3 = slightly uncomplete/slightly unapplicable, 4 = neutral, 5 = slightly complete/slightly applicable, 6 = complete/applicable, 7 = very complete/very applicable) was requested [14].
Phase 8, "Rethinking the conceptual framework", the final phase of the approach, incorporates the revision of the framework following the feedback received as well as the continuous revision framework through iteration, due to the dynamic nature of healthcare context.
The analysis was approved by the Research Ethics Committee of *Università Carlo Cattaneo - LIUC*, *Castellanza-Italy* (P07.2-23) and by the Research Ethics Committee of U*niversity of Pretoria - Faculty of Health Sciences-South Africa* (338/2023).

Results

The results of the conceptualization process are reported in Table I, following the eight phases proposed by *Jabareen* (2009) and described in the previous section, along with the number of documents, topics/concepts, and experts included and involved in the analysis.

Fifty-three articles were selected through the literature review conducted. A full list of the articles is reported in the supplementary material (Supplement 1).
The thematic analysis of the literature led to the identification of three macro areas of interests, being local/individual change, organizational/institutional change, and systemic change.
The content analysis extrapolated forty-two models related to change management applied in the healthcare context. The list of the models presented in each article is reported in table II along with the authors of each model, the related themes, and the reference in which the model was cited.

Tab. I. Framework conceptualization process.

Phase	Results
1	Literature review (number of documents = 53)
2	Thematic analysis (number of topics/concepts = 3)
3	Content analysis (number of topics/concepts = 42)
4	Concepts deconstruction (number of topics/ concepts = 244)
5	Concepts aggregation (number of topics/concepts = 15)
6	Graphical design of the conceptual framework
7	Framework external validation (number experts = 6)
8	Revision of the conceptual framework

In details, the majority of the models (34/42) are concerning organizational/institutional change, thirty models are applicable to local/individual change and twenty-five to systemic change.
The deconstruction of the concepts of each model led to the extrapolation of two-hundred and forty-four actions for change management implementation applied to the healthcare context.
The aggregation of the concepts led to the identification of fifteen macro topics. The list of the concepts, their description, the reference model, and each concept related macro topics are reported in the supplementary material (Supplement 2). As emerged from literature, each topic is applicable to the three levels of change, but the strength of evidence differs. In Table III the number of times each topic was cited in models applicable for each level of change is reported along with how many models cite each topic.
As emerged, more than half of the models include Awareness, Assessment, Vision, Need, Plan and Communication while less than a quarter of the models consider Resistance, Test and Iteration.
All the macro topics were adopted for the formalisation of an integrated and general change management framework to guide local/individual change, organizational/institutional change and systemic change process redesign in healthcare.
The framework was discussed during six semi-structured interviews to experts from different fields from South Africa and Italy and reviewed considering the feedbacks retrieved. The characteristics of the three experts from South Africa are: a nursing and managerial profile, with responsibilities in the coordination of a district clinical specialist team; a medical doctor with coordination responsibilities dealing with issues related to governance, management, and policies; a medical doctor and clinical manager dealing with policies and economic evaluations. The three experts involved from Italy are: a nurse who covered the role of nursing coordinator and who is involved in training by coordinating a university course in the same field; a medical doctor director of a department in a general public hospital; a full professor of organization and human resources management.
From the interviews carried out in the South African context, it emerges that the framework is perceived as inclusive of all the steps useful for implementing a change management program, and also applicable at different levels and in various contexts and businesses in the healthcare sector. Interviewees agree that the focus of a change process should be people. The program should consider the implementation of a communication, information and training plan that makes people aware and able to understand the importance and benefits of change, as well as their role in the change related processes. The main critical aspect experienced by the experts in the field of change management is the resistance to change of the subjects involved, especially those with high seniority or high levels of responsibility.
From the interviews carried out in the Italian context it emerged that the framework is perceived as complete and logical, but these aspects may have a negative impact in terms of complexity and applicability. The applicability is perceived as the most critical aspect since the services in the context considered have specificities as restrictive policies, urgency, high amount of work and professionals with deeply rooted culture and beliefs. Moreover, the issue of resistance to change emerged and this can have an impact in the involvement of professionals. It is recognized as necessary to implement an involvement strategy, a training and communication plan, to define the wins that change could bring to the subjects involved and to implement a strategy for prevention and management of resistance. Therefore, a bottom-up approach should be preferred over a top-down one. Furthermore, the opportunity of creating adapted and simplified frameworks that meet specific needs or are applicable to specific contexts where a framework with many steps could be difficult to apply was suggested.
Considering the synthetic numerical indicators, the average evaluations from South African experts concerning completeness and applicability are both equal to 6.33, while from Italian experts they are respectively equal to 7 and 3.33.
In both contexts the problem of resistance to change and the importance of the themes of involvement, information, communication, and training are highlighted. The South African context relates more to the problem of the will of individuals in terms of change actions, while the Italian context relates more to peculiar aspects of the healthcare sector (*e.g.*, legal constraints, complexity of healthcare processes and population characteristics).
Accordingly, in the South African context interviewees are more positive about the possibility of implementing change actions thanks to the higher level of flexibility of the context, while in the Italian one the applicability is perceived as more difficult.
Based on the previous analysis, the proposed framework consists of 15 steps which are represented in figure 1 and described below.

Step 1: Awareness

At the beginning of any change process, it is necessary to be aware of what is happening in the organization through an analysis of the following elements:

Tab. II. Content analysis.

Model	Reference of the original publication	Theme	Reference in which the model was retrieved
The institutionalizing change model	[15]	Local/individual change, organizational/ institutional change and systemic change	[16]
Beckhard-Harris change map	[17]	Local/individual change and organizational/ institutional change	[7, 18]
Six Steps	[19]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
International Change Theory of Boyatzis	[20]	Organizational/institutional change	[8, 21]
Bullock and Batten's four-phase model	[22]	Local/individual change, organizational/ institutional change and systemic change	[1, 7, 10]
Evaluation, re-evaluation, and action (ERA) Method	[23]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
"What" and "How" method	[24]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
Process Reengineering	[25]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
Deming's System of Profound Knowledge PDSA cycles / Total Quality Management (TQM)	[26, 27]	Local/individual change	[7, 8, 10, 28]
CHSRF's Evidence-Informed Change Management Approach	[29]	Local/individual change, organizational/ institutional change and systemic change	[1, 7]
Wheel	[30]	Local/individual change, organizational/ institutional change and systemic change	[7, 10, 16]
General Electric's (GE's) Change Acceleration Process (CAP) model	[31]	Organizational/institutional change	[8, 32]
Influencer Change Model	[33]	Local/individual change	[8, 28]
Insurrection Method	[34]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
CLARC Change model	[35]	Systemic change	[8, 36]
Prosci ADKAR	[37]	Systemic change	[8, 36]
Hinings and Greenwood's Model of Change Dynamics	[38]	Local/individual change and organizational/ institutional change	[1, 7]
Concern-based adoption model (CBAM)	[39]	Organizational/institutional change	[8, 40]
Institute for Healthcare Improvement's Triple Aim Model	[41]	Systemic change	[1, 7]
Accelerated Implementation Methodology (AIM)	[42]	Systemic change	[8, 43, 44]
Canada Health Infoway's Change Management Framework	[45]	Local/individual change, organizational/ institutional change and systemic change	[1, 7]
Judson Method	[46]	Local/individual change, organizational/ institutional change and systemic change	[7, 10, 16]
Jick & Kanter Ten Commandments for Executing Change	[47]	Local/individual change, organizational/ institutional change and systemic change	[7, 10, 48, 49]
Kanter Big Three Model of Organizational Change	[50]	Local/individual change and organizational/ institutional change	[1, 7]
Participatory action research (PAR)	[51]	Local/individual change, organizational/ institutional change and systemic change	[10, 7]
Kotter's 8-Step Model	[52]	Local/individual change, organizational/ institutional change and systemic change	[1, 4-8, 10, 16, 21, 53-71]

▶

Tab. II (*follows*). Content analysis.

Model	Reference of the original publication	Theme	Reference in which the model was retrieved
Advent Health Clinical Transformation (ACT) Model	[72]	Local/individual change	[8, 72]
Cake model	Landmark Worldwide reported by [40]	organizational/institutional change	[8, 40]
Lewin's 3-Stage Model of Change / Force-Field Model	[73]	Local/individual change, organizational/ institutional change and systemic change	[5-8, 10, 74-84]
Lippitt's Phases of Change Theory	[85]	Local/individual change, organizational/ institutional change and systemic change	[1, 7, 10, 80]
Luecke's Seven steps Method	[86]	Local/individual change, organizational/ institutional change and systemic change	[7, 10, 49]
Lukas Organizational Model for Transformational Change in Healthcare Systems	[9]	Local/individual change and organizational/ institutional change	[1, 7]
Pettigrew's Context/ Content/ Process Model	[87]	Local/individual change and organizational/ institutional change	[1, 7, 88, 89]
National Health Service (NHS) Change Management Guidelines	[90]	Local/individual change, organizational/ institutional change and systemic change	[1, 7]
Prochaska and DiClemente's Change Theory	[91]	Local/individual change, organizational/ institutional change and systemic change	[7, 80]
Riches four-stage model	[92]	Organizational/institutional change	[8, 93]
Roger's Diffusion of Innovation (DOI) Theory	[94]	Organizational/institutional change	[84]
AMICUS - Silversin and Kornacki's model	[95]	Organizational/institutional change	[8, 21, 96]
Six Sigma DMAIC	Smith and Galvin 1986 (Motorola) reported by [97]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
McKinsey 7S Model of Change	[98]	Organizational/institutional change	[8, 83]
Lean Thinking	[99]	Local/individual change, organizational/ institutional change and systemic change	[7, 10]
Young's Nine Stage Framework	[100]	Local/individual change	[8, 101]

internal processes, organizational structure, history of change, culture, problems, enabling factors, context and dynamics, relationships among people, attitudes, orientations, motivations, skills and beliefs of people, agents of change. In addition, the external environment in socio-economic, political, and geographical terms should be investigated to understand the whole environment in qualitative terms.

Step 2: Assessment

The second step requires the understanding of strengths and weaknesses in quantitative terms. This can be achieved through the assessment of processes, level of stress, available resources (technologies, people, and materials), skills, institutional mechanisms and regulations, current outputs and performance, constraints, and risks.

Step 3: vision

Once the current situation has been defined in terms of organization and processes, as well as resources and results, it is useful to define the vision in terms of goals in the short, medium, and long term. It is important to define the target and what need is addressed, what change is expected to be achieved, and then the related strategy, outcomes, and value in qualitative terms.

Step 4: Need

Consequently, it is necessary to define in quantitative terms the objectives to be achieved. Problems and opportunities should be defined and then goals, and objectives should be settled.

Step 5: Wins

To encourage change, short-term payoffs, wins and rewards should be defined for all stakeholders. This will help to demonstrate the value of change and to make it desirable and a priority.

Step 6: Plan

A key step is the definition of the plan for change that should be integrated into the existing organizational

Tab. III. Topics and levels of change.

Topics	Number of citations				Models
	Local/individual change	Organizational/institutional change	Systemic change	Total	
Awareness	26	31	20	77	30
Assessment	22	25	16	63	26
Vision	28	29	27	84	25
Need	22	26	17	65	26
Wins	8	9	9	26	11
Plan	28	29	24	81	31
Communication	36	42	38	116	30
Resistance	7	8	5	20	10
Training	6	7	7	20	11
Test	3	4	2	9	5
Revision	10	10	9	29	11
Implementation	16	17	14	47	20
Monitoring	17	14	14	45	19
Institutionalization	16	14	15	45	16
Iteration	5	3	4	12	6

Fig. 1. 15-Steps conceptual framework.

structure. The pathway should be defined along with the steps to be taken, the actions and the flow. All the subjects who will be affected by change should be involved during the whole process to ensure their understanding and support. In addition, the interactions and influences as well as the time and resources needed in human and material terms should be defined.

Step 7: Communication

To better manage the change process, communication should be addressed. Commitment and collaboration should be promoted by determining how to communicate the change to each professional by detailing the message, the way, and how to explain the implications of each action. Communication should not be unidirectional, but

it is important to receive feedbacks and to interact with all the stakeholders, as well as to generate empowerment. In these terms, the communication and change leaders who can guide, support, engage, and gain approval should also be defined.

Step 8: Resistance

To avoid problems in implementing change, it is useful to identify possible sources of resistance, to define how to prevent them and how to approach them if any problem arises. Response and intervention plans should be established in the event of adverse attitudes or change rejection.

Step 9: Training

In the establishment of an environment suitable for change a key role is played by training. A training plan should be defined for instruction, education, skills and capacity development, and a plan to help or support people should be detailed.

Step 10: Test

Once the path to be taken and the management of detours have been defined, change should be experimented through a test.

Step 11: Revision

After the test, it should be understood what worked well, what could be improved, and what was wrong and should be revised. During this step the plan is revised and adjusted involving all stakeholders, based on the test outputs.

Step 12: Implementation

Once the path has been defined and revised as described in the previous step, change can be implemented. All the actions defined by the plan should be introduced and the new processes should be implemented.

Step 13: Monitoring

When the change has been implemented, it should be checked by periodic and continuous monitoring. Outputs and progress should be measured and reviewed, and feedbacks on results should be collected.

Step 14: Institutionalization

Change should be institutionalized through mechanisms of reinforcement and integration in the organizational culture. Change should be propagated and made a habit.

Step 15: Iteration

Change cannot be a stable process but should be constantly revised and adapted, and therefore the actions should be periodically readapted through the iteration of the previous steps.

Discussion and conclusions

The article describes the stages of development and proposes a 15-step conceptual framework for supporting change in healthcare process innovations. The structuring of the framework integrates 53 evidences from the literature and 42 change management models applied to the healthcare context, through 244 implementation actions.

The focus in the structuring of the framework is not only placed on the steps to follow but also on their implementation. The importance of involving the stakeholders affected by the change is highlighted in each step, as strongly suggested in the literature and by the experts interviewed.

The methodology for the framework conceptualization follows eight development steps proposed by *Jabareen* (2009) and it integrates literature analysis, qualitative methods, and interactive processes of co-creation with international experts [12].

Thanks to the use of an integrated multi-method process, the proposed framework intends to be a generalized tool applicable to different healthcare contexts and it is proposed as a step-by-step guide to support change in healthcare processes.

The validation of the framework is further supported by a real-world analysis. The case study investigated refers to the work of *Basu* (2021) [102]. The analysis investigated the implementation of a District Clinical Specialist Team (DCST) in the Ekurhuleni Health District and its three sub-districts, one of five districts of Gauteng province (South Africa) in the context of maternal health.

The work suggests the importance of awareness and initial assessment to fully understand the organizational structure of the service provider and to define a vision and the needs to be addressed and then to establish an action plan. Therefore, to support change initiatives a specific focus should be given to the role of each actor. This aspect should be achieved establishing wins, implementing a communication, and training plan, and, above all, being prepared to manage resistance and to support the institutionalization of actions. Furthermore, to test and monitor the implementation of actions is necessary in order to understand the results of the changes adopted, and a continuous review is essential in order to follow the changing needs of the context. Finally, the work highlighted that the results of the process re-engineering, in terms of improvement of maternal health indicators, can be related to the management of change, specifically concerning communication and empowerment of the subjects involved who have held the role of change agents [102].

Pilot tests will help to further validate the method and to highlight its outputs in terms of success of change processes.

The analysis is supported by the use of a structured multi-method design for the development of generalizable grounded theory that includes desk research and experts' opinion. The limitations of the analysis are the use of a non-systematic literature review, the inclusion of models applied to heterogeneous healthcare contexts, the lack of an experimental validation and the involvement of experts from only two national contexts.

Future studies should analyse other geographical contexts in order to enlarge the evidence, experimental studies aimed at defining the needs and peculiarities of specific services and test the applicability of the method should be implemented and the framework could be revised based on future changes in the context or specific needs.

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Ethics approval

The analysis was approved by the Research Ethics Committee of Università Carlo Cattaneo – LIUC, Castellanza-Italy (P07.2-23) and by the Research Ethics Committee of University of Pretoria – Faculty of Health Sciences-South Africa (338/2023).

Conflicts of interest statement

The authors report no conflicts of interest in this work.

Authors' contributions

DB, DC and SS conceptualized the work and designed the study. SS collected and analysed the data. SS and UR interpreted the data. SS and UR drafted the article with critical revision from DB and DC. All authors read and approved the final version of the manuscript.

References

[1] Antwi M, Kale M. Change management in healthcare. Kingston, Ontario: The Monieson Centre for Business Research in Healthcare, Queen's University 2014, vol. 1, No. 30.

[2] Mintzberg H. Structure in fives: Designing effective organizations. Englewood Cliffs, NJ: Prentice-Hall 1983.

[3] Lipsitz LA. Understanding health care as a complex system: the foundation for unintended consequences. JAMA 2012;308:243-4. https://doi.org/10.1001/jama.2012.7551.

[4] WHO - World Health Organization. People-centred and integrated health services: an overview of the evidence: interim report. World Health Organization 2015. Available at: https://apps.who.int/iris/handle/10665/155004 (Accessed on: 21/06/2022).

[5] Silvola S, Restelli U, Bonfanti M, Croce D. Co-Design as Enabling Factor for Patient-Centred Healthcare: A Bibliometric Literature Review. Clinicoecon Outcomes Res 2023;15:333-47. https://doi.org/10.2147/CEOR.S403243.

[6] Allen B. Effective design, implementation, and management of change in healthcare. Nurs Stand 2016 14;31:58-71. https://doi.org/10.7748/ns.2016.e10375.

[7] Beasley L, Grace S, Horstmanshof L. Responding and adapting to change: an allied health perspective. Leadersh Health Serv (Bradf Engl) 2020 23;33:339-49. https://doi.org/10.1108/LHS-07-2019-0050.

[8] Harrison R, Fischer S, Walpola RL, Chauhan A, Babalola T, Mears S, Le-Dao H. Where Do Models for Change Management, Improvement and Implementation Meet? A Systematic Review of the Applications of Change Management Models in Healthcare. J Healthc Leadersh 2021;13:85-108. https://doi.org/10.2147/JHL.S289176.

[9] Lukas CV, Holmes SK, Cohen AB, Restuccia J, Cramer IE, Shwartz M, Charns MP. Transformational change in health care systems: an organizational model. Health Care Manage Rev 2007;32:309-20. https://doi.org/10.1097/01.HMR.0000296785.29718.5d.

[10] Al-Haddad S, Kotnour T. Integrating the organisational change literature: a model for successful change. J Organ Change Manag 2015;28:234-62. https://doi.org/10.1108/JOCM-11-2013-0215.

[11] United Nations. World economic situation and prospects. 2023. Available at: https://desapublications.un.org/file/1113/download?_ga=2.76221845.1083795676.1725972495-37073776.1725972495 (Accessed on: 21/06/2022).

[12] Jabareen Y. Building a Conceptual Framework: Philosophy, Definitions, and Procedure. Int J Qual Methods 2009;8:49-62. https://doi.org/10.1177/160940690900800406.

[13] Miles MB, Huberman AM, Saldana J. Qualitative Data Analysis: A Methods Sourcebook. London: SAGE Publications 2014.

[14] Likert R. A technique for the measurement of attitudes. Arch Psychology 1932;22:55.

[15] Armenakis AA, Harris S, Feild H. Paradigms in organizational change: Change agent and change target perspectives. In: Golembiewski R, ed. Handbook of organizational behavior. New York: Marcel Dekker 1999.

[16] Armenakis AA, Bedeian AG. Organizational change: a review of theory and research in the 1990s. J Manag 1999;25:293-315. https://doi.org/10.1177/014920639902500303.

[17] Beckhard R, Harris RT. Organizational Transitions: Managing Complex Change, 2nd ed. Addison-Wesley 1987.

[18] Schein E. Models and tools for stability and change in human systems. The Sol Journal 2002;4:34-46. https://doi.org/10.1162/152417302762251327.

[19] Beer M, Eisenstat RA, Spector B. Why change programs don't produce change. Harvard Business Review 1990;68:158-66.

[20] Boyatzis RE. An overview of intentional change from a complexity perspective. Journal of Management Development 2006;25:607-23. https://doi.org/10.1108/02621710610678445.

[21] Stoller JK. Implementing change in respiratory care. Respir Care 2010;55:749-57.

[22] Bullock R, Batten D. It's just a phase we're going through: a review and synthesis of OD phase analysis. Group Organ Manag 1985;10:383-412. https://doi.org/10.1177/105960118501000403.

[23] Chen CK, Yu CH, Chang HC. ERA model: a customer-orientated organizational change model for the public service. Total Quality Management & Business Excellence 2006;17:1301-22. https://doi.org/10.1080/14783360600753794.

[24] Conner D. Leading at the Edge of Chaos: How to Create the Nimble Organization. New York, John Wiley 1998.

[25] Davenport TH. Process Innovation: Reengineering Work Through Information Technology. Harvard Business Press 1993.

[26] Deming WE. The New Economics. Massachusetts Institute of Technology Press 1993.

[27] Deming WE. Out of the crisis. Massachusetts Institute of Technology, Center for Advanced Eng Study 1986.

[28] Gazarin M, Ingram-Crooks J, Hafizi F, Hall L, Weekes K, Casselman C, Burnett S, Lennard M, Pinches A, Tse D. Improving urinary catheterisation practices in a rural hospital in Ontario. BMJ Open Qual 2020;9:e000703. https://doi.org/10.1136/bmjoq-2019-000703.

[29] Dickson GS. Evidence-informed change management in Canadian healthcare organizations. Canadian Electronic Library, Canadian Health Services Research Foundation 2012.

[30] Galpin TJ. The Human Side of Change: A Practical Guide to Organization Redesign. 1st ed. San Francisco: Jossey-Bass Publishers1996.

[31] Garvin DA. Learning in Action: A Guide to Putting the Learning Organization to Work, Boston: Harvard Business School Press 2000.

[32] Detwiller M, Petillion W. Change management and clinical engagement: critical elements for a successful clinical information system implementation. Comput Inform Nurs 2014;32:267-73; quiz 274-5. https://doi.org/10.1097/CIN.0000000000000055.

[33] Grenny J, Patterson K, Maxfield D, McMillan R, Al Switzler. The new science of leading change. New York: McGraw-Hill Education 2013.

[34] Hamel G. Leading the Revolution, Boston, MA: Harvard Business School Press 2000.

[35] Hiatt JM, Creasey TJ. Change Management: The People Side of Change. Fort Collins, CO: Prosci Learning Center Publications 2012.

[36] Balluck J, Asturi E, Brockman V. Use of the ADKAR® and CLARC ® Change Models to Navigate Staffing Model Changes During the COVID-19 Pandemic. Nurse Lead 2020;18:539-46. https://doi.org/10.1016/j.mnl.2020.08.006.

[37] Hiatt JM. ADKAR: A Model for Change in Business, Government, and Our Community. Prosci Inc 2006.

[38] Hinings CR, Greenwood R. The dynamics of strategic change. B. Blackwell 1989.

[39] Hord SM, Rutherford WL, Luling-Austin L, Hall GE. Taking charge of change. Alexandria, VA: Association for Supervision and Curriculum Development 1987.

[40] Lin MCJ, Hughes B, Katica M, Dining-Zuber C, Plsek P. Service design and change of systems: human-centered approaches to implementing and spreading service design. Int J Design 2011;5:73-86.

[41] IHI - Institute for Healthcare Improvement. Berwick DM, Nolan TW, Whittington J. The Triple Aim: Care, health, and cost. Health Aff 2008;27:759-69. https://doi.org/https://doi.org/10.1377/hlthaff.27.3.759.

[42] IMA - Implementing Management Association. Leading People Through Business Changes: How the Accelerating Implementation Methodology (AIM) Improves Business Outcomes. White Paper. Available at: https://www.imaworldwide.com/white-paper-leading-people-through-business-changes?hsCtaTracking=73685e9c-6fac-489a-959e-68224eadbe3d%7Cd5ed55bf-34be-42f1-b0b1-7bd5e84d50e8. (Accessed on: 01/09/2022).

[43] Spira C, Kwizera A, Jacob S, Amongin D, Ngonzi J, Namisi CP, Byaruhanga R, Rushwan H, Cooper P, Day-Stirk F, Berrueta M, García-Elorrio E, Belizán JM. Improving the quality of maternity services in Uganda through accelerated implementation of essential interventions by healthcare professional associations. Int J Gynaecol Obstet 2017;139:107-13. https://doi.org/10.1002/ijgo.12241.

[44] Spira C, Dhital R, Jacob S, Dangal G, Gurung G, Prasad Shrestha L, Prasad Bista K, Bajracharya K, Bajrachayra L, Baral G, Maiya Kaway N, Rushawn H, Cooper P, Day-Stirk F, Berrueta M, Gibbons L, García-Elorrio E, Belizán JM. Improving the quality of maternity services in Nepal through accelerated implementation of essential interventions by healthcare professional associations. Int J Gynaecol Obstet 2018;143:379-86. https://doi.org/10.1002/ijgo.12678.

[45] Infoway CH. A Framework and Toolkit for Managing eHealth Change: People and Processes. Canada Health Infoway. 2013. Available at: https://www.infoway-inforoute.ca/en/component/edocman/4037-a-framework-and-toolkit-for-managing-ehealth-change/view-document?Itemid=101 (Accessed on: 01/09/2022).

[46] Judson AS. Changing Behavior in Organizations: Minimizing Resistance to Change. Cambridge, Mass: Blackwell Business 1991.

[47] Kanter RM, Stein B, Jick T. The Challenge of Organizational Change: How Companies Experience it and Leaders Guide it. New York, NY - Toronto - New York, NY: Free Press - Maxwell Macmillan Canada - Maxwell Macmillan International 1992.

[48] Spence Laschinger HK, Gilbert S, Smith LM, Leslie K. Towards a comprehensive theory of nurse/patient empowerment: applying Kanter's empowerment theory to patient care. J Nurs Manag 2010;18:4-13. https://doi.org/10.1111/j.1365-2834.2009.01046.x.

[49] Todnem R. Organisational change management: a critical review. J Change Manag 2005;5:369-80. https://doi.org/10.1080/14697010500359250.

[50] Kanter RM. Challenge of organizational change: How companies experience it and leaders guide it. Free Press 2003.

[51] Kemmis S, McTaggart R. Participatory action research: communicative action and the public sphere. In: Denzin, Norman K, Lincoln, Yvonna S, eds. The Sage Handbook of Qualitative Research. California, USA: Sage Publications, Thousand Oaks 2005, pp. 559-603.

[52] Kotter JP, Cohen, DS. The Heart Of Change. Bucuresti: Meteor Press 2008.

[53] Andersen SE, Knudsen JD; Bispebjerg Intervention Group. A managed multidisciplinary programme on multi-resistant Klebsiella pneumoniae in a Danish university hospital. BMJ Qual Saf 2013;22:907-15. https://doi.org/10.1136/bmjqs-2012-001791.

[54] Baloh J, Zhu X, Ward MM. Implementing team huddles in small rural hospitals: How does the Kotter model of change apply? J Nurs Manag 2018;26:571-78. https://doi.org/10.1111/jonm.12584.

[55] Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, Anto JM, Bachert C, Bateman ED, Bedbrook A, Bennoor K, Bewick M, Bindslev-Jensen C, Bosnic-Anticevich S, Bosse I, Brozek J, Brussino L, Canonica GW, Cardona V, Casale T, Cepeda Sarabia AM, Chavannes NH, Cecchi L, Correia de Sousa J, Costa E, Cruz AA, Czarlewski W, De Carlo G, De Feo G, Demoly P, Devillier P, Dykewicz MS, El-Gamal Y, Eller EE, Fonseca JA, Fontaine JF, Fokkens WJ, Guzmán MA, Haahtela T, Illario M, Ivancevich JC, Just J, Kaidashev I, Khaitov M, Kalayci O, Keil T, Klimek L, Kowalski ML, Kuna P, Kvedariene V, Larenas-Linnemann D, Laune D, Le LTT, Carlsen KL, Lourenço O, Mahboub B, Mair A, Menditto E, Milenkovic B, Morais-Almeida M, Mösges R, Mullol J, Murray R, Naclerio R, Namazova-Baranova L, Novellino E, O'Hehir RE, Ohta K, Okamoto Y, Okubo K, Onorato GL, Palkonen S, Panzner P, Papadopoulos NG, Park HS, Paulino E, Pawankar R, Pfaar O, Plavec D, Popov TA, Potter P, Prokopakis EP, Rottem M, Ryan D, Salimäki J, Samolinski B, Sanchez-Borges M, Schunemann HJ, Sheikh A, Sisul JC, Rajabian-Söderlund R, Sooronbaev T, Stellato C, To T, Todo-Bom AM, Tomazic PV, Toppila-Salmi S, Valero A, Valiulis A, Valovirta E, Ventura MT, Wagenmann M, Wang Y, Wallace D, Waserman S, Wickman M, Yorgancioglu A, Zhang L, Zhong N, Zidarn M, Zuberbier T; Mobile Airways Sentinel Network (MASK) Study Group. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol 2019;143:864-79. https://doi.org/10.1016/j.jaci.2018.08.049.

[56] Burden M. Using a change model to reduce the risk of surgical site infection. Br J Nurs 2016;25:949-55. https://doi.org/10.12968/bjon.2016.25.17.949.

[57] Carman AL, Vanderpool RC, Stradtman LR, Edmiston EA. A Change-Management Approach to Closing Care Gaps in a Federally Qualified Health Center: A Rural Kentucky Case Study.

Prev Chronic Dis 2019;16:180589. https://doi.org/10.5888/pcd16.180589.

[58] Champion C, Sadek J, Moloo H. Strategic Change in Surgical Quality Improvement: The Ottawa Hospital (TOH) Comprehensive Unit-Based Safety Program (CUSP) Experience. Healthc Q 2017;20:69-71. https://doi.org/10.12927/hcq.2017.25231.

[59] Diaz Alonso I. Navigating triage to meet targets for waiting times. Emerg Nurse 2013;21:20-6. https://doi.org/10.7748/en2013.06.21.3.20.e1145.

[60] Dort JC, Sauro KM, Schrag C. Designing and integrating a quality management program for patients undergoing head and neck resection with free-flap reconstruction. J Otolaryngol Head Neck Surg 2020;49:41. https://doi.org/10.1186/s40463-020-00436-3.

[61] Dredge A, Oates L, Gregory H, King S. Effective change management within an Australian community palliative care service. Br J Community Nurs 2017;22:536-41. https://doi.org/10.12968/bjcn.2017.22.11.536.

[62] Henry LS, Christine Hansson M, Haughton VC, Waite AL, Bowers M, Siegrist V, Thompson EJ. Application of Kotter's Theory of Change to Achieve Baby-Friendly Designation. Nurs Womens Health 2017;21:372-82. https://doi.org/10.1016/j.nwh.2017.07.007.

[63] Hopkins S, Surpin J, Stanowski A. Lessons learned from implementation of gainsharing. Healthc Financ Manage 2015;69:78-83.

[64] John T. Setting up recovery clinics and promoting service user involvement. Br J Nurs 2017;26:671-76. https://doi.org/10.12968/bjon.2017.26.12.671.

[65] Mørk A, Krupp A, Hankwitz J, Malec A. Using Kotter's Change Framework to Implement and Sustain Multiple Complementary ICU Initiatives. J Nurs Care Qual 2018;33:38-45. https://doi.org/10.1097/NCQ.0000000000000263.

[66] Pollack J, Pollack, R. Using Kotter's eight stage process to manage an organisational change program: presentation and practice. Systematic and Action Research 2014;28:51-66. https://doi.org/10.1007/s11213-014-9317-0.

[67] Rafman H, Lim SN, Quek SC, Mahadevan M, Lim C, Lim A. Using systematic change management to improve emergency patients' access to specialist care: the Big Squeeze. Emerg Med J 2013;30:447-53. https://doi.org/10.1136/emermed-2012-201096.

[68] Reddeman L, Foxcroft S, Gutierrez E, Hart M, Lockhart E, Mendelsohn M, Ang M, Sharpe M, Warde P, Brundage M, Reddeman L, Foxcroft S, Gutierrez E, Hart M, Lockhart E, Mendelsohn M, Ang M, Sharpe M, Warde P, Brundage M. Improving the Quality of Radiation Treatment for Patients in Ontario: Increasing Peer Review Activities on a Jurisdictional Level Using a Change Management Approach. J Oncol Pract 2016;12:81-2, 61-70. https://doi.org/10.1200/JOP.2015.006882.

[69] Small A, Gist D, Souza D, Dalton J, Magny-Normilus C, David D. Using Kotter's Change Model for Implementing Bedside Handoff: A Quality Improvement Project. J Nurs Care Qual 2016;31:304-9. https://doi.org/10.1097/NCQ.0000000000000212.

[70] Sorensen TD, Pestka D, Sorge LA, Wallace ML, Schommer J. A qualitative evaluation of medication management services in six Minnesota health systems. Am J Health Syst Pharm 2016;73:307-14. https://doi.org/10.2146/ajhp150212.

[71] Townsend AB, Valle-Ortiz M, Sansweet T. A Successful ED Fall Risk Program Using the KINDER 1 Fall RiskAssessment Tool. J Emerg Nurs 2016;42:492-97. https://doi.org/10.1016/j.jen.2016.03.028.

[72] Kuhlman J, Moorhead D, Kerpchar J, Peach DJ, Ahmad S, O'Brien PB. Clinical Transformation Through Change Management Case Study: Chest Pain in the Emergency Department. eClinicalMedicine 2019;10:78-83. https://doi.org/10.1016/j.eclinm.2019.04.010.

[73] Lewin K. Frontiers in Group Dynamics: Concept, Method and Reality in Social Science; Social Equilibria and Social Change. Human Relations 1947;1,5-41. https://doi.org/10.1177/001872674700100103.

[74] Abd El-Shafy I, Zapke J, Sargeant D, Prince JM, Christopherson NAM. Decreased Pediatric Trauma Length of Stay and Improved Disposition With Implementation of Lewin's Change Model. J Trauma Nurs 2019;26:84-88. https://doi.org/10.1097/JTN.0000000000000426.

[75] Bowers B. Managing change by empowering staff. Nurs Times 2011;107:19-21.

[76] Bradley S, Mott S. Adopting a patient-centred approach: an investigation into the introduction of bedside handover to three rural hospitals. J Clin Nurs 2014;23:1927-36. https://doi.org/10.1111/jocn.12403.

[77] Burnes B. Kurt Lewin and complexity theories: back to the future? J Change Manag 2004;4:309-25. https://doi.org/10.1080/1469701042000303811.

[78] Chaboyer W, McMurray A, Johnson J, Hardy L, Wallis M, Sylvia Chu FY. Bedside handover: quality improvement strategy to "transform care at the bedside". J Nurs Care Qual 2009;24:136-42. https://doi.org/10.1097/01.NCQ.0000347450.90676.d9.

[79] Jacelon CS, Furman E, Rea A, Macdonald B, Donoghue LC. Creating a professional practice model for postacute care: adapting the Chronic Care Model for long-term care. J Gerontol Nurs 2011;37:53-60. https://doi.org/10.3928/00989134-20100831-02.

[80] Kritsonis A. Comparison of change theories. International Journal of Scholarly Academic Intellectual Diversity 2004;8:1-7.

[81] Manchester J, Gray-Miceli DL, Metcalf JA, Paolini CA, Napier AH, Coogle CL, Owens MG. Facilitating Lewin's change model with collaborative evaluation in promoting evidence based practices of health professionals. Eval Program Plann 2014;47:82-90. https://doi.org/10.1016/j.evalprogplan.2014.08.007.

[82] Radtke K. Improving patient satisfaction with nursing communication using bedside shift report. Clin Nurse Spec 2013;27:19-25. https://doi.org/10.1097/NUR.0b013e3182777011.

[83] Sokol R, Schuman-Olivier Z, Batalden M, Sullivan L, Shaughnessy AF. A Change Management Case Study for Safe Opioid Prescribing and Opioid Use Disorder Treatment. J Am Board Fam Med 2020;33:129-137. https://doi.org/10.3122/jabfm.2020.01.190223.

[84] Tetef S. Successful Implementation of New Technology Using an Interdepartmental Collaborative Approach. J Perianesth Nurs 2017;32:225-30. https://doi.org/10.1016/j.jopan.2015.05.118.

[85] Lippitt R, Watson J, Westley B. The Dynamics of Planned Change. New York: Harcourt, Brace and World. Int J Soc Psychiatry 1958;5:315-16. https://doi.org/10.1177/002076406000500417.

[86] Luecke R. Harvard Business Essentials. Managing Change and Transition. Boston, MA: Harvard Business School Press 2003.

[87] Pettigrew A. The awakening giant, change and continuity in ICI. Context and Action in the Transformation of the Firm. J Manag Stud 1985;24:649-70. https://doi.org/10.1111/j.1467-6486.2012.01054.x.

[88] Byers V. The challenges of leading change in health-care delivery from the front-line. J Nurs Manag 2017;25:449-56. https://doi.org/10.1111/jonm.12342.

[89] Pettigrew A, Woodman R, Cameron K. Studying organisational change and development: challenges for future research. Acad Manage J 2001;44:697-713. https://doi.org/10.2307/3069411.

[90] Phelan D. Best Practice Change Management Guidelines. National Health Service 2010. Available at: www.nhsemployers.org/~/media/Employers/Documents/SiteCollectionDocuments/Best_Practice_Change_Management_guidelines.pdf (Accessed on: 01/09/2022).

[91] Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: Toward an integrative model of

change. J Consult Clin Psychol 1983;51:390-5. https://doi.org/10.1037//0022-006x.51.3.390.

[92] Riches A. The four emotional stages of change 2009. Available at: https://refresher.com/Archives/!stagesofchange.html (Accessed on: 01/09/2022).

[93] Sale C, Page D, Penniment M. Change management for radiation therapists - transitioning to the new Royal Adelaide Hospital. J Med Radiat Sci 2019;66:212-7. https://doi.org/10.1002/jmrs.345.

[94] Rogers EM. Diffusion of Innovations. New York: Free Press 1962.

[95] Silversin J, Kornacki MJ. Leading physicians through change. Tampa, Florida: ACPE 2000.

[96] Westerlund A, Garvare R, Höög E, Nyström M. Facilitating system-wide organizational change in health care. Int J Qual Serv Sci 2015;7:72-89.

[97] Montgomery DC, Woodall WH. An Overview of Six Sigma. International Statistical Review / Revue Internationale de Statistique 2008;76:329-46. https://doi.org/10.1111/j.1751-5823.2008.00061.x.

[98] Waterman R. The seven elements of strategic fit. J Bus Strategy 1982;3:68-72.

[99] Womack JP, Jones DI. Lean Thinking: Banish Waste and Create Wealth in Your Corporation. Productivity Press 1996.

[100] Young M. A meta-model of change. J Organ Change 2009;22:524-48. https://doi.org/10.1108/09534810910983488.

[101] Hennerby C, Joyce P. Implementation of a competency assessment tool for agency nurses working in an acute paediatric setting. J Nurs Manag 2011;19:237-45. https://doi.org/10.1111/j.1365-2834.2011.01223.x.

[102] Basu JK. Evaluation of the effects of a district clinical specialist team on maternal and women's health services in the Ekurhuleni district. A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy. September 2021.

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Supplementary material

Supplement 1. Documents included in the analysis

Reference	Citation
Abd El-Shafy et al., 2019. [74]	Abd El-Shafy I, Zapke J, Sargeant D, Prince JM, Christopherson NAM. Decreased Pediatric Trauma Length of Stay and Improved Disposition With Implementation of Lewin's Change Model. J Trauma Nurs 2019;26:84-88. https://doi.org/10.1097/JTN.0000000000000426
Al-Haddad et al., 2015. [10]	Al-Haddad S, Kotnour T. Integrating the organisational change literature: a model for successful change. J Organ Change Manag 2015;28:234-62. https://doi.org/10.1108/JOCM-11-2013-0215
Allen, 2016. [6]	Allen B. Effective design, implementation, and management of change in healthcare. Nurs Stand 2016;31:58-71. https://doi.org/10.7748/ns.2016.e10375
Andersen et al., 2013 [53]	Andersen SE, Knudsen JD; Bispebjerg Intervention Group. A managed multidisciplinary programme on multi-resistant Klebsiella pneumoniae in a Danish university hospital. BMJ Qual Saf 2013;22:907-15. https://doi.org/10.1136/bmjqs-2012-001791
Antwi et al., 2014 [1]	Antwi M, Kale M. Change management in healthcare. Kingston, Ontario: The Monieson Centre for Business Research in Healthcare, Queen's University 2014, vol. 1, No. 30.
Armenakis et al., 1999 [15]	Armenakis AA, Harris S, Feild H. Paradigms in organizational change: Change agent and change target perspectives. In: Golembiewski R, ed. Handbook of organizational behavior. New York: Marcel Dekker 1999
Armenakis et al., 1999 [16]	Armenakis AA, Bedeian AG. Organizational change: a review of theory and research in the 1990s. J Manag 1999;25:293-315. https://doi.org/10.1177/014920639902500303
Balluck et al., 2020 [36]	Balluck J, Asturi E, Brockman V. Use of the ADKAR® and CLARC® Change Models to Navigate Staffing Model Changes During the COVID-19 Pandemic. Nurse Lead 2020;18:539-46. https://doi.org/10.1016/j.mnl.2020.08.006
Baloh et al., 2018 [54]	Baloh J, Zhu X, Ward MM. Implementing team huddles in small rural hospitals: How does the Kotter model of change apply? J Nurs Manag 2018;26:571-8. https://doi.org/10.1111/jonm.12584
Beasley et al., 2020 [7]	Beasley L, Grace S, Horstmanshof L. Responding and adapting to change: an allied health perspective. Leadersh Health Serv (Bradf Engl) 2020;33:339-49. https://doi.org/10.1108/LHS-07-2019-0050
Bousquet et al., 2019 [55]	Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, Anto JM, Bachert C, Bateman ED, Bedbrook A, Bennoor K, Bewick M, Bindslev-Jensen C, Bosnic-Anticevich S, Bosse I, Brozek J, Brussino L, Canonica GW, Cardona V, Casale T, Cepeda Sarabia AM, Chavannes NH, Cecchi L, Correia de Sousa J, Costa E, Cruz AA, Czarlewski W, De Carlo G, De Feo G, Demoly P, Devillier P, Dykewicz MS, El-Gamal Y, Eller EE, Fonseca JA, Fontaine JF, Fokkens WJ, Guzmán MA, Haahtela T, Illario M, Ivancevich JC, Just J, Kaidashev I, Khaitov M, Kalayci O, Keil T, Klimek L, Kowalski ML, Kuna P, Kvedariene V, Larenas-Linnemann D, Laune D, Le LTT, Carlsen KL, Lourenço O, Mahboub B, Mair A, Menditto E, Milenkovic B, Morais-Almeida M, Mösges R, Mullol J, Murray R, Naclerio R, Namazova-Baranova L, Novellino E, O'Hehir RE, Ohta K, Okamoto Y, Okubo K, Onorato GL, Palkonen S, Panzner P, Papadopoulos NG, Park HS, Paulino E, Pawankar R, Pfaar O, Plavec D, Popov TA, Potter P, Prokopakis EP, Rottem M, Ryan D, Salimäki J, Samolinski B, Sanchez-Borges M, Schunemann HJ, Sheikh A, Sisul JC, Rajabian-Söderlund R, Sooronbaev T, Stellato C, To T, Todo-Bom AM, Tomazic PV, Toppila-Salmi S, Valero A, Valiulis A, Valovirta E, Ventura MT, Wagenmann M, Wang Y, Wallace D, Waserman S, Wickman M, Yorgancioglu A, Zhang L, Zhong N, Zidarn M, Zuberbier T; Mobile Airways Sentinel Network (MASK) Study Group. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol 2019;143:864-79. https://doi.org/10.1016/j.jaci.2018.08.049. Erratum in: J Allergy Clin Immunol 2019;144:1456
Bowers et al., 2011 [75]	Bowers B. Managing change by empowering staff. Nurs Times 2011;107:19-21
Bradley et al., 2013 [76]	Bradley S, Mott S. Adopting a patient-centred approach: an investigation into the introduction of bedside handover to three rural hospitals. J Clin Nurs 2014;23:1927-36. https://doi.org/10.1111/jocn.12403
Burden et al., 2016 [56]	Burden M. Using a change model to reduce the risk of surgical site infection. Br J Nurs 2016;25:949-55. https://doi.org/10.12968/bjon.2016.25.17.949
Burnes, 2003 [77]	Burnes B. Kurt Lewin and complexity theories: back to the future? J Change Manag 2004;4:309-25
Byers, 2017 [88]	Byers V. The challenges of leading change in health-care delivery from the front-line. J Nurs Manag 2017;25:449-56. https://doi.org/10.1111/jonm.12342
Carman et al., 2019 [57]	Carman AL, Vanderpool RC, Stradtman LR, Edmiston EA. A Change-Management Approach to Closing Care Gaps in a Federally Qualified Health Center: A Rural Kentucky Case Study. Prev Chronic Dis 2019;16:180589. https://doi.org/http://dx.doi.org/10.5888/pcd16.180589

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Supplement 1 *(follows).* Documents included in the analysis

Reference	Citation
Chaboyer et al., 2009 [78]	Chaboyer W, McMurray A, Johnson J, Hardy L, Wallis M, Sylvia Chu FY. Bedside handover: quality improvement strategy to "transform care at the bedside". J Nurs Care Qual 2009;24:136-42. https://doi.org/10.1097/01.NCQ.0000347450.90676.d9
Champion et al., 2017 [58]	Champion C, Sadek J, Moloo H. Strategic Change in Surgical Quality Improvement: The Ottawa Hospital (TOH) Comprehensive Unit-Based Safety Program (CUSP) Experience. Healthc Q 2017;20:69-71. https://doi.org/10.12927/hcq.2017.25231
Detwiller et al., 2014 [32]	Detwiller M, Petillion W. Change management and clinical engagement: critical elements for a successful clinical information system implementation. Comput Inform Nurs 2014;32:267-73; quiz 274-5. https://doi.org/10.1097/CIN.0000000000000055
Diaz Alonso et al., 2013 [59]	Diaz Alonso I. Navigating triage to meet targets for waiting times. Emerg Nurse 2013;21:20-6. https://doi.org/10.7748/en2013.06.21.3.20.e1145
Dort et al., 2020 [60]	Dort JC, Sauro KM, Schrag C. Designing and integrating a quality management program for patients undergoing head and neck resection with free-flap reconstruction. J Otolaryngol Head Neck Surg 2020;49:41. https://doi.org/10.1186/s40463-020-00436-3
Dredge et al., 2017 [61]	Dredge A, Oates L, Gregory H, King S. Effective change management within an Australian community palliative care service. Br J Community Nurs 2017;22:536-41. https://doi.org/10.12968/bjcn.2017.22.11.536
Gazarin et al., 2020 [28]	Gazarin M, Ingram-Crooks J, Hafizi F, Hall L, Weekes K, Casselman C, Burnett S, Lennard M, Pinches A, Tse D. Improving urinary catheterisation practices in a rural hospital in Ontario. BMJ Open Qual 2020;9:e000703. https://doi.org/10.1136/bmjoq-2019-000703
Harrison et al., 2020 [8]	Harrison R, Fischer S, Walpola RL, Chauhan A, Babalola T, Mears S, Le-Dao H. Where Do Models for Change Management, Improvement and Implementation Meet? A Systematic Review of the Applications of Change Management Models in Healthcare. J Healthc Leadersh 2021;13:85-108. https://doi.org/10.2147/JHL.S289176
Hennerby et al., 2011 [101]	Hennerby C, Joyce P. Implementation of a competency assessment tool for agency nurses working in an acute paediatric setting. J Nurs Manag 2011;19:237-45. https://doi.org/10.1111/j.1365-2834.2011.01223.x
Henry et al., 2017 [62]	Henry LS, Christine Hansson M, Haughton VC, Waite AL, Bowers M, Siegrist V, Thompson EJ. Application of Kotter's Theory of Change to Achieve Baby-Friendly Designation. Nurs Womens Health 2017;21:372-82. https://doi.org/10.1016/j.nwh.2017.07.007
Hopkins et al., 2015 [63]	Hopkins S, Surpin J, Stanowski A. Lessons learned from implementation of gainsharing. Healthc Financ Manage 2015;69:78-83
Jacelon et al., 2011 [79]	Jacelon CS, Furman E, Rea A, Macdonald B, Donoghue LC. Creating a professional practice model for postacute care: adapting the Chronic Care Model for long-term care. J Gerontol Nurs 2011;37:53-60. https://doi.org/10.3928/00989134-20100831-02
John et al., 2017 [64]	John T. Setting up recovery clinics and promoting service user involvement. Br J Nurs 2017;26:671-6. https://doi.org/10.12968/bjon.2017.26.12.671
Kritsonis, 2004 [80]	Kritsonis A. Comparison of change theories. International Journal of Scholarly Academic Intellectual Diversity 2004;8:1-7
Kuhlman et al., 2019 [72]	Kuhlman J, Moorhead D, Kerpchar J, Peach DJ, Ahmad S, O'Brien PB. Clinical Transformation Through Change Management Case Study: Chest Pain in the Emergency Department. eClinicalMedicine 2019;10:78-83. https://doi.org/10.1016/j.eclinm.2019.04.010
Lin et al., 2011 [40]	Lin MCJ, Hughes B, Katica M, Dining-Zuber C, Plsek P. Service design and change of systems: human-centered approaches to implementing and spreading service design. Int J Design 2011;5:73-86
Manchester et al., 2014 [81]	Manchester J, Gray-Miceli DL, Metcalf JA, Paolini CA, Napier AH, Coogle CL, Owens MG. Facilitating Lewin's change model with collaborative evaluation in promoting evidence based practices of health professionals. Eval Program Plann 2014;47:82-90. https://doi.org/10.1016/j.evalprogplan.2014.08.007
Mork et al., 2018 [65]	Mørk A, Krupp A, Hankwitz J, Malec A. Using Kotter's Change Framework to Implement and Sustain Multiple Complementary ICU Initiatives. J Nurs Care Qual 2018;33:38-45. https://doi.org/10.1097/NCQ.0000000000000263.
Pettigrew et al., 2001 [89]	Pettigrew A, Woodman R, Cameron K. Studying organisational change and development: challenges for future research. Acad Manage J 2001;44:697-713
Pollack et al., 2014 [66]	Pollack J, Pollack, R. Using Kotter's eight stage process to manage an organisational change program: presentation and practice. Systematic and Action Research 2014.
Radtke et al., 2013 [82]	Radtke K. Improving patient satisfaction with nursing communication using bedside shift report. Clin Nurse Spec 2013;27:19-25. https://doi.org/10.1097/NUR.0b013e3182777011
Rafman et al., 2013 [67]	Rafman H, Lim SN, Quek SC, Mahadevan M, Lim C, Lim A. Using systematic change management to improve emergency patients' access to specialist care: the Big Squeeze. Emerg Med J 2013;30:447-53. https://doi.org/10.1136/emermed-2012-201096

Supplement 1 *(follows).* Documents included in the analysis

Reference	Citation
Reddeman et al., 2016 [68]	Reddeman L, Foxcroft S, Gutierrez E, Hart M, Lockhart E, Mendelsohn M, Ang M, Sharpe M, Warde P, Brundage M. Improving the Quality of Radiation Treatment for Patients in Ontario: Increasing Peer Review Activities on a Jurisdictional Level Using a Change Management Approach. J Oncol Pract 2016;12:81-2, e61-70. https://doi.org/10.1200/JOP.2015.006882
Sale et al., 2019 [93]	Sale C, Page D, Penniment M. Change management for radiation therapists - transitioning to the new Royal Adelaide Hospital. J Med Radiat Sci 2019;66:212-7. https://doi.org/10.1002/jmrs.345
Schein, 2002 [18]	Schein E. Models and tools for stability and change in human systems. The Sol Journal 2002;4:34-46. https://doi.org/10.1162/152417302762251327
Small et al., 2016 [69]	Small A, Gist D, Souza D, Dalton J, Magny-Normilus C, David D. Using Kotter's Change Model for Implementing Bedside Handoff: A Quality Improvement Project. J Nurs Care Qual. 2016 Oct-Dec;31(4):304-9. https://doi.org/10.1097/NCQ.0000000000000212. PMID: 27500693
Sokol et al., 2020 [83]	Sokol R, Schuman-Olivier Z, Batalden M, Sullivan L, Shaughnessy AF. A Change Management Case Study for Safe Opioid Prescribing and Opioid Use Disorder Treatment. J Am Board Fam Med. 2020 Jan-Feb;33(1):129-137. https://doi.org/10.3122/jabfm.2020.01.190223. PMID: 31907254
Sorensen et al., 2016 [70]	Sorensen TD, Pestka D, Sorge LA, Wallace ML, Schommer J. A qualitative evaluation of medication management services in six Minnesota health systems. Am J Health Syst Pharm 2016;73:307-14. https://doi.org/10.2146/ajhp150212
Spence Laschinger et al., 2010 [48]	Spence Laschinger HK, Gilbert S, Smith LM, Leslie K. Towards a comprehensive theory of nurse/patient empowerment: applying Kanter's empowerment theory to patient care. J Nurs Manag 2010;18:4-13. https://doi.org/10.1111/j.1365-2834.2009.01046.x
Spira et al., 2017 [43]	Spira C, Kwizera A, Jacob S, Amongin D, Ngonzi J, Namisi CP, Byaruhanga R, Rushwan H, Cooper P, Day-Stirk F, Berrueta M, García-Elorrio E, Belizán JM. Improving the quality of maternity services in Uganda through accelerated implementation of essential interventions by healthcare professional associations. Int J Gynaecol Obstet 2017;139:107-13. https://doi.org/10.1002/ijgo.12241
Spira et al., 2018 [44]	Spira C, Dhital R, Jacob S, Dangal G, Gurung G, Prasad Shrestha L, Prasad Bista K, Bajracharya K, Bajrachayra L, Baral G, Maiya Kaway N, Rushawn H, Cooper P, Day-Stirk F, Berrueta M, Gibbons L, García-Elorrio E, Belizán JM. Improving the quality of maternity services in Nepal through accelerated implementation of essential interventions by healthcare professional associations. Int J Gynaecol Obstet 2018;143:379-86. https://doi.org/10.1002/ijgo.12678
Stoller et al., 2010 [21]	Stoller JK. Implementing change in respiratory care. Respir Care 2010;55:749-57
Tetef et al., 2017 [84]	Tetef S. Successful Implementation of New Technology Using an Interdepartmental Collaborative Approach. J Perianesth Nurs 2017;32:225-30. https://doi.org/10.1016/j.jopan.2015.05.118
Todnem, 2005 [49]	Todnem R. Organisational change management: a critical review. J Change Manag 2005;5:369-380
Townsend et al., 2016 [71]	Townsend AB, Valle-Ortiz M, Sansweet T. A Successful ED Fall Risk Program Using the KINDER 1 Fall RiskAssessment Tool. J Emerg Nurs 2016;42:492-7. https://doi.org/10.1016/j.jen.2016.03.028
Westerlund et al., 2015 [96]	Westerlund A, Garvare R, Höög E, Nyström M. Facilitating system-wide organizational change in health care. Int J Qual Serv Sci 2015;7:72-89. https://doi.org/10.1108/IJQSS-01-2015-000

Supplement 2 Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Recognize when a significant shift impacts key success factors	Control the processes	"What" and "How" method	Awareness, Assessment
Identify which factors are in need of adjustment	Identify criticalities	"What" and "How" method	Need
Determine what changes are necessary in each factor	Define the objective	"What" and "How" method	Vision
Formalize decision to proceed with changes	Identify the actions	"What" and "How" method	Plan
Execute changes to achieve full intent	Implement the change	"What" and "How" method	Implementation
Define the change	State a definition of change and outcomes	Accelerated Implementation Methodology (AIM)	Need, Vision
Build agent capacity	Identify Change Agents and sustain competency development	Accelerated Implementation Methodology (AIM)	Awareness
Assess the climate	Check for implementation history and current level of stress	Accelerated Implementation Methodology (AIM)	Assessment
Generate Sponsorship	Create commitment	Accelerated Implementation Methodology (AIM)	Communication
Determine change approach	Define if change is compliance-driven or commitment-driven	Accelerated Implementation Methodology (AIM)	Vision
Develop target readiness	Identify sources of resistance and how to manage them	Accelerated Implementation Methodology (AIM)	Resistance
Build communication plan	Define messages, audience and implement a feedback loop	Accelerated Implementation Methodology (AIM)	Communication, Monitoring, Iteration
Develop reinforcement strategy	Create reinforcement mechanisms to reinforce performance expectations	Accelerated Implementation Methodology (AIM)	Institutionalization
Create cultural fit	Create consistency of the change with the corporate culture	Accelerated Implementation Methodology (AIM)	Vision
Prioritize action	Develop an Implementation Plan that is integrated with the technical project plan	Accelerated Implementation Methodology (AIM)	Plan
Design	Define change needed, assemble team, develop vision, communicate, and mitigate barriers	Advent Health Clinical Transformation (ACT) Model	Plan, Vision, Communication
Pilot	Define short run wins	Advent Health Clinical Transformation (ACT) Model	Wins
Implement	Maintain focus and educate	Advent Health Clinical Transformation (ACT) Model	Training, Implementation
Sustain	Institutionalize into culture and measure	Advent Health Clinical Transformation (ACT) Model	Monitoring, Institutionalization
Performance	Continual feedback	Advent Health Clinical Transformation (ACT) Model	Monitoring, Iteration
Leadership	Define a guide that can understand, support, explain, and implement	AMICUS Silversin and Kornacki's model	Communication
Shared vision	Establish a vision statement	AMICUS Silversin and Kornacki's model	Vision
Culture and compact	Information and awareness	AMICUS Silversin and Kornacki's model	Awareness
Aligning the team	Create a coalition	AMICUS Silversin and Kornacki's model	Communication
Involving physicians early	Engage physicians	AMICUS Silversin and Kornacki's model	Communication
Developing tension	Create urgency	AMICUS Silversin and Kornacki's model	Communication

Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Addressing resistance	Identify and define how to approach resistances	AMICUS Silversin and Kornacki's model	Resistance
Building consistency	Define durable actions	AMICUS Silversin and Kornacki's model	Plan
Why change	Define the need	Beckhard-Harris change map	Need
Define the desired future state	Define the objective	Beckhard-Harris change map	Need
Describing the present state	Describe problems	Beckhard-Harris change map	Awareness, Assessment
Getting from here to there	Define the route	Beckhard-Harris change map	Plan
Managing during the transition stage	Measure the progress	Beckhard-Harris change map	Monitoring
Exploration	Define the need for change	Bullock and Batten's four-phase model	Need
Planning	Understand the problem	Bullock and Batten's four-phase model	Plan
Action	Identify, agree, and implement change	Bullock and Batten's four-phase model	Assessment, Implementation
Integration	Stabilize and embed change	Bullock and Batten's four-phase model	Institutionalization
Conversation of acknowledgment	Understand the goals	Cake model	Need
Conversation of action	Define what to do	Cake model	Plan
Conversation of possibilities and opportunities	Scan the variety of possibilities of how to achieve that goal	Cake model	Awareness
Conversation of relatedness and purpose	Explore staff's capabilities	Cake model	Assessment
Governance and leadership	Define mechanisms that guide and regulate the course of an organization	Canada Health Infoway's Change Management Framework	Assessment
Stakeholder engagement	Informing / involving / consulting / collaborating / empowering people who can affect or who are affected by the achievement of an organization's objective	Canada Health Infoway's Change Management Framework	Awareness, Communication
Communications	Deliver the right message, to the right person, through the right channel, at the right time	Canada Health Infoway's Change Management Framework	Communication
Workflow analysis and integration	Workflow analysis and integration	Canada Health Infoway's Change Management Framework	Plan
Training and education	Provide instruction for knowledge and skill development	Canada Health Infoway's Change Management Framework	Training
Monitoring and evaluation	Oversee and assess impacts	Canada Health Infoway's Change Management Framework	Monitoring
Planning	Understand context and dynamics and determine the readiness and capacity	CHSRF's Evidence-Informed Change Management Approach	Awareness, Plan
Implementing	Take actions improving effectiveness and efficiency	CHSRF's Evidence-Informed Change Management Approach	Implementation
Spreading	Propagate change	CHSRF's Evidence-Informed Change Management Approach	Institutionalization

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Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Sustaining	Monitor and adjust processes	CHSRF's Evidence-Informed Change Management Approach	Monitoring, Revision
Communicator	Explain changes and their impact	CLARC Change model	Communication
Liaison	Report to leaders the impact of change and to staff the feedbacks	CLARC Change model	Communication
Advocate	Promote positive attitude	CLARC Change model	Communication
Resistance Manager	Understand and address resistance	CLARC Change model	Resistance
Coach	Help to build knowledge	CLARC Change model	Training
Innovation Configurations	Define a goal	Concern-based adoption model (CBAM)	Need
Stage of Concerns	Identify staff members' attitudes and beliefs	Concern-based adoption model (CBAM)	Awareness
Levels of Use	Understand how staff are using a program	Concern-based adoption model (CBAM)	Assessment
Plan	Plan the change	Deming's System of Profound Knowledge PDSA cycles / Total Quality Management (TQM)	Plan
Do	Carry out or test the change	Deming's System of Profound Knowledge PDSA cycles / Total Quality Management (TQM)	Implementation, Test
Study/Check	Examine the results	Deming's System of Profound Knowledge PDSA cycles / Total Quality Management (TQM)	Monitoring
Act	Adopt the change or run again the cycle	Deming's System of Profound Knowledge PDSA cycles / Total Quality Management (TQM)	Revision, Iteration
Evaluate total performance	Measure the as-is performance	Evaluation, re-evaluation, and action (ERA) Method	Assessment
Re-evaluate system design management and culture	Measure the as-is organization	Evaluation, re-evaluation, and action (ERA) Method	Awareness
Act: Develop a change strategy, an action plan and conduct training	Plan the change and train	Evaluation, re-evaluation, and action (ERA) Method	Plan, Training
Leading Change	Develop leadership commitment	General Electric's (GE's) Change Acceleration Process (CAP) model	Communication
Creating A Shared Need	Define a need for all the stakeholders	General Electric's (GE's) Change Acceleration Process (CAP) model	Need
Shaping a Vision	Articulate a clear and legitimate vision	General Electric's (GE's) Change Acceleration Process (CAP) model	Vision
Mobilizing Commitment	Execute an influence strategy	General Electric's (GE's) Change Acceleration Process (CAP) model	Implementation
Making change last	Assess helping and hindering factors	General Electric's (GE's) Change Acceleration Process (CAP) model	Awareness
Monitoring process	Measure progresses	General Electric's (GE's) Change Acceleration Process (CAP) model	Monitoring

Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Changing Systems and Structures	Identify what influence the change and adapt it	General Electric's (GE's) Change Acceleration Process (CAP) model	Revision
Power dependencies	Define relations within the organization	Hinings and Greenwood's Model of Change Dynamics	Awareness
Interest dissatisfaction	Define orientation and motivation of members	Hinings and Greenwood's Model of Change Dynamics	Awareness
Value commitments	Determine the skill of leadership in generating commitment	Hinings and Greenwood's Model of Change Dynamics	Communication
Market context	Understand needs of market and constraints	Hinings and Greenwood's Model of Change Dynamics	Need
Institutional context	Understand institutional needs and constraints	Hinings and Greenwood's Model of Change Dynamics	Assessment
Capacity for action	Understand environmental, technological, and size-related constraints	Hinings and Greenwood's Model of Change Dynamics	Assessment
Organizational change	Determine implementation actions	Hinings and Greenwood's Model of Change Dynamics	Plan
Clarify measurable results	Specify goals/outcomes	Influencer Change Model	Assessment
Find vital behaviours	Determine needs	Influencer Change Model	Need
Use six sources of influence	Personal/Social/Structural Motivation/ Ability	Influencer Change Model	Awareness
Individuals and Families	Develop relationships, involve, and empower	Institute for Healthcare Improvement's Triple Aim Model	Communication
Redesign of "Primary Care" Services and Structures	Develop health promotion	Institute for Healthcare Improvement's Triple Aim Model	Communication
Prevention and Health Promotion	Reduce the need of healthcare	Institute for Healthcare Improvement's Triple Aim Model	Plan
Cost Control	Make economic evaluations	Institute for Healthcare Improvement's Triple Aim Model	Wins, Monitoring
System Integration	Match services and demand	Institute for Healthcare Improvement's Triple Aim Model	Vision
Build a point of View	Identify opportunities and a business concept	Insurrection Method	Need
Write a manifesto	Draw implications and explain inevitability	Insurrection Method	Vision
Create a coalition	Identify voluntary recruits	Insurrection Method	Communication
Pick your targets and your moments	Involve someone with power and use the right moment	Insurrection Method	Communication
Co-opt and neutralize	Create a win-win situation	Insurrection Method	Wins
Find a translator	Identify forward thinking	Insurrection Method	Communication
Win small, win early, win often	Demonstrate the success	Insurrection Method	Wins, Monitoring
Isolate, infiltrate, integrate	Spread the idea	Insurrection Method	Communication
The ideal self	Define the objective	International Change Theory of Boyatzis	Need

Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
The real self	Analyse strengths and gaps	International Change Theory of Boyatzis	Awareness, Assessment
A learning agenda	Reinforce strengths and reduce gaps	International Change Theory of Boyatzis	Plan
Practice	Experiment with and practice new habits	International Change Theory of Boyatzis	Test
Get support	Create supportive helps	International Change Theory of Boyatzis	Communication, Training
Analyze the organization and its need for change	Analyse the status of the organization, strengths, weaknesses and needs	Jick & Kanter Ten Commandments for Executing Change	Awareness, Assessment, Need
Create a vision and a common direction	Create a central vision	Jick & Kanter Ten Commandments for Executing Change	Vision
Separate from the past	Disengaging from the past	Jick & Kanter Ten Commandments for Executing Change	Vision
Create a sense of urgency	Convince that change is necessary	Jick & Kanter Ten Commandments for Executing Change	Communication
Support a strong leader role	Choose a leader to guide, drive, and inspire the team	Jick & Kanter Ten Commandments for Executing Change	Communication, Plan
Line up political sponsorship	Create a supportive environment with managers, change implementors and recipients of change	Jick & Kanter Ten Commandments for Executing Change	Communication
Craft an implementation plan	Develop a change plan	Jick & Kanter Ten Commandments for Executing Change	Plan
Develop enabling structures	Create new mechanisms for implementing change	Jick & Kanter Ten Commandments for Executing Change	Implementation
Communicate, involve people and be honest	Create empowered and aware environment using full involvement, communication, and disclosure	Jick & Kanter Ten Commandments for Executing Change	Communication
Reinforce and institutionalize change	Make the change the new normal and top priority to prove the commitment	Jick & Kanter Ten Commandments for Executing Change	Implementation, Wins, Institutionalization
Analyze and plan change	Analyse the organization and make a plan	Judson Method	Assessment, Plan
Communicate the change	Communicate to people	Judson Method	Communication
Gain acceptance of new behaviours	Eliminate resistances	Judson Method	Resistance
Change from status quo to a desired state	Implement and empower others to act on the change	Judson Method	Implementation
Consolidate and institutionalize the new state	Reinforce and institutionalize change	Judson Method	Institutionalization
Motions	Define motion (Organization – Environmental / Intraorganizational Components / Intraorganizational Individuals)	Kanter et al. "Big Three" Model of Organizational Change	Assessment
Changes	Define change (Identity / Coordination / Control)	Kanter et al. "Big Three" Model of Organizational Change	Need

Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Roles	Defile role (Strategist / Implementer / Recipient)	Kanter et al. "Big Three" Model of Organizational Change	Awareness, Communication
Increase Urgency	Create a sense of urgency	Kotter's 8-Step Model	Communication
Build the Guiding Team	Pull together a guiding team	Kotter's 8-Step Model	Communication
Get the Vision Right	Create clear, simple, uplifting visions	Kotter's 8-Step Model	Vision
Communicate for Buy-In	Communicate the vision through simple, heartfelt messages	Kotter's 8-Step Model	Communication
Empower Action	Empower people to act on the vision	Kotter's 8-Step Model	Communication, Vision
Create short-term wins	Create short-term wins to make results tangible	Kotter's 8-Step Model	Wins
Don't Let Up	Maintain momentum and state of emergency	Kotter's 8-Step Model	Communication
Make change stick	Anchor changes in corporate culture	Kotter's 8-Step Model	Institutionalization
Specify the value desired by the customer	Define the objective	Lean Thinking	Need
Identify the value stream for each product that adds value	Identify the value	Lean Thinking	Vision
Make the product flow continuously	Create a continuous flow	Lean Thinking	Plan
Introduce pull between all steps from the next upstream activity	Eliminate push actions	Lean Thinking	Plan
Begin the process again until reaching perfection	Iterate the process	Lean Thinking	Revision, Iteration
Unfreeze	Information and awareness for those who will be affected by the change	Lewin's 3-Stage Model of Change	Awareness, Communication
Change	Introduction of change and transition	Lewin's 3-Stage Model of Change	Implementation
Freeze	Refreezing and stabilization of change	Lewin's 3-Stage Model of Change	Institutionalization
Scout	Diagnose the problem	Lippitt's Phases of Change Theory	Need
Enter	Make an assessment of capacity and motivation	Lippitt's Phases of Change Theory	Awareness, Assessment
Diagnose	Diagnosing the system's client problem and identify agent's commitment to change, power, and stamina	Lippitt's Phases of Change Theory	Vision
Plan	Establishing alternative routes defining strategies and action plan	Lippitt's Phases of Change Theory	Plan
Act	Transforming intentions into actual efforts and select and understand the role of change agents	Lippitt's Phases of Change Theory	Awareness
Stabilize and evaluate	Stabilise change with communication, coordination, and feedbacks	Lippitt's Phases of Change Theory	Communication, Monitoring
Terminate	Withdraw from helping relationships	Lippitt's Phases of Change Theory	Implementation
Mobilize energy and commitment by jointly identifying problems and solutions	Accept the need and the urgency and identify problems	Luecke's Seven steps Method	Awareness, Assessment, Need
Develop a shared vision of how to organize and manage for competitiveness	Develop a vision and motivate employees to accept change	Luecke's Seven steps Method	Vision, Resistance, Wins

Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Identify the leadership	Use a strong leadership in supporting change	Luecke's Seven steps Method	Communication
Focus on results, not on activities	Measure the results	Luecke's Seven steps Method	Monitoring
Start change at peripheries and let it spread without pushing from top	Implement the natural change	Luecke's Seven steps Method	Implementation
Instil success through policies, procedures and systems	Guide the transition	Luecke's Seven steps Method	Plan
Review and adjust strategies in response to arising problems	Monitor and adjust strategies for any problem	Luecke's Seven steps Method	Monitoring, Revision
Impetus to transform	Manage external pressures	Lukas Organizational Model for Transformational Change in Healthcare Systems	Awareness
Leadership commitment and support	Acknowledgement of senior management of the necessity of change	Lukas Organizational Model for Transformational Change in Healthcare Systems	Communication
Improvement initiatives	Engage staff in meaningful problem solving and initiatives to better operations	Lukas Organizational Model for Transformational Change in Healthcare Systems	Communication, Plan
Alignment from top to bottom	Alignment to achieve consistency of organization	Lukas Organizational Model for Transformational Change in Healthcare Systems	Vision
High quality patient care	Integration to bridge traditional intra-organizational boundaries between individual components	Lukas Organizational Model for Transformational Change in Healthcare Systems	Resistance, Implementation
Strategy	Define a plan of action	McKinsey 7S Model of Change	Vision, Need
Systems	Schedule daily activities and procedures	McKinsey 7S Model of Change	Plan
Structure	Organizational structure	McKinsey 7S Model of Change	Awareness
Staff	Map people and capabilities	McKinsey 7S Model of Change	Assessment
Skills	Define skills and competencies needed	McKinsey 7S Model of Change	Training
Shared Values	Understand goal and core values	McKinsey 7S Model of Change	Need
Style	Strategical leadership	McKinsey 7S Model of Change	Communication
Know where you're going and why	Define outcome, develop business case, and select the team	National Health Service (NHS) Change Management Guidelines	Need, Plan
Analyse and design	Design the process and the strategy	National Health Service (NHS) Change Management Guidelines	Plan, Vision
Gain commitment	Develop commitment	National Health Service (NHS) Change Management Guidelines	Communication
Deliver it	Implement and execute the actions	National Health Service (NHS) Change Management Guidelines	Implementation
Reinforce it	Revise the actions	National Health Service (NHS) Change Management Guidelines	Revision

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Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Sustain it	Make it sustainable and create continuous improvement	National Health Service (NHS) Change Management Guidelines	Institutionalization, Iteration
Identify problems	Define the need	Participatory action research (PAR)	Need
Consult an external expert	Involve external experts	Participatory action research (PAR)	Communication
Gather data and perform initial diagnosis	Measure and evaluate	Participatory action research (PAR)	Assessment
Give feedback to management	Return to management	Participatory action research (PAR)	Communication
Jointly diagnose problems	Determine the problems in group	Participatory action research (PAR)	Need
Perform a joint action planning	Plan the steps in group	Participatory action research (PAR)	Plan
Act	Implement the change	Participatory action research (PAR)	Implementation
Gather data after action	Measure and revise	Participatory action research (PAR)	Monitoring, Revision
Content	Define area, target, and assumptions	Pettigrew's Context/ Content/ Process Model	Need, Vision
Context	Define internal context (strategy, structure, culture, management, and political processes) and external context (national, economic, political, and social)	Pettigrew's Context/ Content/ Process Model	Awareness, Assessment
Process	Define actions, reactions, interactions, models of change, implementation approach and patterns	Pettigrew's Context/ Content/ Process Model	Plan, Resistance, Implementation
Identify and select processes for redesign	Identify processes and prioritize in terms of urgency (most important or higher conflict)	Process Reengineering	Need
Identify enablers for new process design	Map capabilities	Process Reengineering	Awareness, Assessment
Define the business strategy and process vision	Specify business objectives	Process Reengineering	Need, Vision
Understand the current process's flow and structure	Analyse processes and systems	Process Reengineering	Awareness, Assessment
Design the new process	Design involving users	Process Reengineering	Plan
Prototype the new process	Prototype and refine with successive iterations	Process Reengineering	Test, Revision, Iteration
Implement the process and associated systems	Implement the new processes to support change	Process Reengineering	Implementation
Communicate ongoing results of the effort	Use communication strategies	Process Reengineering	Communication
Build commitment toward change at each step	Create cohesion	Process Reengineering	Institutionalization
Pre-contemplation	Acknowledge the problems	Prochaska and DiClemente's Change Theory	Awareness, Assessment, Need
Contemplation	Raise consciousness of the issue	Prochaska and DiClemente's Change Theory	Awareness, Communication
Preparation	Plan the change	Prochaska and DiClemente's Change Theory	Plan
Action	Engage in change activities	Prochaska and DiClemente's Change Theory	Implementation

▶

Supplement 2 *(follows)*. Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Maintenance	Reinforce the change	Prochaska and DiClemente's Change Theory	Institutionalization
Relapse	Revisit the actions	Prochaska and DiClemente's Change Theory	Revision
Awareness	Define nature of change, needs and risks and draft communication program	Prosci ADKAR	Awareness, Communication
Desire	Define goals and demonstrate commitment	Prosci ADKAR	Need
Knowledge	Define steps for change and training strategy	Prosci ADKAR	Plan, Training
Ability	Facilitate capability building	Prosci ADKAR	Training
Reinforcement	Define rewards and give feedbacks	Prosci ADKAR	Wins, Monitoring
Denial	Management of shock, disbelief or rejection using communication	Riches four-stage model	Resistance, Communication
Resistance	Management of adverse attitude and resistance using acknowledgement	Riches four-stage model	Resistance
Exploration	Exploration and testing of change using support, training, and short-term goals	Riches four-stage model	Training, Wins, Test
Commitment	Managing the acceptance of change as a new routine using recognition	Riches four-stage model	Implementation
Awareness	Define categories for adopter of innovation (Innovators, Early Adopters, Early Majority, Late Majority and Laggards)	Roger's Diffusion of Innovation (DOI) Theory	Awareness
Persuasion	Definition of the attitude (favourable or unfavourable)	Roger's Diffusion of Innovation (DOI) Theory	Awareness
Decision	Understand pros and cons	Roger's Diffusion of Innovation (DOI) Theory	Assessment, Wins
Implementation	Puts the innovation to use	Roger's Diffusion of Innovation (DOI) Theory	Implementation
Continuation	Checks the results	Roger's Diffusion of Innovation (DOI) Theory	Monitoring
Define	Build Awareness	Six Sigma DMAIC	Awareness
Measure	Define the need	Six Sigma DMAIC	Need, Assessment
Analyze	Create desire to change	Six Sigma DMAIC	Communication, Monitoring, Wins
Improve	Define abilities and train knowledge	Six Sigma DMAIC	Training
Control	Reinforce the change	Six Sigma DMAIC	Institutionalization
Jointly diagnosis change	Mobilise commitment	Six Steps	Awareness, Communication
Develop a shared vision	Define how to organize and manage	Six Steps	Vision, Plan
Foster consensus for change	Create cohesion and competence	Six Steps	Training
Spread revitalization to all department	Revitalise from bottom to top	Six Steps	Revision
Institutionalize revitalization through policies	Define policies, structures, and systems	Six Steps	Institutionalization
Monitor and adjust strategies	Respond to problems	Six Steps	Monitoring, Resistance
The change message	Identification of five key change beliefs: discrepancy, appropriateness, self-efficacy, principal support, personal valence	The institutionalizing change model	Assessment

Supplement 2 *(follows).* Concepts deconstruction and aggregation

Concept	Description	Reference	Topics
Commitment	Make emphasis on change recipient involvement and participation: compliance, identification, and internalization	The institutionalizing change model	Awareness
Readiness	Use effective Organizational Diagnosis	The institutionalizing change model	Awareness
Adoption	Create readiness for change	The institutionalizing change model	Communication
Strategies	Define the strategy: active participation, management of internal / external information, formalization activities, diffusion practices, rites and ceremonies, human resource management practices, persuasive communication	The institutionalizing change model	Plan, Vision, Communication
Institutionalize revitalization through policies	Understand managerial influence strategies and institutionalize into culture	The institutionalizing change model	Institutionalization
Assessment	Assess the change measuring	The institutionalizing change model	Monitoring
Reinforcement	Reinforce using change agents and targets attributes	The institutionalizing change model	Wins, Institutionalization
Establish the need to change	Create urgency	Wheel	Need, Communication
Develop and spread a vision of a planned change	Communicate and disseminate	Wheel	Vision, Communication
Diagnose and analyze the current situation	Focus on the current state	Wheel	Awareness
Generate recommendations	Identify potential paths	Wheel	Assessment, Plan
Detail the recommendations	Lists the options	Wheel	Plan
Pilot test the recommendations	Test the change	Wheel	Test
Prepare the recommendations for rollout	Refine recommendations and prepare a plan	Wheel	Revision
Roll out the recommendations	Implement the change	Wheel	Implementation
Measure, reinforce, and refine the change	Monitors, adapts, and reinforces the changes	Wheel	Monitoring, Institutionalization
Pre-change	Definition of potential changes, risks, and problems	Young's Nine Stage Framework	Awareness, Assessment, Resistance
Stimulus	Awareness to the signs of a potential need for change	Young's Nine Stage Framework	Need
Consideration	Identify the reasons for change	Young's Nine Stage Framework	Vision
Validate need	Define who, what, when and why change	Young's Nine Stage Framework	Plan
Preparation	Define progress criteria and monitoring	Young's Nine Stage Framework	Monitoring
Commit	Identify the commitment necessary to overcome resistance	Young's Nine Stage Framework	Resistance
Do-check-act	Activate a guided process of change to keep the transition phase aligned	Young's Nine Stage Framework	Communication, Monitoring
Results	Build a continuous learning process	Young's Nine Stage Framework	Training
New normal	Establish an embedded new behavioural norm to deliver unconscious results	Young's Nine Stage Framework	Institutionalization

HEALTHCARE MANAGMENT

Barriers and challenges of establishing family physician policy for urban population; evidence from a qualitative study in Iran

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Keywords

Family physician • Health care reform • Conflict of interest • Referral system • Payment system • Iran • Health policy

Summary

Background. *Family physicians play a crucial role in healthcare delivery systems worldwide. In Iran, the family physician program has been introduced in only two provinces, with its expansion to other regions currently stalled due to various challenges. This study aims to identify the barriers and challenges hindering the effective implementation of the family physician program in urban areas of Iran.*
Methods. *This qualitative study utilized purposeful sampling to select health system policymakers, senior administrators, and physicians as participants. Data were collected through semi-structured interviews with 32 participants until saturation was reached. The data were analyzed using grounded theory, involving open, axial, and selective coding to identify key themes and sub-themes.*
Results. *The primary challenge in implementing the urban family physician program was conflicting interests among stakeholders, identified as the core category. Key contributing factors included payment mechanism complexities, stewardship, structural issues, financial constraints, and cultural elements. Specialist physicians, in particular, resisted the program's implementation, often employing reverse referral as a coping strategy. These challenges collectively hindered the nationwide rollout of the program.*
Conclusions. *Addressing the barriers to implementing urban family physician policies requires a comprehensive reassessment of stakeholder roles and a restructuring of the payment system. Additionally, proactive efforts to resolve the complex contextual challenges within the healthcare system are essential for the successful implementation of these policies.*

Introduction

The family physician program stands as a globally recognized cornerstone of healthcare systems [1]. The World Health Organization (WHO) has emphasized the pivotal role of implementing the family physician program as a strategic imperative to enhance healthcare service quality, foster equitable healthcare distribution, and curtail costs [2]. Therefore, family physicians bear the responsibility of furnishing comprehensive and high-quality healthcare services to safeguard and enhance individual, familial, and communal well-being [3]. Moreover, evidential discourse underscores the indispensability of this program in realizing universal health coverage (UHC) [4, 5]. As a result more than 100 nations are affiliated with the World Organization of Family Doctors (WONCA) and have embraced this paradigm. In these countries, the family physician program, open to all citizens, is delineated, and family physicians fulfil the role of gatekeepers within the healthcare framework [6]. Considering the absolute benefits of family physician programs, most nations would be motivated to establish such initiative. Nevertheless, the rollout of the family physician program has been a tapestry of accomplishments and trials. Manca et al. underscored in the Canadian context the pivotal attributes of comprehensive care, preventive care, and care continuity engendered by this program [7]. Meanwhile, Scler's study spotlighted the United States, where issues in payment systems and conflicts of interest with insurers, alongside disparate care quality and coverage among payer entities, emerged as primary program challenges [8]. In other studies, the most important challenges of the family physician program were weak governance, financing and payment system problems, weak referral system and cultural considerations [9, 10].

Family physician program in Iran

In the Iranian context, after a comprehensive analysis of diverse healthcare systems and a nuanced assessment of

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the Canadian and British family physician models, the Ministry of Health and Medical Education (MoHME) inaugurated a family physician program tailored for rural regions in 2005 [11]. Subsequently, efforts were directed toward extending this program to urban areas, with Fars and Mazandaran provinces serving as pilot zones since 2012. However, despite a decade's passage, this initiative remains confined to a mere two out of the nation's 31 provinces, a trajectory that fails to exhibit nationwide proliferation [12]. Owing to the relative novelty of this program within the country, empirical inquiry delving into the predicaments and challenges of the urban family physician program (UFPP) has been scant. Behzadifar et al. uncovered persisting obstacles to the realization of the family physician program's positive health impact, necessitating targeted measures to surmount these impediments. Iranian health decision-makers and policy architects are compelled to confront these challenges head-on, harnessing all available capacities to surmount them [13]. Mehrolhassani et al. have investigated the challenges of implementing the urban family physician program in Iran. The study's findings revealed that the most significant challenge in UFPP was the international pressure and rush to implement the program without prior infrastructure preparation. Also, the budget limitations and diversity of insurance organizations and their interactions with the health system have been among the most important challenges in implementing the program [14].
In this study, the challenges and obstacles of urban family physician implementation have been updated and the relationship between the factors has been investigated in a deeper way using the grounded theory method. A new approach has been used to investigate obstacles and challenges and categorize them into two causal and contextual categories. Strategic recommendations for policymakers and managers in Iran and similar contexts have been presented lastly.

Methods

Study design

This research adopts a qualitative approach to delve into the intricacies of challenges and issues pertaining to the UFPP in Iran.

Setting and sampling

The study was conducted within the premises of the MoHME in Tehran, as well as Fars and Mazandaran Universities of Medical Sciences, two provinces each hosted the UFPP. The provincial healthcare network encompassed both public and private hospitals, community health centers, and health insurance organizations. The participants for this study were meticulously selected through purposive sampling. This encompassed individuals possessing expertise or research experience in the domain of family physician practice, seasoned senior managers with a minimum of five years in policymaking and family physician program implementation, as well as urban family physicians. Additionally, a snowball sampling technique was incorporated, originating from the initial interviewees, to identify potential further participants. This recruitment process persisted until data saturation was reached, culminating in 32 interviewees (Tab. I.). The interviews were conducted in person, with the lead author venturing to Fars, Mazandaran, and Tehran provinces.

Data collection

A topic guide, meticulously shaped by the literature review and the insights of the research team, underpinned the data collection process. This guide encompassed overarching inquiries touching upon executive hurdles of the UFPP, training and evaluation, referral systems, electronic health records, financing, and payment systems. The interview sessions were scheduled at times and locations catering to the participants' preferences. Each interview was embarked upon with a preamble outlining the study objectives and ensuring the confidentiality of responses. Upon agreement, informed consent forms were obtained. With participants' consensus, the interview sessions were recorded. Moreover, during these interviews, detailed notes were compiled to facilitate probing questions and recap the session's main takeaways, aligning with the principle of "member checking" [14]. On average, each interview spanned about an hour. In instances where face-to-face interviews were unfeasible, telephone interviews were conducted with three participants.

Data analysis

The initial two interviews and preliminary analyses were a collaborative effort of researchers RM and AA. After aligning on the interview methodology and coding procedures, RM and AA continued with the subsequent interviews. The data analysis was anchored in the grounded theory approach, serving to unearth the axial and causal relationships between the study's thematic components. RM, RS and SA transcribed the interviews verbatim. Following a comprehensive review of the transcripts, the researchers established open codes, subsequently progressing to axial codes in accordance with Strauss and Corbin's framework [15]. Thereafter, selective coding was enacted, culminating in the identification of the core category by discerning logical and causal interconnections among themes and sub-themes. The entire coding process and the delineation of relationships were subject to collective scrutiny and endorsement by all authors. The initial manuscript framework was constructed by RM and AA, and subsequently refined under the aegis of RS, SA and MB. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Ethical Issues/Statement

This study was part of a PhD thesis supported by the School of Health Management, Iran University of Medical Sciences, Iran (IUMS/SHIMS-97-4-37-13765) and received ethical sanction from the National Institute for Ethics in Biomedical Research (Ethics Code: IR.IUMS.REC.1397.920). Key ethical principles

Tab. I. Characteristics of the study participants.

No	Position	Organization	City	Experience Years
1	Policy maker	MoHME	Tehran	28
2	Executive assistant to the deputy for curative affairs	University of Medical Sciences	Shiraz	22
3	Executive assistant to the deputy for curative affairs	University of Medical Sciences	Mazandaran	28
4	Executive director of the deputy for public health	University of Medical Sciences	Shiraz	14
5	Executive director of the deputy for public health	University of Medical Sciences	Mazandaran	19
6	Senior director of the health insurance organization	University of Medical Sciences	Shiraz	26
7	Senior director of the health insurance organization	University of Medical Sciences	Mazandaran	20
8	Senior manager of the family physician program	University of Medical Sciences	Mazandaran	16
9	Executive assistant of the district health networks	the district health networks	Shiraz	20
10	Senior director of the Social Security Insurance Organization	University of Medical Sciences	Sari	19
11	Senior manager the family physician program of the Social Security Insurance Organization	Social Security Organization	Shiraz	20
12	Policy maker	MoHME	Tehran	27
13	Professor of public health department	MoHME	Tehran	22
14	Senior manager	National institute for health research	Tehran	28
15	Associate professor of medical department	University of Medical Sciences	Tehran	12
16	Researcher	Islamic Parliament Research Center of the Islamic Republic of Iran	Tehran	5
17	Director of family physician program	MoHME	Tehran	18
18	Manager of the district health networks	University of Medical Sciences	Shiraz	11
19	Specialist physician in the private sector	University of Medical Sciences	Shiraz	25
20	Specialist physician in the private sector	University of Medical Sciences	Mazandaran	15
21	Specialist physician in private sector	University of Medical Sciences	Shiraz	18
22	Specialist physician in public sector	University of Medical Sciences	Mazandaran	22
23	Specialist physician in public sector	University of Medical Sciences	Shiraz	21
24	Family physician in private sector	University of Medical Sciences	Mazandaran	16
25	Family physician in private sector	University of Medical Sciences	Shiraz	17
26	Family physician in private sector	University of Medical Sciences	Mazandaran	20
27	Family physician in private sector	University of Medical Sciences	Shiraz	17
28	Family physician in public sector	University of Medical Sciences	Mazandaran	19
29	Family physician in public sector	University of Medical Sciences	Shiraz	27
30	Family physician in public sector	University of Medical Sciences	Mazandaran	17
31	Family health expert in private sector	University of Medical Sciences	Shiraz	18
32	Family health expert in public sector	University of Medical Sciences	Mazandaran	5

including obtaining informed and voluntary consent, confidentiality of information shared, anonymity of research participants and beneficence were considered.

Results

The participants boasted an average professional tenure of 15 years, all marked by a minimum of five years' engagement in policymaking, program implementation, research, and field work within the family physician domain (Tab. I).

In the initial stage of coding, a total of 1679 open-source codes surfaced. Subsequent scrutiny, involving a comparative analysis and the integration of analogous codes, yielded a refined set of 483 codes—those directly aligned with the research question. These distilled codes were further grouped into categories, which in turn amalgamated to forge sub-themes. This hierarchical structuring culminated in the establishment of broader thematic clusters. Four cardinal themes emerged and their interrelation is illustrated in Figure 1.

Central to the emergent theory, Conflict of Interest (COI), emerged as the fulcrum around which the study's narrative revolved. This core category profoundly underscored its status as the principal impediment obstructing the nationwide rollout of the UFPP. Concomitantly, the referral and payment systems, designated as the "causal factors", significantly contributed to fomenting COI. Simultaneously, the study unveiled the pertinence of "Contextual factors" within the healthcare ecosystem, namely stewardship, structural dynamics, financial dynamics, and cultural elements, all exerting their influence in challenging the execution of reform initiatives like the UFPP.

The participants' perspectives highlighted specific strategies adopted by stakeholders to address UFPP issues and mitigate COI. These strategies encompassed

lobbying and a concept termed "reverse referral," collectively christened as coping strategies. Each theme is elucidated as follows:

Theme 1 (Core category): Conflict of interest

The insights gleaned from the interview data unequivocally underscored how COI cast a substantial pall over the comprehensive and nation-level deployment of the UFPP. The participants' narratives illuminated that the lack of cohesive stewardship and the incongruence in the objectives of two pivotal ministries, the Ministry of Health and Medical Education and the Ministry of Cooperatives, Labor and Social Welfare(MoCLSW), intensified the COI predicament. The MoHME, entrusted with the mantle of UFPP execution, was handicapped by a dearth of authoritative clout to orchestrate the actions of other stakeholders.

"An underlying challenge in implementing the UFPP is the existence of conflicting interests due to the presence of two ministries with differing orientations.By ignoring the stewardship of the MoHME, the MoCLSW created problems in the implementation process of the program and implemented parallel programs such as the pilot project of "Amin's physician" in Gilan in 2013." (Participant 14)

A substantial hurdle lay in the dominant role of physicians within Iran's healthcare fabric. Their potent positions held within the system were paradoxically antagonistic to the UFPP's implementation, potentially curbing the excessive delivery of specialized care a practice sustained by a fee-for-service (FFS) model. Simultaneously, the dual roles donned by physicians as both policymakers and implementers, straddling the public and private spheres, exacerbated COI concerns.

"The intersection of physicians' roles as policymakers within the MoHME and the Supreme Council for Health Insurance, coupled with their legislative positions within the parliament, manifests overt conflicts of interest." (Participant 12)

Theme 2: Casual factor; Fee-for-service Payment system

This theme includes the triggering factor for the COI. The healthcare system in Iran is dominated by the FFS payment mechanism especially at the secondary and tertiary health care. Hence healthcare properties such as hospitals are paid per service they provide. Even public hospitals, besides the budget paid by government, charge per service they provide, payable jointly by patients and the insurance organizations/companies. The FFS mechanism applies to the individual payment level as well; physicians who work in the public hospitals or clinics also receive the main part of their revenue through fee-for-service mechanism. Private sector hospitals and clinics are fully paid based on FFS. Even pharmacies which are generally private, are paid through the amount of medication they sell to patients. Hence by establishing UFPP, with its inherent role of gatekeeping, the referral of patients to the secondary and tertiary level is regulated and this can affect the earnings at both the property and individual levels.

"The intrinsic nature of the referral system inherently breeds a conflict of interest, as it limits inadequate referrals and induced demands." (Participant 20)

"Our prevalent FFS payment mechanism inherently generates this Conflict of Interest. The more patients a doctor attends to within the FFS system, the greater their earnings." (Participants 18, 19).

Theme 3: Contextual factors

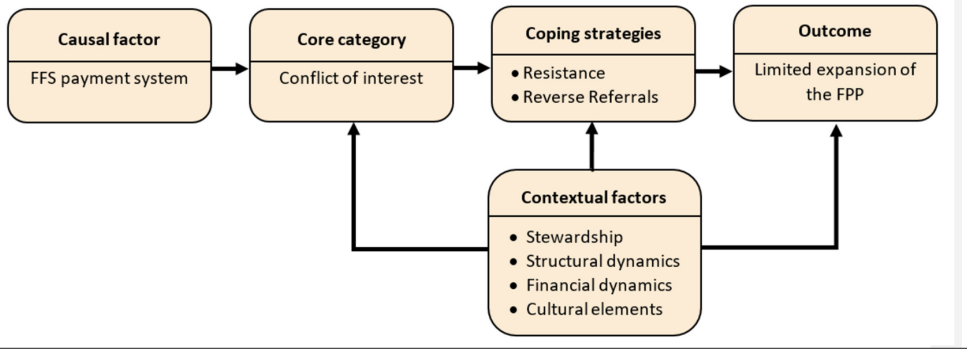
It was recognized that COI not only manifested but also grew within the landscape of Iran's healthcare system. Vital contextual factors encompassing stewardship, structural dynamics, financial considerations, and cultural facets emerged as pivotal determinants impacting UFPP implementation.

Stewardship

Stewardship, a foundational pillar of any healthcare system, exerts a direct influence on other core functions, namely resource provisioning and service delivery. Within Iran's healthcare ecosystem, the lack of evidence-informed policy crafting, a top-down decision-making paradigm, paucity of stakeholder participation in policy formulation, lack of transparency and accountability, and managerial instability collectively contribute to policy faltering.

"Our policy-making oftentimes overlooks historical experiences and fails to engage key stakeholders in UFPP formulation... For the UFPP one day the president

Fig. 1. Theoretical framework of the reasons for Non-expansion of UFPP in the country.



asked the [MoHME] minister to establish it within one year, and one year later the minister formally opened the UFPP in Shiraz while no negotiation had been made with the key stakeholders like specialist doctors, general doctors, insurance organizations and companies, pharmacies and drug industries, etc. Even people were not aware of such program and the program was not promoted in public" (Participants 11, 15).

Structural dynamics

The bedrock for policy implementation rests in the establishment of requisite structural foundations. Within Iran's healthcare landscape, deficits in human resources, particularly a scarcity of General Practitioners (GPs) and specialists – a pivotal prerequisite for UFPP execution – loom large. Moreover, inadequacies in healthcare network development, a lack of interconnectivity between primary, secondary, and tertiary tiers of healthcare delivery, a frail primary healthcare infrastructure, and dearth of electronic health records and clinical guidelines surfaced as recurrent concerns.

"Our electronic infrastructure remains ill-equipped for the UFPP and referral system implementation; we have various electronic features within our healthcare system working unconnected and incompatible with each other … and the absence of adequate family physicians compounds this deficiency." (Participants 20, 27).

Financial dynamics

In the realm of financial considerations, uncertainty surrounding sustainable resources emerged as a foremost obstacle tarnishing UFPP implementation. The inefficiencies and inadequacies besetting insurance organizations, owing to a fragmented health insurance apparatus and an absence of fund pooling, exacerbated the situation. Furthermore, the convergence of UFPP implementation with prevailing political and economic sanctions in Iran cast further shadows on the program's progress.

"Within 2-3 years post UFPP launch, allocated financial resources were slashed by half, diverted to non-UFPP endeavors… So since 2012 no minister at the MoHME would risk applying a nationwide UFPP. It would be a big risk for them endangering their credits" (Participants 4, 7).

Cultural elements

Foremost among the UFPP's predicaments was the absence of adequate education and a suitable cultural milieu predating its rollout. The pervasive trend towards overspecialization in Iran exacerbated resistance towards prevention-focused initiatives.

"Our approach has sorely lacked culture-building. Patients used to take an appointment from a specialist doctor for a simple headache. Everyone likes bypassing GPs." (Participants 12, 26).

Theme 4: Coping strategies

The existence of COI, coupled with causal and contextual health system factors within the UFPP's implementation, elicited negative responses from stakeholders, termed "coping strategies," targeted to shut down or game the UFPP, including lobbying and reverse referrals.

Resistance against UFPP implementation

Originally rooted in the endeavor to sway legislative votes, the concept of lobbying has permeated the UFPP landscape. Some stakeholders, through members of parliament,, were engaged prior to, during, or following parliament's decision-making sessions, in order to cancel or postpone the expansion of UFPP to the rest of the country.

"The UFPP targets the legitimate xand illicit interests of numerous stakeholders; they impede the UFPP and safeguard their personal interests. The parliament has been influenced a lot by such stakeholders" (Participant 12).

Reverse Referrals

A few years after implementation of the UFPP in Shiraz, due to huge resistance against the referral mechanism among specialist doctors and patients, the government allowed the UFPP run with optional referrals. Through such initiative patients can refer directly to specialist physician with no order from a family physician, while a referral through a family physician route would benefit the specialist doctors by a higher FFS payable by insurance organizations. This framework incentivizes specialists to redirect patients to family physicians for referral tickets, even if patients initiate contact directly with specialists. Such dysfunctional consequence increases the cost of running the UFPP.

"In the UFPP, substantial incentives lure specialists to refer patients back and forth, favouring the insidious phenomenon of 'reverse referrals'. By such behaviour government and payers would incur a higher financial burden." (Participant 4).

Discussion

Efforts to enhance health system performance through policy interventions must inherently grapple with the intricate challenges of implementation [16]. Despite Iran's accentuation on UFPP within its upper-ier health policies, the program's nationwide deployment has been confined solely to the provinces of Fars and Mazandaran, with its broader realization quashed. The study's core category underscores the pivotal role of COI as the fundamental obstacle impairing nationwide UFPP implementation. The COI originates from intricacies within the payment system. With FFS as the dominant payment mechanism, the family physician, acting as a gatekeeper within the referral system, curtails patient access to hospitals and specialists and such gauging role would affect volume of patients refer to the secondary level of care and so the earning at this level. For a better understanding of the potential effect of establishing UFPP on patients access to the secondary care and the resulted revenue for care providers we should remind that Iran's urban population have not ever needed a referral order and they could access

specialist care in public and private sector. Furthermore, data on secondary care in Iran show a huge rate of inappropriate services, including inappropriate hospital admissions, inappropriate diagnostic services [17], and even inappropriate interventions, such as invasive procedures [18] that induced to patients [19], especially due to asymmetric information between patients and healthcare providers [20].

Hence introduction of a gatekeeping role could affect earnings in the secondary care level with a dominant FFS payment mechanism [21]. Hence, although FFS mechanisms for the secondary care may improve access to healthcare services [22], it can result in COI against preventive mechanisms and gatekeeping policies such as family physician programs. Current evidence is in consistent with this conclusion [23]. Alternatives such as reforming payment systems, amalgamating methodologies, and implementing pay-for-performance (P4P) initiatives can steer healthcare professionals' conduct [24, 25].

Besides the payment mechanism, the family physician program's tribulations unfold against the backdrop of contextual factors within the healthcare system, encompassing stewardship, structural, financial, and cultural complexities. The top-down implementation of healthcare policies has a long history in Iran's health system [26], and the UFPP was no exception to this rule. The implementation was ordered directly from Iran's president to the minister, with a strict deadline [27]. While this approach may prove effective for small-scale interventions [28], establishing a UFPP with substantial and influential stakeholders, including public and private sector physicians, hospitals, and pharmaceutical industries, would pose significant challenges [29]. The global experience around successful implementation of family physician programs also supports gradual and bottom-up or clear and agreed processes among the key stakeholders [30]. Stakeholder engagement, recognized as pivotal, should underpin policy development from formulation to evaluation, particularly as stakeholders hold the power to influence policy outcomes [31-33].

Lack of technical infrastructure such as electronic records, which is a chronic problem in Iran's health system [34] and shortage of trained family physicians [13] also were among structural barriers that halted to expansion of the UFPP. Evidence also suggests that without a comprehensive electronic medical record system and e-referrals, which interconnects all levels of care, family physician programmes will be challenged [35].

Iran's UFPP was also challenged by lack of financial support which is one of the essential pre-requisites of any family physician policy in the world [10].

Last but not the least, the governmen in Iran did not consider role of public and their culture in the implementation of the UFPP. The public's interest in specialized care and bypassing GPs which is a general trend in most Iranian urban population [36], as well as insurance companies' coverage even on non-referred consultations and procedures, meant that UFPP would face low adherence by people. Such resistance caused the MoHME step back from compulsory referrals to optional referrals so that patients could bypass the GP if they preferred to do so. Political, social, and economic elements, alongside national and cross-sectoral determinants, exert substantial influence on referral system execution [37]. International experience over the establishment of family physicians also shows that government should work on cultural aspects of care and behaviour of people towards promotion of preventive care rather than treatment car [38, 39]. Cultivating trust in family physicians through robust education and media campaigns are essential strategies [40, 41]. Overall, as a result of different sources of conflicting interests, Iran's UFPP was challenged seriously, and various stakeholders showed their resistance against its establishment. The blurred border of public and private organizations in Iran's health system also reinforced the resistance against the establishment and expansion of the UFPP. Such resistance is caused by dual engagement of stakeholders, including specialized physicians, in the public and private sectors [42]. However, where the UFPP is established, such as the Fars Province, the policy was gamed through the "reverse referral" phenomenon which would increase the operational cost of UFPP and threaten the cost-effectiveness of the policy [43, 44].

Conclusions

Successful implementation of preventive medicine policies, such as family physicians programs hinges on a comprehensive re-evaluation of mechanisms, particularly addressing the COI barrier via payment system reform. FFS payment systems in secondary care can cause COI against preventive initiatives and gatekeeping policies. Strengthening infrastructures, assuring financial resources, integrating stakeholder perspectives, and meticulous monitoring are paramount. Robust commitment from governmental and parliamentary bodies, alongside transparent regulations and stringent oversight, are prerequisites for successful reform implementation.

Key messages

1. Implications for policy-makers

Establishing preventive and gatekeeping policies such as family physician programs can trigger conflict of interests for those earn from healthcare market.

Fee-for-service payment mechanism for reimbursing secondary care within public sector can cause conflict of interest against preventive care policies.

Establishing family physician programs need a comprehensive understanding of the main stakeholders' interests and powers and conducting necessary negotiations with them.

2. Implications for public

By conducting this study we tried to help policymakers for better establishment of health care reforms, especially preventive programs. Programs such as family physician,

when established without sufficient initiations and consideration of stakeholders, can cause resistance which will result in waste of resources for governments and the public. Governments and policymakers should define payment systems that are not contrary to the interests of those working in the health care system, including healthcare providers and the related industries such as pharmaceutical companies. People should be considered by policymakers when a policy is going to be established and their concerns should be addressed.

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Data availability statement

Not applicable.

Informed consent 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

AA and RM: designed the study, RM, AA, MB, RS conceived the manuscript; AA, RM, MB, NA,SA drafted the manuscript; AA, RM, RS: revised the manuscript; AA,MB, MM performed a search of the literature; MB, MM critically revised the manuscript;: conceptualization, and methodology; AA,RS,RM: investigation and data curation; AA,RM: original draft preparation; MM, MB: Final editing. All authors have read and approved the latest version of the paper for publication.

References

[1] Verulava T, Dangadze B, Jorbenadze R, Lordkipanidze A, Karimi L, Eliava E, Maglakelidze T. The Gatekeeper Model: patient's view on the role of the family physician. J Family Med Prim Care 2020;22:75-9. https://doi.org/10.5114/fmpcr.2020.92511.

[2] Starfeld B. Improving equity in health: a research agenda. Int J Health Serv 2001;31:545-66. https://doi.org/10.2190/dgj8-4mqw-up9j-lqc1.

[3] Gossa W, Wondimagegn D, Demeke Mekonnen WE, Abebe Z, Fetters MD. Key informants' perspectives on development of Family Medicine training programs in Ethiopia. Adv Med Educ Pract 2016;7:261. https://doi.org/10.2147/AMEP.S94522.

[4] Van der Voort CT, Van Kasteren G, Chege P, Dinant G-J. What challenges hamper Kenyan family physicians in pursuing their family medicine mandate? A qualitative study among family physicians and their colleagues. BMC Fam Pract 2012;13:32. https://doi.org/10.1186/1471-2296-13-32.

[5] De Maeseneer J, Flinkenflögel M. Primary health care in Africa: do family physicians fit in? Br J Gen Pract 2010;60:286-92. https://doi.org/10.3399/bjgp10X483977.

[6] Stavdal A, Flegg K, Donald L, Lygidakis H, Wass V, Pena M, Moosa S, Abubakar D, Jamal M, Farhat T, Vinker S, Ponzo J, Markuns J, Aziz T, Randenikumara S, Gokdemir O, Barros E. Wonca Final Annual Report 2022.

[7] Manca DP, Varnhagen S, Brett-MacLean P, Allan GM, Szafran O, Ausford A, Rowntree C, Rumzan I, Turner D. Rewards and challenges of family practice: Web-based survey using the Delphi method. Can Fam Physician 2007;53:277-86.

[8] Sklar M, Seijo C, Goldman RE, Eaton CB. Beyond checkboxes: A qualitative assessment of physicians' experiences providing care in a patient-centred medical home. J Eval Clin Pract 2019;25:1142-51. https://doi.org/10.1111/jep.13136.

[9] Budi RS, Adisasmito WBB. Implementation of the primary health care system in various countries: a systematic review. BKM Public Health and Community Medicine 2023;39:e7168. https://doi.org/10.22146/bkm.v39i04.7168.

[10] Mohammadibakhsh R, Aryankhesal A, Sohrabi R, Alihosseini S, Behzadifar M. Implementation Challenges of Family Physician Program: a Systematic Review on Global Evidence. Med J Islam Repub Iran 2023;37:21. https://doi.org/10.47176/mjiri.37.21.

[11] Damari B, Vosough Moghaddam A, Rostami Gooran N, Kabir MJ. Evaluation of the Urban Family Physician and Referral System Program in Fars and Mazandran Provinces: History, Achievements, Challenges and Solutions. J Sch Public Health Inst Public Health Res 2016;14:17-38.

[12] Fardid M, Jafari M, Moghaddam AV, Ravaghi H. Challenges and strengths of implementing urban family physician program in Fars Province, Iran. J Educ Health Promot 2019;8:36. https://doi.org/10.4103/jehp.jehp_211_18.

[13] Behzadifar M, Behzadifar M, Heidarvand S, Gorji HA, Aryankhesal A, Taheri Moghadam S, Mohammadibakhsh R, Bragazzi NL. The challenges of the family physician policy in Iran: a systematic review and meta-synthesis of qualitative researches. Fam Pract 2018;35:652-60. https://doi.org/10.1093/fampra/cmy035.

[14] Candela AG. Exploring the function of member checking. The Qualitative Report 2019;24:619-28. https://doi.org/10.46743/2160-3715/2019.3726.

[15] Corbin J, Strauss A. Basics of qualitative research: techniques and procedures for developing grounded theory. Sage publications 2015.

[16] Aftab W, Siddiqui FJ, Tasic H, Perveen S, Siddiqi S, Bhutta ZA. Implementation of health and health-related sustainable development goals: progress, challenges and opportunities–a systematic literature review. BMJ Glob Health 2020;5:e002273. https://doi.org/10.1136/bmjgh-2019-002273.

[17] Naseriasl M, Amini A, Doshmangir L, Adham D, Janati A. Challenges of establishing specialty referral system in iran's health sector (a qualitative study). Acta Medica Mediterranea 2017;33:921-6. https://doi.org/10.19193/0393-6384_2017_1s_137.

[18] Alinia C, Takian A, Saravi N, Yusefzadeh H, Piroozi B, Olyaeemanesh A. Physician induced demand for knee replacement surgery in Iran. BMC Health Serv Res 2021;21:763. https://doi.org/10.1186/s12913-021-06697-6.

[19] Etemadi M, Ashtarian K, Ganji N. A model of financial support for the poor to access health services in Iran: Delphi technique. Int J Health Gov 2023;28:165-78. https://doi.org/10.1108/IJHG-07-2022-0071.

[20] Seyedin H, Afshari M, Isfahani P, Rakhshan A, Hasanzadeh E, Taherimirghaed M. Main Factors leading to supplier-induced demand in Iran: a comprehensive review. Health Scope 2020;9. https://doi.org/10.5812/jhealthscope.96366.

[21] Daminabo B, Ajao E. Factors influencing the utilisation of the referral system in selected primary health care centres among nurses in Rivers State, Nigeria. International Journal of Academic Research in Business, Arts and Science 2020;2:28-39. https://doi.org/10.5281/zenodo.3819581.

[22] Nasseh K, Vujicic M, Yarbrough C. A ten-year, state-by-state, analysis of Medicaid fee-for-service reimbursement rates for dental care services. Am Dent Assoc 2014;20:21.

[23] Rafiei N, Vatankhah S, Kabir MJ. Primary care physician payment mechanisms toward universal health coverage: A study of Iran and selected countries. Int J Health Plann and Manage 2022;37:372-86. https://doi.org/10.1002/hpm.3340.

[24] Martin B, Jones J, Miller M, Johnson-Koenke R. Health Care Professionals' Perceptions of Pay-for-Performance in Practice: a Qualitative Metasynthesis. Inquiry 2020;57:0046958020917491. https://doi.org/10.1177/004695802091749.

[25] Doshmangir L, Bazyar M, Doshmangir P, Mostafavi H, Takian A. Infrastructures Required for the Expansion of Family Physician Program to Urban Settings in Iran. Arch Iran Med 2017;20:589-97.

[26] Khayatzadeh-Mahani A, Sedoghi Z, Mehrolhassani MH, Yazdi-Feyzabadi V. How Health in All Policies are developed and implemented in a developing country? A case study of a HiAP initiative in Iran. Health Promot Int 2016;31:769-81. https://doi.org/10.1093/heapro/dav062.

[27] Lankarani KB, Honarvar B, Shahabi S, Zarei F, Behzadifar M, Hedayati M, Shahabi S, Fardid M, Rafiei F, Martini M, Nejad SR. The challenges of urban family physician program over the past decade in Iran: a scoping review and qualitative study with policy-makers. J Prev Med Hyg 2023;64:E232. https://doi.org/10.15167/2421-4248/jpmh2023.64.2.3029.

[28] Shams L, Nasiri T, Amiri MM, Abdolahi Z. Challenges of rural family physician policy in Iran. Int J Prev Med 2023;14:43. https://doi.org/10.4103/ijpvm.ijpvm_24_22.

[29] Luo L, Zhang S, Xiang J. Development of the family doctor service: an evolutionary game theory analysis. Econ Res-Ekon Istraz 2023;36:2106507. https://doi.org/10.1080/1331677X.2022.2106507.

[30] Yuan S, Wang F, Li X, Jia M, Tian M. Facilitators and barriers to implement the family doctor contracting services in China: findings from a qualitative study. BMJ Open 2019;9:e032444. https://doi.org/10.1136/bmjopen-2019-032444.

[31] Mohammadibakhsh R, Aryankhesal A, Jafari M, Damari B. Family physician model in the health system of selected countries: a comparative study summary. J Educ Health Promot 2020;9:160. https://doi.org/10.4103/jehp.jehp_709_19.

[32] Dong L, Keshavjee K. Why is information governance important for electronic healthcare systems? A Canadian experience. J Adv Humanit Soc Sci 2016;2:250-60. https://doi.org/10.20474/jahss-2.5.1.

[33] Nguyen Long LA, Foster M, Arnold G. The impact of stakeholder engagement on local policy decision making. Policy Sci 2019;52:549-71. https://doi.org/10.1007/s11077-019-09357-z.

[34] Behzadifar M, Behzadifar M, Saran M, Shahabi S, Bakhtiari A, Azari S Bragazzi NL. The role of Iran's context for the development of health technology assessment: challenges and solutions. Health Econ Rev 2023;13:23. https://doi.org/10.1186/s13561-023-00438-7.

[35] Bashar MA, Bhattacharya S, Tripathi S, Sharma N, Singh A. Strengthening primary health care through e-referral system. J Family Med Prim Care 2019;8:1511. https://doi.org/10.4103/jfmpc.jfmpc_184_19.

[36] Bayati M, Keshavarz K, Lotfi F, KebriaeeZadeh A, Barati O, Zareian S, Amiri A, Delavari S. Effect of two major health reforms on health care cost and utilization in Fars Province of Iran: family physician program and health transformation plan. BMC Health Serv Res 2020;20:1-9. https://doi.org/10.1186/s12913-020-05257-8.

[37] Kabir MJ, Amiri HA, Hassanzadeh-Rostami Z, Momtahen R, Zafarmand R, Shirvani SDN. Achievements and Challenges in Implementing Urban Family Physician Program in Iran: Viewpoint of Managers and Executives. J Manage Strat Health Sys 2019. https://doi.org/10.18502/mshsj.v4i2.1410.

[38] DeCamp M, Pomerantz D, Cotts K, Dzeng E, Farber N, Lehmann L, Reynolds PP, Sulmasy LS, Tilburt J. Ethical issues in the design and implementation of population health programs. J Gen Int Med 2018;33:370-5. https://doi.org/10.1007/s11606-017-4234-4.

[39] Alidoost S, Rezapour A, Sohrabi R, Mohammadibakhsh R, Sarabi-Asiabar A, Rafiei N. Causes of revenue deficits of university hospitals and strategies to reduce them. J Hosp 2019;18:67-78.

[40] Arya N, Dahlman B, Gibson C, Ponka D, Haq C, Rouleau K, Hansel S. Developing family practice to respond to global health challenges: The Besrour Papers: a series on the state of family medicine in the world. Can Fam Physician 2017;63:602-6.

[41] Besigye IK, Onyango J, Ndoboli F, Hunt V, Haq C, Namatovu J. Roles and challenges of family physicians in Uganda: A qualitative study. Afr J Prim Health Care Fam Med 2019;11:1-9. https://doi.org/10.4102/phcfm.v11i1.2009.

[42] Moghri J, Arabloo J, Rahatlou MB, Saadati M, Yousefzadeh N. Current knowledge of physicians' dual practice in Iran: A scoping review and defining the research agenda for achieving universal health coverage. PloS one 2022;17:e0277896. https://doi.org/10.1371/journal.pone.0277896.

[43] Bayat M, Shokri A, Khodadost M, Fattahi H, Mirbahaeddin E, Harirchi I, Akbari-Sari A, Zalani GS, Khalilnezhad R. Factors influencing medical specialists' dual practice in the Islamic Republic of Iran. EMHJ 2018;24:877-87. https://doi.org/10.26719/2018.24.9.877.

[44] Raeisi AR, Yarmohammadian MH, Mohammadibakhsh R, Gangi H. Determining the performance indicators based on Iranian balanced scorecard model in AL-Zahra Hospital of Isfahan University of Medical Science. Health Information Management 2013;10:601-10.

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HEALTHCARE MANAGMENT

Strategies for Creating Tax-Based Sustainable Financial Resources in Iran's Health System: a Qualitative Study

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Keywords

Taxation • Financial Sustainability • Resource Creation • Health System • Iran

Summary

Background. *"Ensuring uninterrupted and free access to health services highlights the critical need for sustainable health financing. Given that tax revenues are essential for achieving universal health coverage, this study, conducted in 2024, aims to identify strategies for generating sustainable financial resources through taxation.*

Methods. *This qualitative study gathered data through in-depth, semi-structured interviews with 10 experts. Participant selection continued until data saturation was achieved, using purposeful and snowball sampling to ensure maximum diversity. Thematic analysis was employed for data analysis, using Atlas.ti software (version 8).*

Findings. *The study identified strategies for generating tax-based sustainable financial resources across five main topics: transportation, services, production, individuals, and 11 subtopics. These subtopics include traffic control schemes, highway and road tolls, taxes on urban and intercity transportation systems, fines for traffic violations and vehicle inspection deficiencies, equipment and device imports, corporate sales and revenue, health-damaging products, environmental pollutants, industrial production and petroleum products, businesses and occupations, and long-term exit or migration taxes for health professionals.*

Conclusions. *Implementing tax policies on the identified items requires strong political support, fostering a shared understanding among stakeholders at various levels of policy-making and implementation, and aligning executive program designs with existing infrastructure. Enhancing regulatory systems and increasing transparency in resource allocation are also essential to improving the implementation of health-related tax policies. Further research should carefully examine the economic and social side effects of these taxes on different sectors of society.*

Introduction

One of the key objectives of any health system is to provide appropriate financial mechanisms to support households in accessing health services [1]. As a result, the importance of sustainable health financing is emphasized to ensure uninterrupted and worry-free access to these services [2]. Sustainable health financing refers to a government's ability to meet the financial needs of the health sector and ensure the timely provision of resources to achieve the health system's goals without compromising the government's financial stability [3].

The general challenges related to sustaining health system financing include the rising costs of healthcare services driven by factors such as technological advancements, demographic changes, and increasing consumer expectations. Additionally, governments often face difficulties in generating sufficient financial resources to meet the health system's commitments [4].

According to the World Health Organization, a health system is financially sustainable if it can maintain a continuous balance between its commitments to stakeholders and the financial resources available to meet those commitments [5]. In Iran, Article 10 of the General Health Policies highlights the importance of sustainable financing [6], and recent resource shortages in the health system have further underscored the need to focus on sustainability [5].

There are various methods for financing a health system, including general taxation, national and social health insurance, private or voluntary health insurance, out-of-pocket payments, external aid, and charitable contributions [7]. In many OECD countries and nations with national health systems (NHS), financing heavily relies on income-based tax revenues [8]. The primary advantage of tax-based financing is its sustainability and the broad participation of all members of society, regardless of their health status, facilitating risk pooling and sharing across the population. This approach also mitigates issues such as adverse selection and risk selection, which are common in other financing systems [9].

Studies have shown that tax revenues are one of the key determinants in advancing toward universal health coverage [10]. For example, a study by Tangcharoensathien et al. (2020) demonstrated that government health expenditures, strong political commitment, and the prioritization of a tax-funded medical welfare scheme were crucial to achieving

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universal health coverage in Thailand [11]. Similarly, Javadinasab et al. found that various methods exist for sustainably financing health promotion services. These methods include indirect taxes on goods, taxes on health-related behaviors such as tobacco, alcohol, and gambling, leveraging the capacity of social insurance funds in Germany and Turkey, and relying on government budgets in all the studied countries. According to their findings, the choice of financing method or a combination thereof depends on the political, social, and cultural structure of each country [12].

However, an important consideration when financing health services through taxation is that the use of these resources—and their allocation to the health system—must pass through the filter of political decisions. Governments and politicians must decide, within the political decision-making process, whether tax revenues should be allocated to health, education, defense, or infrastructure [8]. Therefore, conducting a study to identify tax-based sustainable financing strategies and examining each of these strategies is essential to support policymakers in making informed political decisions in this area.

A review of the existing literature reveals that most studies on sustainable financing strategies have focused on health insurance or specific areas of health services, with the majority conducted outside Iran. While some of these studies mention sustainable financing methods, including tax-based approaches, no comprehensive study has focused specifically on taxation. Moreover, the selection of the best strategies for creating tax-based sustainable financial resources is influenced by the political, social, and cultural context of each country. Given Iran's specific circumstances – such as the impact of comprehensive sanctions on the domestic economy, resulting in economic instability, and the emergence of the concept of a resilient economy in response to these sanctions – identifying tax-based sustainable financing strategies could play a critical role in building financial capacity. In light of this, the present study was conducted to identify tax-based sustainable financing strategies for Iran's health system.

Methods

In this study, expert interviews were conducted to identify methods for creating tax-based sustainable financial resources. This qualitative research, conducted in 2024, followed an inductive approach, moving from the micro-level to the macro-level [13]. The study was grounded in the principles of phenomenology, which focuses on understanding individuals' experiences, perceptions, and feelings regarding the phenomenon or subject under investigation [14].

A total of 10 participants were interviewed, including managers and policymakers from the Ministry of Health, hospital managers, and faculty members and researchers in health services management, health policy, and health economics from medical universities across the country. Participants were selected based on their expertise and experience in the subject matter. The inclusion criteria required at least three years of experience in their current position, a willingness to participate, relevant education or experience related to the subject, decision-making or policymaking experience in the field, and a record of producing scientific articles, books, or research related to the study topic.

The majority of participants were male (60%), held Ph.D. or postdoctoral degrees (80%), and 40% were faculty members. Half of the participants had 20 to 30 years of work experience, with degrees in health services management, health economics, general economics, and health and public policy.

Data collection was carried out through semi-structured interviews, a common qualitative data collection method due to its flexibility and depth [15]. The interview guide included questions on financing methods in the country's health system and served as a tool to structure the conversation while allowing the interviewer to explore topics in various ways. The guide was developed based on existing literature and expert feedback.

As is typical in qualitative research, the exact sample size was not predetermined, and sampling continued until data saturation was reached. Sampling was purposive and snowball-based, focusing on individuals with the most relevant knowledge on the topic. The number of interview sessions and participants was determined at the discretion of the research team.

The average interview duration was 45 minutes, with a range of 20 to 70 minutes. To ensure participant comfort and maintain focus and efficiency, flexibility was provided in scheduling interviews. For participants unable to attend face-to-face interviews due to time constraints or distance, telephone or virtual interviews were used as acceptable alternatives [16].

For data analysis, thematic analysis was employed. Using an inductive approach, the researchers first familiarized themselves with the range and diversity of the content. They identified key concepts and themes and developed a thematic framework based on these insights. All interviews were reviewed according to this thematic framework, organized under appropriate thematic categories, and compared for concepts, contradictions, experiences, and existing research. Patterns and relationships were then inferred from the findings. As a result, the methods, components, and dimensions for creating tax-based sustainable financial resources in Iran's health system were extracted from the interview texts and categorized under relevant themes. Atlas.ti version 8 software was used for this analysis.

In qualitative research, terms such as Credibility, Dependability, Conformability, and Transferability are used in place of traditional concepts like validity and reliability [17]. To enhance the credibility and transferability of the findings, researchers took several measures, including conducting pilot interviews, maintaining long-term engagement with the research environment, increasing the diversity of the sample, staying continuously engaged with the data, allowing sufficient time for interviews, gathering extensive

information and evidence, and reviewing interviews multiple times.

Before conducting the interviews, a participant information form was sent via email or fax to inform participants about the study. At the start of the interviews, held at the participants' workplaces, the researchers provided explanations about the study's objectives and assured the confidentiality of the information. Informed consent was obtained from all participants. With their consent, the interviews were recorded, and note-taking was also employed during the sessions.

Findings

The aim of this study was to identify strategies for creating sustainable tax-based financial resources. The experts' opinions were categorized into five Topics, which are summarized below (Tab. I):

Transportation

Traffic Schemes and Odd-Even Day Plans

All participants in the study agreed that a portion of the revenue generated from traffic schemes and odd-even day plans should be allocated to the health system. These schemes, implemented to reduce pollution in Tehran, aim to improve public health by limiting vehicle emissions. Therefore, it is essential that part of the revenue be directed toward the health sector, which is responsible for maintaining and promoting public health.

"This scheme aims to prevent air pollution and consequently protect individuals' health, so a percentage of this revenue should be injected into the health system." (P 5).

Tolls for Highways and Roads

Traffic accidents are the leading cause of death in the country and result in numerous fatalities and serious, sometimes lifelong injuries each year. These accidents impose significant costs on the health system, especially emergency services and hospitals. To mitigate the financial burden on the health sector due to traffic accidents, all interview participants agreed that a percentage of tolls collected from highways and roads should be allocated to the health system.

"According to the sixth item of the 2024 budget, a percentage should be allocated to the health system from the road maintenance fund." (P 4).

Tolls for Urban and Road Transport Systems

Aging urban transport fleets are a significant source of air pollution in large cities, contributing to a range of health problems, both short- and long-term, and increasing healthcare costs. Most interview participants suggested that municipalities should be required to pay taxes to compensate for the damage caused by pollution from outdated transportation fleets. However, one participant disagreed with the idea of imposing such taxes, citing potential conflicts between municipalities and the health system.

"I'm not very supportive because it creates significant challenges between municipalities and the health system." (P 8).

Fines for Traffic Violations and Lack of Vehicle Inspection

Certain traffic violations are enforced to protect people's lives and health, while vehicle inspections are required to ensure that vehicles function properly, reducing emissions and the risk of accidents due to technical failures. Given that these regulations are meant to safeguard public health and safety, all interview participants agreed that a significant portion of the revenue from these fines should be allocated to the health system. Many participants noted that current third-party vehicle insurance amounts are insufficient to cover the true costs of health-related issues caused by traffic accidents.

"Traffic fines are imposed to protect individuals' health, and vehicles without inspection are inherently unsafe and harmful." (P 2).

Service Sector

Importing Equipment and Machinery

Most participants expressed opposition to taxing imports of equipment and machinery, citing concerns about the potential negative impact on production. However, some

Tab. I. Strategies for Creating Sustainable Tax-Based Financial Resources.

Main Theme	Topics	Subtopics
Strategies for Creating Sustainable Tax-Based Financial Resources	Transportation	Traffic schemes and odd-even day plans
		Tolls for Highways and Roads
		Tolls for Urban and Road Transport Systems
		Fines for Traffic Violations and Lack of Vehicle Inspection
	Service Sector	Importing Equipment and Machinery
		Sales and Revenue of Companies and Institutions
	Production Sector	Products and Goods Harmful to Health
		Environmental Pollutants
		Industrial Factory Productions and Petroleum Products
	Individual Sector	Businesses and Enterprises
		Long-Term Exit Fees or Migration of Health Specialists

suggested that only imports of equipment that harm the health system should be taxed for the benefit of the health sector. A minority believed that taxes should be applied to all imported equipment.

"Taxes on industrial machinery and equipment should be collected from the importer before installation and from the employer during operation." (P 9).

Sales and Revenue of Companies and Institutions

The topic of taxing the sales and revenue of companies and institutions for the health system was also discussed. Three perspectives emerged from the interviews: the first supported taxing high-revenue companies, the second proposed taxing companies and institutions that are harmful to health, and the third suggested taxing all companies specifically for the benefit of the health system. Since both public and private companies generate tax revenue, participants reasoned that they could serve as an important source of financial resources for the health sector.

"Tax should be levied on the net profit of companies. Even if a company's product has negative externalities, a higher tax should be imposed. Therefore, the criteria for determining companies and the amount of tax should also be based on the harm caused and the extent of the damage." (P 6).

Production Sector

Products and Goods Harmful to Health

All interview participants agreed that taxes should be imposed on products harmful to health, such as cigarettes and tobacco, and the revenue should be allocated to the health system. Given that these products are major risk factors for diseases like lung cancer, bladder cancer, and cardiovascular conditions, which place a substantial financial burden on the health sector, it is essential for the tax revenue from such products to help offset these expenses. Additionally, many interviewees suggested that harmful food items, such as sugary drinks and unhealthy fats, should also be subject to similar taxes.

"Taxes should be collected from both the producers and consumers of all harmful products and goods. The current value-added tax system is not effective, as it merely increases prices." (P 3)

"Harmful products should be identified, especially food items, and taxes should be imposed based on the external effects of each. Taxes should be levied on both producers and consumers, with an additional 10% on the value-added tax." (P 4).

"Harmful products fall into two categories: 1) those that harm only the individual consumer, like sugary drinks, where taxes should be imposed on the producer; and 2) those that harm others as well, like cigarettes, where taxes should be levied on both the producer and the consumer." (P 7).

Additionally, Participant 10 highlighted that the issue of taxing harmful products should be considered during the process of issuing production and health licenses.

Environmental Pollutants

Environmental pollutants have been increasing and pose a significant threat to public health, with both direct and indirect impacts. All interviewees agreed that taxes should be imposed on environmental pollutants due to their harmful effects on public health, which lead to higher costs for the health system.

"Why is all the revenue from pollutants deposited into municipal and environmental accounts? What about the health system?" (P 2).

"Pollutants should be identified and categorized, and taxes should be imposed according to the severity of their impact on health, with the revenue being allocated to the health system." (P 4).

Industrial Factory Productions and Petroleum Products

All interviewees agreed that taxes should be imposed on industrial factory productions to benefit the health system. They also noted that the current 10% value-added tax dedicated to the health sector is insufficient and should be revised. Some participants suggested expanding the list of taxable items to include new products.

"A higher percentage should be collected compared to the past, and new products should be added to the existing list." (P 6).

Additionally, some participants believed that the criteria for taxing manufacturing factories should be based on the harm caused by their products or the level of pollution emitted by these factories.

Individual Sector

Businesses and Enterprises

All participants agreed that taxes should be imposed on businesses and enterprises, both within and outside the health sector.

"Taxes should be earmarked; otherwise, it is challenging to mandate every business to pay taxes specifically for health purposes. However, if taxes are not earmarked, the government could allocate a portion of the total taxes collected from businesses to the health sector".

Some interviewees suggested that taxes should be collected only from high-income businesses, while others proposed a progressive tax system, where the tax rate increases with higher income, considering this approach fairer.

Long-Term Exit Fees or Migration of Health Specialists

The majority of interviewees supported taxing long-term exit or migration fees for health professionals leaving the country. Given the trend of migration among healthcare professionals, this approach could help cover their educational costs and potentially deter them from leaving.

"When someone has been educated in the country and wants to leave, they have imposed costs on the country's educational system. Therefore, they should pay a portion of the free education costs. The main problem is

identifying individuals planning long-term departure." (P 3).

One interviewee disagreed with taxing permanent migration of specialists, citing high implementation costs as a major obstacle.

"In my opinion, due to the very high administrative costs, it is not feasible." (P 5).

Discussion

One key finding from the interviews is the identification of the transportation sector as a viable method for generating sustainable tax-based financial resources. This includes strategies such as implementing traffic plans, odd-even traffic schemes, tolls on highways and roads, fees for outdated urban and road transportation fleets, traffic fines, and penalties for lack of vehicle technical inspections. Similarly, Javadinasab et al. [12] suggest levying pollution charges in cities with populations over one million to address environmental pollution, support public transportation development, and contribute to the financial sustainability of Iran's health system. Another study also proposes increasing taxes on airline tickets as a potential strategy for generating financial resources [18]. To achieve financial sustainability, it is crucial to ensure that health-related revenues from transportation fees and fines are collected efficiently and systematically.

Regarding the "services sector," the interviewees identified methods such as "taxes on imports of equipment and devices" and "taxes on the sales and revenues of companies and institutions" as promising for creating sustainable tax-based financial resources. Tadaion and Moradi [18] and Javadinasab et al. [12] have similarly suggested higher value-added taxes as a sustainable financing strategy for Iran's insurance system. For example, the government of Ghana funded part of its national health insurance by increasing the value-added tax by 2.5% [19]. Another proposed strategy includes taxing foreign currency transactions to generate sustainable financial resources for the health sector [18].

In comparison, health systems in some OECD countries and nations with national health systems rely heavily on income-based tax revenues. In contrast, developing and low-income countries often depend more on consumption-based tax revenues, resulting in lower overall tax revenue [8]. Therefore, it is recommended that Iranian policymakers, particularly in the health sector, work to enhance the infrastructure necessary for implementing income-based taxes and ensure that a portion of these revenues is allocated to the health system.

The study reveals that the "production sector" is a promising strategy for enhancing the sustainability of financial resources in the health system. This sector includes taxing health-damaging products and goods, environmental pollutants, industrial manufacturing, and petroleum products. The World Health Organization supports taxing harmful products like tobacco, cigarettes, and alcoholic beverages as effective strategies [8]. Tadaion, Moradi, Mosaddegh Rad, and colleagues have also proposed taxes on harmful goods and environmentally polluting industries as sustainable financing strategies for Iran's health insurance system [18, 20]. The government of Ghana partially funded its national health insurance by increasing taxes on health-damaging products [21]. Similarly, Javadinasab et al. suggested taxing unhealthy foods and sugary drinks, with revenues allocated to health services, and imposing a pollution fee on oil refineries and petrochemical units as strategies for sustainable financial resources in Iran's health system [12].

Taxing unhealthy foods and sugary drinks has been shown to be a successful method for financing health promotion services, promoting behavioral change, and generating sustainable resources. Wu et al. (2020) demonstrated that increasing cigarette taxes led to approximately 1.5 million men quitting smoking, with the highest cessation rates among low-income groups, and a long-term reduction in mortality from tobacco-related diseases [22]. Goodchild et al. found that raising the price of cigarettes by one dollar in 181 countries helped prevent mortality, supported sustainable development goals, and could enhance the health system's financial capacity [23]. Given that cigarette prices in Iran are still below the global average, the tax policy on these products remains underdeveloped. Thus, taxes on health-harmful products are highly recommended due to their dual benefits of improving public health and increasing revenue.

In the "individuals" sector, experts identified businesses and long-term exit taxes or emigration of specialized healthcare personnel as viable methods for generating tax-based financial resources. Oketch et al. (2013) also highlighted exit taxes as an alternative sustainable financing mechanism for public healthcare in Kenya [24]. Implementing such taxes requires cultural sensitiity and overcoming societal resistance through public education on the benefits of these tax allocations for overall well-being and health. This strategy necessitates careful planning and policy development to ensure its success.

Conclusions

This study identifies various tax-based strategies across the transportation, services, production, and individual sectors for supporting the health sector. Implementing these policies necessitates strong political backing, a cohesive understanding among stakeholders at all levels of policymaking and execution, and alignment with existing infrastructure.

Given potential public resistance to some proposed taxes, it is advisable for governments to concurrently develop educational and promotional programs to enhance public understanding and acceptance of these policies. To improve the effectiveness of health-related

tax policies, there is a need to strengthen monitoring systems and ensure transparency in the allocation of resources. Additionally, future research should examine the economic and social impacts of these tax strategies on different sectors of society to ensure comprehensive evaluation and adaptation.

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Ethics approval

The study was approved by the ethical committee at Iran University of Medical Sciences (IR.IUMS.REC.1400.1079).

Consent for publication

Not applicable.

Conflict of interests statement

The authors declare that they have no competing interests.

Authors' contributions

Design and execution of the study: GT, HAG, and MB. Analyzed and interpreted the data: GT, HAG, AR, and MJS. Wrote the main manuscript: GT, HAG, MB, and MJS. Revised the manuscript: GT and HABG. Editing: GT, MM, MB, and HAG. All authors approved the final version for submit and publication

References

[1] Ghiasvand H, Hadian M, M. M. Relationship between health insurance and high costs of medical services in hospitals related to Iran University of Medical Sciences. J EcoN Res 2010; 94:207.

[2] Moszynski P. Cambodia's AIDS strategy could fail without sustainable financing. BMJ 2010;341:c7301. https://doi.org/10.1136/bmj.c7301.

[3] Thomson S, Foubister T, Figueras J, Kutzin J, Permanand G, Bryndová L. Addressing financial sustainability in health systems. World Health Organization 2009.

[4] World Health Organization, Kutzin J, Witter S, Jowett M, Bayarsaikhan D. Developing a national health financing strategy: a reference guide. World Health Organization 2017.

[5] Owusu-Sekyere E, Bagah DA. Towards a sustainable health care financing in Ghana: Is the National Health Insurance the solution? Pub Health Res 2014;4:185-94. https://doi.org/10.5923/j.phr.20140405.06.

[6] Behzadifar M, Gorji HA, Rezapour A, Rezvanian A, Bragazzi NL, Vatankhah S. Hepatitis C virus-related policy-making in Iran: a stakeholder and social network analysis. Health Res Policy Syst 2019;17:42. https://doi.org/10.1186/s12961-019-0442-1.

[7] Papanicolas I, Smith P. Health system performance comparison: an agenda for policy, information, and research. World Health Organization 2012.

[8] World Health Organization. Tax-based financing for health systems: options and experiences. World Health Organization 2004.

[9] OECD. Mobilising tax revenues to finance the health system in Côte d'Ivoire. OECD Publishing 2020. https://doi.org/10.1787/aa17c32d-en.

[10] Reeves A, Gourtsoyannis Y, Basu S, McCoy D, McKee M, Stuckler D. Financing universal health coverage-effects of alternative tax structures on public health systems: cross-national modelling in 89 low-income and middle-income countries. Lancet 2015;386:274-80. https://doi.org/10.1016/S0140-6736(15)60574-8.

[11] Tangcharoensathien V, Thammatach-Aree J, Witthayapipopsakul W, Viriyathorn S, Kulthanmanusorn A, Patcharanarumol W. Political economy of Thailand's tax-financed universal coverage scheme. Bull World Health Organ 2020;98:140-5. https://doi.org/10.2471/BLT.19.239343.

[12] Javadinasab H, Masoudi Asl I, Vosoogh-Moghaddam A, Najafi B. Sustainable financing of health promotion services in selected countries: Best experience for developing countries. Med J Islam Repub Iran 2019;33:52. https://doi.org/10.34171/mjiri.33.52.

[13] Creswell JW, Creswell JD. Research design: Qualitative, quantitative, and mixed methods approaches. SAGE publications, Inc 2018.

[14] Mosadeghrad AM, Tajvar M, Ehteshami F. Donors' Participation in Iran's Health System: Challenges and Solutions. Int J Health Policy Manag 2022;11:2514-24. https://doi.org/10.34172/ijhpm.2021.177.

[15] Jaafaripooyan E, Javadi Ghale E, Arab M, sharifi T. Challenges of Charity Hospitals in Tehran: Evidence of Private Sector Participation in the Provision of Health Care. J Health Res 2018;3:323-37.

[16] Meho LI. E-mail interviewing in qualitative research: A methodological discussion. J Am Soc Inf Sci Tec 2006;57:1284-95. https://doi.org/10.1002/asi.20416.

[17] Busetto L, Wick W, Gumbinger C. How to use and assess qualitative research methods. Neurol Res Pract. 2020;2:14. https://doi.org/10.1186/s42466-020-00059-z

[18] Tadaion M, Moradi T. Iran Health System Financing Sustainability; its Situation, Indicators, and Solutions to Explain the Article 10 of General Health Policies. 2019;2:307-25.

[19] Blanchet NJ, Fink G, Osei-Akoto I. The effect of Ghana's National Health Insurance Scheme on health care utilisation. Ghana Med J 2012;46:76-84.

[20] Mosadeghrad A M, Abbasi M, Abbasi M, Heidari M. Sustainable Health Financing Methods in Developing Countries: A Scoping Review. sjsph 2023;20:358-78.

[21] Seddoh A, Akor S. Policy initiation and political levers in health policy: lessons from Ghana's health insurance. BMC Public

Health 2012;12:S10. https://doi.org/10.1186/1471-2458-12-S1-S10.

[22] Wu DC, Sheel V, Gupta P, Essue BM, Luong L, Jha P. Impact of cigarette tax increase on health and financing outcomes in four Indian states. Gates Open Res 2020;4:49. https://doi.org/10.12688/gatesopenres.13127.1.

[23] Goodchild M, Perucic AM, Nargis N. Modelling the impact of raising tobacco taxes on public health and finance. Bull World Health Organ 2016;94:250-7. https://doi.org/10.2471/BLT.15.164707.

[24] Okech TC. Alternative sustainable financing of public health care in Kenya. Int J Bus Soc Sci 2013;3:176-93.

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HEALTHCARE MANAGMENT

Assessing equity in the distribution of hospital beds in Lorestan, western Iran: a regional analysis

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Keywords

Equity • Hospital Beds • Gini Coefficient • Lorenz Curve • Universal Health Coverage • Health Policy • Iran

Summary

Background. *Equity in health service delivery ensures that resources are distributed based on need, minimizing barriers to access and reducing health disparities. Hospital beds are a critical healthcare resource, essential for providing timely and effective medical care. This study aims to evaluate the equity in the distribution of hospital beds in Lorestan Province, western Iran, using the Gini coefficient and Lorenz curve as analytical tools.*
Methods. *Data on the number of hospital beds and population statistics for each city in Lorestan were collected from the Lorestan University of Medical Sciences and the Statistical Center of Iran. The equity of hospital bed distribution was assessed using the Gini coefficient and Lorenz curve, with analyses conducted using R statistical software.*
Results. *Lorestan Province, with a population of 1,678,873, has significant disparities in hospital bed distribution. The Gini coefficient for hospital beds was 0.27, indicating moderate inequality. The Lorenz curve showed a substantial deviation from the equity line, highlighting the imbalance. Khorramabad and Aligudarz exhibited the highest inequality, while Rumeshkan, Kuhdasht, and Poldokhtar had more equitable distributions.*
Conclusions. *The study reveals notable inequities in hospital bed distribution in Lorestan Province, emphasizing the need for targeted policy interventions. Strategic resource allocation, infrastructure development, and policy reforms are essential to enhance healthcare equity. Continuous monitoring and consideration of additional healthcare resources and socioeconomic factors are recommended for comprehensive future assessments.*

Introduction

Equity in access to health services ensures that all individuals, regardless of their socioeconomic status, geographic location, gender, or ethnicity, have the opportunity to obtain the healthcare they need [1]. Equity in health service delivery means that resources are distributed based on need, and barriers to accessing these services are minimized [2]. Universal Health Coverage (UHC) aims to ensure that all people receive the health services they need without suffering financial hardship. By ensuring that vulnerable and marginalized populations have access to health services, equity reduces health disparities and improves overall health outcomes [3]. Equitable access to healthcare leads to early detection and treatment of diseases, reducing morbidity and mortality rates. Equity in health services fosters social cohesion and equity, contributing to societal well-being and stability [4]. Healthier populations are more productive and contribute more effectively to the economy. Equitable health systems thus support economic growth and development [5].

Hospital beds are a critical resource in healthcare systems. They are essential for providing inpatient care, which includes not only routine medical and surgical care but also intensive care for severe illnesses and conditions [6]. Adequate availability of hospital beds ensures that patients can receive timely medical intervention, which is crucial for effective treatment and recovery. Access to hospital beds is linked to the quality of care provided. Overcrowded hospitals can lead to suboptimal care and increased risk of infections and other complications [7]. Proper allocation of hospital beds impacts patient outcomes positively by ensuring that individuals receive the necessary care without delays. This is particularly vital in emergencies and for critical care patients [8]. Adequate hospital bed availability supports public health efforts, especially during pandemics or health crises, by providing the infrastructure needed to handle sudden increases in patient volume. Efficient use of hospital beds can reduce healthcare costs by minimizing unnecessary admissions and optimizing resource utilization [9].

Equitable distribution of hospital beds means ensuring that all regions, especially underserved and rural areas, have sufficient beds to meet the healthcare needs of their populations [10]. It involves considering factors such as population density, disease burden, and geographical

challenges. Equitable distribution of hospital beds ensures that all individuals, regardless of location, have access to necessary inpatient care [11]. This reduces geographic disparities in health outcomes and optimizes the use of healthcare resources, preventing the overloading of some hospitals while others remain underutilized. It contributes to health equity by addressing the needs of marginalized and vulnerable populations who might otherwise face barriers to accessing inpatient care [12]. It also supports the efficiency of the healthcare system by allocating resources based on need and demand, thereby improving overall system performance. Additionally, equitable distribution positively impacts community health by ensuring that local populations have access to essential healthcare services, which is crucial for community-wide disease prevention and management [13]. Equitable distribution of hospital beds is essential for achieving UHC, improving patient outcomes, and ensuring the efficient functioning of the healthcare system. It plays a significant role in reducing health inequalities and enhancing the general health and well-being of the population [14].

The aim of this study is to evaluate the equity in the distribution of hospital beds in Lorestan Province, located in western Iran. Despite the recognized importance of equitable distribution of hospital beds, many regions, particularly in low- and middle-income countries, continue to face significant disparities. This is often due to a lack of comprehensive data and analysis that can guide effective resource allocation [15]. This study seeks to fill this gap by providing a detailed regional analysis of hospital bed distribution, highlighting areas of inequity and potential areas for improvement. For policymakers and decision-makers, this study offers critical insights into the current state of hospital bed allocation in Lorestan Province. By identifying disparities and highlighting underserved areas, this research provides a foundation for informed decision-making aimed at enhancing healthcare equity. The findings can guide the development of targeted interventions and resource allocation strategies that ensure all residents have adequate access to inpatient care. Furthermore, this study contributes to the broader discourse on UHC by emphasizing the necessity of equitable resource distribution as a cornerstone of health equity. Policymakers can use the insights gained from this analysis to support initiatives aimed at reducing health disparities, improving patient outcomes, and achieving UHC goals. The study's evidence-based recommendations can inform strategic planning and policy formulation, ultimately fostering a more equitable and efficient healthcare system in Lorestan and similar regions.

Methods

Lorestan province

Lorestan is a province located in the western part of Iran. It is characterized by its mountainous terrain. The capital city of Lorestan is Khorramabad. As of the latest administrative divisions, Lorestan province comprises 11 counties. Each of these counties includes several cities and rural districts. Figure 1 shows the location of Lorestan Province in western Iran. The geographical location of Lorestan Province is shown in Figure 1.

Fig. 1. Geographic location of Lorestan Province.

Data collection

In Lorestan province, Lorestan University of Medical Sciences (LUMS) is responsible for providing health services, including the establishment of hospitals. All government hospitals and services in the province are offered at government-regulated prices. Data on the number of hospitals and hospital beds in each city were collected from the Lorestan University of Medical Sciences website (https://lums.ac.ir). Population statistics for each city were obtained from the statistical center of Iran (https://amar.org.ir/). Since the data used in this study is publicly accessible and available online to any researcher, there was no need to obtain an ethics code.

Data analysis

To assess the equity in the distribution of hospital beds, we employed two widely used Gini coefficient [16] and the Lorenz curve indicators [17]. The Gini coefficient is a measure of statistical dispersion intended to represent the inequality of a distribution. A Gini coefficient of 0 indicates perfect equality, where every city has the same number of hospital beds per capita. A Gini coefficient of 1 indicates maximum inequality, where one city has all the hospital beds. Interpret the Gini coefficient and its range: **0**: Perfect equality. Every region has an equal number of hospital beds. **1**: Perfect inequality. All hospital beds are concentrated in one region, and other regions have none. Understanding the Coefficient: Low Gini Coefficient (close to 0): Indicates a more equitable distribution of hospital beds. Regions have similar numbers of beds, showing relatively fair access across the board. High Gini Coefficient (close to 1): Indicates greater inequality in distribution. This suggests that some regions have a disproportionate number of beds compared to others, reflecting disparities in access to healthcare resources.

To calculate the Gini coefficient for the distribution of hospital beds in Lorestan, we first computed the number of hospital beds per 1,000 population for each city. We then applied the Gini coefficient formula to this distribution. The Lorenz curve is a graphical representation of the distribution of resources (in this case, hospital beds). It plots the cumulative percentage of the total number of hospital beds against the cumulative percentage of the population. The degree of curvature of the Lorenz curve indicates the level of inequality: the closer the curve is to the line of equality (45-degree line), the more equitable the distribution. Conversely, the further the Lorenz curve is from the line of equality, the more inequitable the distribution. We analyzed the distribution of hospital beds across the cities in Lorestan using the Gini coefficient and the Lorenz curve. The results provided a quantitative and visual representation of the equity in hospital bed distribution. This analysis allowed us to identify areas with significant disparities and propose targeted policy interventions to improve equity in healthcare resource allocation. The analyses were conducted using the R statistical software, with significance determined at a p-value of less than 0.05.

Results

The population of Lorestan province was 1,678,873 people. There are 18 hospitals across the 11 cities of Lorestan province. Table I displays the population, number of hospitals, number of hospital beds, beds per 1,000 people, and hospitals per 100,000 people.

The cities with the most hospitals were Khorramabad (6 hospitals), Borujerd (2 hospitals), and Aligudarz (2 hospitals). and each of the remaining cities had one hospital. In 2023, the Gini coefficient for hospital beds in Lorestan province, compared to the population of each city, was estimated at 0.27. Figure 2 displays the Gini coefficient calculated for hospital beds in each city of Lorestan province.

The highest Gini coefficients for hospital beds were observed in the cities of Khorramabad, Aligudarz, and Delfan. The lowest Gini coefficients were observed in the cities of Rumeshkan, Poldokhtar, and Selseleh.

Figure 3 presents the Lorenz curve for the number of beds and active population in Lorestan province in 2023. According to this figure, the Lorenz curve deviates significantly from the optimal limit (Equity line, 45 degrees). This increased distance between the curve and the justice line indicates a lack of proper distribution of hospital beds in Lorestan.

Discussion

In this study, we assessed the equity in the distribution of hospital beds across Lorestan province in western Iran. Our analysis revealed a notable disparity in the allocation of hospital beds relative to population distribution among the 11 cities. With a Gini coefficient of 0.27, the results indicate a moderate level of inequality in the distribution of hospital beds. The Lorenz curve further underscores this inequity, with a substantial deviation from the 45-degree equity line, illustrating a significant imbalance between population needs and hospital bed availability.

When comparing our findings to other studies, our Gini coefficient of 0.27 is higher than those reported by Mosadeghrad AM (0.10) [18], Rezaei S (0.19) [19], Mosadeghrad AM (0.26) [20], and Rezaei S (0.19) [21]. These lower Gini coefficients suggest that these regions have a more equitable distribution of hospital beds. Conversely, our Gini coefficient is lower than those reported by Chavehpour Y (0.55) [22], Asl IM (0.46) [13], Mosadeghrad AM (0.28) [23], Mosadeghrad AM (0.29) [24], and Mosadeghrad AM (0.61) [25], indicating that these studies found greater inequity in the distribution of hospital beds compared to our findings.

The variation in Gini coefficients across different studies highlights the disparities in healthcare resource allocation in various regions. Our study's Gini coefficient being in the middle range of these comparisons suggests that while there is room for improvement, Lorestan's distribution of hospital beds is relatively more equitable than regions with higher Gini coefficients but less equitable than

Tab. I. Population, number of hospitals, number of hospital beds, beds per 1,000 people, and hospitals per 100,000 people in Lorestan province in 2023.

City	Population	Number of Hospitals	Number of hospital beds	Beds per 1000 People	Hospitals per 100000 People
Khorramabad	506471	6	929	1.88	1.18
Borujerd	326452	2	549	1.68	0.61
Aligudarz	137534	2	259	1.88	1.45
Dorud	174508	1	189	1.08	0.57
Azna	71586	1	96	1.34	1.39
Rumeshkan	39058	1	0	0.0	2.56
Kuhdasht	166658	1	128	0.76	0.60
Delfan	65547	1	118	1.80	1.52
Selseleh	75559	1	79	1.04	1.32
Poldokhtar	73744	1	29	0.39	1.35
Sarab-e Dowreh	41756	1	64	1.53	2.39

Fig. 2. Gini coefficient calculated for each city in Lorestan province in 2023.

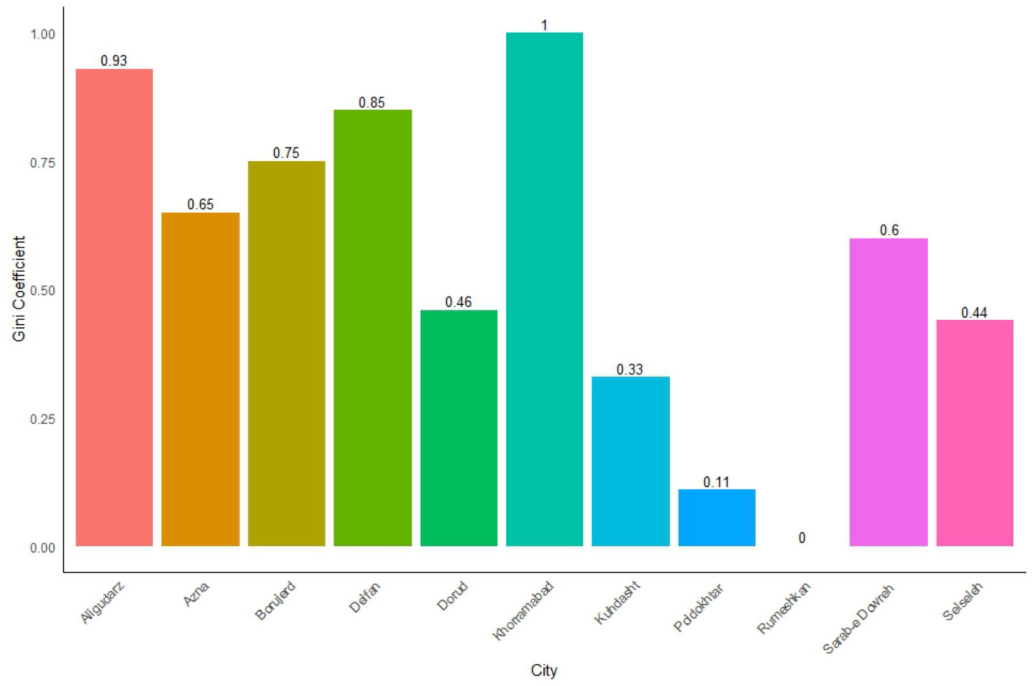
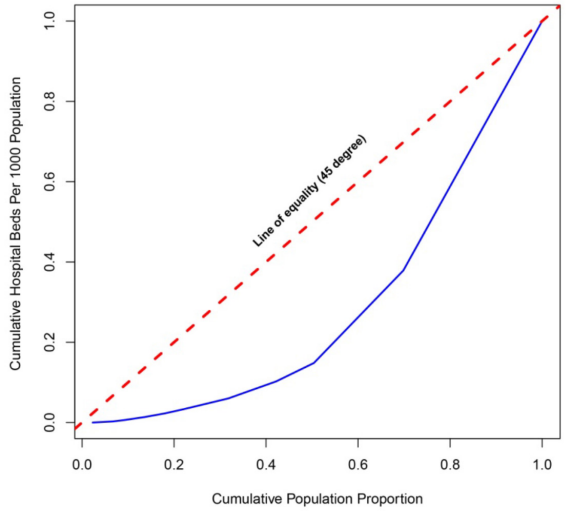


Fig. 3. Lorenz curve of hospital bed distribution based on population in Lorestan province.



those with lower coefficients. These findings underscore the need for targeted policies to address and reduce the inequities in hospital bed distribution to ensure more equitable access to healthcare services for all populations within Lorestan province.

The differences in Gini coefficients calculated for the distribution of hospital beds in different studies can be attributed to several factors [13]. Different regions may have varying levels of healthcare infrastructure development, population density, and healthcare needs. These regional differences can significantly impact the equity in the distribution of hospital beds. Variations in study design, data collection methods, and analysis techniques can lead to different Gini coefficients [25]. For instance, differences in the time periods studied, the population data used, and the specific metrics for hospital bed distribution can all affect the results. The effectiveness and focus of healthcare policies and investments in different regions can lead to disparities in resource allocation. Regions with more robust healthcare policies and better investment in healthcare infrastructure may show lower Gini coefficients [22]. Socioeconomic conditions, such as income levels, employment rates, and education, can influence healthcare access and distribution. Regions with higher socioeconomic status may have better access to hospital beds and more equitable distribution [19]. Geographical factors, such as the urban-rural divide, terrain, and transportation infrastructure, can impact the accessibility and distribution of hospital beds. Regions with challenging geography may face more significant disparities [25]. Differences in population demographics, such as age distribution, prevalence of diseases, and population growth rates, can affect healthcare needs and the distribution of hospital beds. Regions with older populations or higher disease prevalence may require more hospital beds [26]. The balance between the demand for healthcare services and the supply of hospital beds can vary across regions. Areas with higher demand but limited supply may exhibit higher Gini coefficients [18]. The level of support and intervention from government and healthcare institutions can play a crucial role in ensuring equitable distribution. Regions with proactive

government policies and strong institutional frameworks may achieve better equity in hospital bed distribution. These factors, individually or in combination, can contribute to the observed differences in Gini coefficients across various studies. Understanding these underlying reasons can help policymakers and healthcare planners devise strategies to address inequities and improve the overall distribution of healthcare resources [22].

Khorramabad, the provincial capital with a population of 506,471, has a Gini coefficient of 1.00, indicating the highest level of inequality. This suggests that hospital beds are not equitably distributed relative to the population. Aligudarz, with a Gini coefficient of 0.93, also exhibits significant inequality. Despite a smaller population of 137,534, the distribution of hospital beds in this city is highly uneven. Borujerd and Delfan have Gini coefficients of 0.75 and 0.85, respectively. These values indicate substantial but slightly lower inequality compared to Khorramabad and Aligudarz. Borujerd, with a population of 326,452 and 549 hospital beds, and Delfan, with 65,547 people and 118 beds, demonstrate a more equitable distribution than the highest inequality cities, yet still reflect notable disparities. Dorud (0.46), Selseleh (0.44), Azna (0.65), and Sarab-e Dowreh (0.60) present more moderate levels of inequality. These cities, with varying populations and hospital bed counts, show a somewhat better balance in the distribution of healthcare resources. However, there is still room for improvement to achieve more equitable access. Rumeshkan (0.00), Kuhdasht (0.33), and Poldokhtar (0.11) exhibit the lowest Gini coefficients, indicating relatively more equitable distributions of hospital beds. Rumeshkan, notably, has no hospital beds, which simplifies its Gini coefficient calculation to 0.00. Kuhdasht and Poldokhtar, despite having fewer beds, show a more equitable distribution relative to their populations.

Implications for Health Policy

Resource Allocation. The disparities highlighted by the Gini coefficients suggest a need for targeted resource allocation to address inequities. Cities with high inequality, such as Khorramabad and Aligudarz, require strategic interventions to ensure a more balanced distribution of hospital beds.

Infrastructure Development. Investment in healthcare infrastructure, particularly in cities with fewer hospital beds like Rumeshkan and Poldokhtar, can enhance equity. Ensuring that all cities have at least a minimum threshold of hospital beds is crucial for equitable healthcare access.

Policy Reforms. Policymakers should consider reforms that promote equitable healthcare distribution, such as incentives for hospitals to expand services in underserved areas and regulations that ensure equitable access to healthcare resources.

Monitoring and Evaluation. Continuous monitoring of the distribution of healthcare resources using tools like the Gini coefficient can help track progress and identify areas needing further intervention.

By addressing these disparities, Lorestan province can move towards a more equitable healthcare system, ensuring that all residents have fair access to necessary medical services regardless of their location.

Limitations

While this study provides valuable insights into the equity of hospital bed distribution in Lorestan Province, several limitations should be acknowledged. The study relies on publicly available data from Lorestan University of Medical Sciences and the Statistical Center of Iran. Any inaccuracies or limitations within these data sources could affect the findings. For instance, discrepancies in reporting hospital bed counts or population figures could influence the Gini coefficient and Lorenz curve analysis. The study focuses solely on the distribution of hospital beds and does not consider other critical healthcare resources such as medical staff, equipment, or outpatient services. Thus, the overall equity of healthcare access might be broader than what hospital bed distribution alone can reveal. The study does not account for geographical challenges and transportation issues that might affect access to hospital services. In mountainous and rural areas of Lorestan, physical access to hospitals can be a significant barrier despite an equitable distribution of beds. The analysis is based on data from a single year (2023), which may not capture temporal changes and trends in hospital bed distribution and healthcare needs over time. Longitudinal data would provide a more comprehensive understanding of equity trends and the impact of policy changes. The study does not integrate socioeconomic and demographic variables, such as income levels, education, and age distribution, which could influence healthcare needs and access. Including these factors might offer a more nuanced understanding of inequities in hospital bed distribution. The study does not directly assess the impact of hospital bed distribution on health outcomes. While equitable distribution is critical, the ultimate goal is to improve health outcomes. Future research should link hospital bed distribution to patient health outcomes to validate the implications of equity in resource allocation. Although the study compares Gini coefficients with other regions, differences in healthcare systems, policies, and socioeconomic contexts between Lorestan and other areas could limit the generalizability of these comparisons. The study provides recommendations for policy interventions but does not assess the feasibility and potential impact of these interventions. Further research is needed to evaluate the practical implementation and effectiveness of proposed policy measures in improving equity.

While this study provides valuable insights into the equity of hospital bed distribution in Lorestan province, it is important to acknowledge certain limitations. Firstly, the analysis was confined to a single province in western Iran, which may limit the generalizability of the findings to the broader context of Iran. The healthcare infrastructure, population distribution, and regional factors specific to Lorestan may differ from those in other provinces, leading to variations in equity levels. Therefore, caution should be exercised when extrapolating these results to other regions within the

country. Further research involving a broader range of provinces or a nationwide study would be necessary to draw more comprehensive conclusions about the equity of hospital bed distribution across Iran.

Conclusions

This study provides a comprehensive analysis of the equity in hospital bed distribution across Lorestan Province, western Iran, revealing significant disparities. With a Gini coefficient of 0.27, our findings indicate a moderate level of inequality, supported by the Lorenz curve's deviation from the equity line. Cities like Khorramabad and Aligudarz exhibit the highest inequality, while Rumeshkan, Kuhdasht, and Poldokhtar show more equitable distributions. These disparities underscore the need for targeted policy interventions to ensure a fair allocation of healthcare resources. Our study highlights the critical role of equitable hospital bed distribution in achieving UHC, improving patient outcomes, and fostering overall societal well-being. Addressing these inequities requires a multifaceted approach, including strategic resource allocation, infrastructure development, policy reforms, and continuous monitoring. By implementing these measures, policymakers can enhance healthcare access and equity, particularly in underserved and rural areas. While our analysis focuses on hospital beds, future research should incorporate other healthcare resources and consider socioeconomic and demographic factors for a more comprehensive assessment. Ultimately, improving equity in healthcare resource distribution is essential for reducing health disparities, enhancing system efficiency, and promoting the general health and well-being of the population in Lorestan Province.

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Data availability statement

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Informed consent statement

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Conflict of interests 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

MaB, PE, SS and FS: designed the study, MeB, SA, MM, BDT conceived the manuscript; MaB, MM, MeB, SS,SA drafted the manuscript; FS, MeB, MM: revised the manuscript; MaB,MeB, MM performed a search of the literature; MeB, SA, SS, PE, and FS critically revised the manuscript;: conceptualization, and methodology; MaB,SS,MM: investigation and data curation;MeB,FS: original draft preparation; MM, MaB: Final editing. All authors have read and approved the latest version of the paper for publication.

References

[1] Dong E, Sun X, Xu T, Zhang S, Wang T, Zhang L, Gao W. Measuring the inequalities in healthcare resource in facility and workforce: A longitudinal study in China. Front Public Health 2023;11:1074417. https://doi.org/10.3389/fpubh.2023.1074417.

[2] Chisolm DJ, Dugan JA, Figueroa JF, Lane-Fall MB, Roby DH, Rodriguez HP, Ortega AN. Improving health equity through health care systems research. Health Serv Res 2023;58:289-99. https://doi.org/10.1111/1475-6773.14192.

[3] Fisher M, Freeman T, Mackean T, Friel S, Baum F. Universal Health Coverage for Health Equity: From Principle to Practice; A Response to the Recent Commentaries. Int J Health Policy Manag 2022;11:1601-3. https://doi.org/10.34172/ijhpm.2022.7218.

[4] Lee H, Kim D, Lee S, Fawcett J. The concepts of health inequality, disparities and equity in the era of population health. Appl Nurs Res 2020;56:15136. https://doi.org/10.1016/j.apnr.2020.151367.

[5] Jindal M, Chaiyachati KH, Fung V, Manson SM, Mortensen K. Eliminating health care inequities through strengthening access to care. Health Serv Res 2023;58:300-10. https://doi.org/10.1111/1475-6773.14202.

[6] Rouhifard M, Vosoogh-Moghaddam A, Moshiri E. The roles and functions of future hospitals in health promotion: A systematic review in Iran. J Educ Health Promot 2022;11:316. https://doi.org/ 10.4103/jehp.jehp_1661_21.

[7] Freijser L, Annear P, Tenneti N, Gilbert K, Chukwujekwu O, Hazarika I,Mahal A. The role of hospitals in strengthening primary health care in the Western Pacific. Lancet Reg Health West Pac 2023;33:100698. https://doi.org/10.1016/j.lanwpc.2023.100698.

[8] Bastani P, Mohammadpour M, Bahmaei J, Ravangard R, Mehralian G. Hospital management by health services management graduates: the change paradigm in Iran. Heliyon 2021;7:e08414. https://doi.org/10.1016/j.heliyon.2021.e08414.

[9] De Regge M, De Pourcq K, Meijboom B, Trybou J, Mortier E, Eeckloo K. The role of hospitals in bridging the care continuum: a systematic review of coordination of care and follow-up for adults with chronic conditions. BMC Health Serv Res 2017;17:550. https://doi.org/10.1186/s12913-017-2500-0.

[10] Saw Chien G, Chee-Khoon C, Wai VH, Ng CW. Equitable Distribution of Public Hospitals According to Health Needs in Malaysia: Does It Exist or Not? Asia Pac J Public Health 2015;27:79S-85S. https://doi.org/10.1177/1010539515591847.

[11] Lu L, Zeng J. Inequalities in the geographic distribution of hospital beds and doctors in traditional Chinese medicine from

2004 to 2014. Int J Equity Health 2018;17:165. https://doi.org/10.1186/s12939-018-0882-1.

[12] Omrani-Khoo H, Lotfi F, Safari H, Zargar Balaye Jame S, Moghri J, Shafii M. Equity in Distribution of Health Care Resources; Assessment of Need and Access, Using Three Practical Indicators. Iran J Public Health 2013;42:1299-308.

[13] Asl IM, Abolhallaje M, Raadabadi M, Nazari H, Nazari A, Salimi M, Javani A. Distribution of hospital beds in Tehran Province based on Gini coefficient and Lorenz curve from 2010 to 2012. Electron Physician 2015;7:1653-7. https://doi.org/10.19082/1653. eCollection 2015 Dec.

[14] Pan J, Shallcross D. Geographic distribution of hospital beds throughout China: a county-level econometric analysis. Int J Equity Health 2016;15:179. https://doi.org/10.1186/s12939-016-0467-9.

[15] Ghiasvand H, Mohamadi E, Olyaeemanesh A, Kiani MM, Armoon B, Takian A. Health equity in Iran: A systematic review. Med J Islam Repub Iran 2021;35:51. https://doi.org/10.47176/mjiri.35.51.

[16] Park JW, Kim CU. Getting to a feasible income equality. PLoS One 2021;16:e0249204. https://doi.org/10.47176/mjiri.35.51.

[17] Mody A, Pfeifauf K, Geng EH. Using Lorenz Curves to Measure Racial Inequities in COVID-19 Testing. JAMA Netw Open 2021;4:e2032696. https://doi.org/10.1001/jamanetworkopen.2020.32696.

[18] Mosadeghrad AM, Janbabaei G, Kalantari B, Darrudi A, Dehnavi H. Equity in distribution of hospital beds in Iran. Sci J Kurdistan Uni Med Sci 2020;24:12-36. https://doi.org/10.29252/sjku.24.6.12.

[19] Rezaei S, Karami Matin B, Kazemi Karyani A, Pourreza A. Distribution of physicians and hospital beds based on Gini coefficient and Lorenz curve: A national survey. J Kermanshah Uni Med Sci 2016;20:30-6. https://doi.org/10.22110/jkums.v20i1.2186.

[20] Mosadeghrad AM, Dehnavi H, Darrudi A. Equity in hospital beds distribution in Zanjan Province, Iran. Payesh 2020;19:255-66. https://doi.org/10.29252/payesh.19.3.255.

[21] Rezaei S, Bazyar M, Fallah R, Chavehpour Y, Homaie Rad E. Assessment of Need and Access to Physician and Hospital Beds: A Cross Sectional Province Based Study in Iran. Shiraz E-Med J 2015;6:e26351. https://doi.org/10.17795/semj26351.

[22] Chavehpour Y, Rashidian A, Woldemichael A, Takian A. Inequality in geographical distribution of hospitals and hospital beds in densely populated metropolitan cities of Iran. BMC Health Serv Res 2019;19:614. https://doi.org/10.1186/s12913-019-4443-0.

[23] Mosadeghrad AM, Dehnavi H, Darrudi A. Equity in distribution of hospital beds in Semnan Province. Hakim Health Sys Res 2020:320-31. https://doi.org/10.61186/payesh.23.2.171.

[24] Mosadeghrad AM, Dehnavi H, Darrudi A. Equity in distribution of hospital beds in Tehran province. Payesh 2024;23:171-84. https://doi.org/10.61186/payesh.23.2.171.

[25] Mosadeghrad AM, Dehnavi H, Darrudi A. Equity of hospital bed distribution in Tehran city: brief report. Tehran Uni Med J 2021;79:156-62.

[26] Hatam N, Zakeri M, Sadeghi A, Darzi Ramandi S, Hayati R, Siavashi E. Equity analysis of hospital beds distribution in Shiraz, Iran 2014. Med J Islam Repub Iran 2016;30:393.

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History of Medicine and Ethics

A historico-medical perspective on ancient epidemics and their impact on past human societies

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Keywords

COVID-19 • Epidemics • History of medicine • Immunology • Plague • Prevention • Infectious diseases

Summary

The present article reviews the major historical plague epidemics that characterised human history by combining data derived from historical sources and biomedical evidence emerged in recent years thanks to advancements of palaeogenetics and palaeopathology.

Notes are offered on the Plague of Athens, the Antonine Plague, the Plague of Cyprian, the Justinian Plague, the Black Death down to more recent centuries and presenting key aspects that continued to be preserved over time and would also partly characterise the recent COVID-19 pandemic.

Introduction

The severe impact of the COVID-19 pandemic, amounting to more than 704,753, 890 cases worldwide and 7,010,681 deaths as of April 13, 2024 [1], on the world's population has led the international scientific community to reflect deeply on the history of epidemic-pandemic phenomena and the anthropic response, at medical as well as social and political levels. Indeed, those events have powerfully shaped the economic, political, and social aspects of human civilization [2-4]. Epidemic outbreaks have defined some of the basic tenets of modern medicine, pushing the scientific community to develop principles of epidemiology, prevention, immunization, and antimicrobial treatments [2-4].
The aim of this contribution is to retrace the main pestilential events that have disrupted human societies, starting from the mythical Achaean plague narrated in the Iliad to the plague of the 14th century AD, thus emphasising the interaction between scientific-epidemiological and socio-cultural components.

History of plague

Plague is an infectious disease of bacterial origin caused by the bacillus *Yersinia pestis*, a Gram-negative bacterium belonging to the enterobacteria family [5]. The disease is primarily a murine zoonosis, and its reservoir is made up of various species of rodents including the common rat (*Rattus rattus*). Many types of animals, such as rock squirrels, wood rats, ground squirrels, prairie dogs, chipmunks, mice, voles, and rabbits can be affected by plague. Wild carnivores can become infected by eating other infected animals. The vector is the rat flea (*Xenopsylla cheopis*): when the latter bites an infected rat to feed on its blood, it receives the bacterium in the esophagus, where it multiplies [6]. The decimation of infected rat colonies forces fleas to seek alternative hosts, such as humans. In this case too, contagion occurs through the bite of the flea, which regurgitates the bacterium and carries it into the human blood. Added to these modes of transmission is, in the case of the pulmonary form, contagion from person to person through droplets, the respiratory droplets spread by coughing, and it can also be transmitted by animal scratches or by the inhalation of infected particles from animals having a respiratory infection; furthermore infection through the handling of infected animals is also documented or during the autopsy of infected animals [7-9].
Plague has occurred in people of all ages, though 50% of cases occur in people ages 12-45. It occurs in both men and women, though historically is slightly more common among men, probably because of increased outdoor activities that put them at higher risk. Modern antibiotics are effective in treating plague. Without prompt treatment, the disease can cause serious illness or death. Human plague infections continue to occur in

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rural areas in the western United States, but significantly more cases occur in parts of Africa and Asia [10].
However, if the exact aetiology of the plague has only been clarified relatively recently, the disease has been well known since ancient times and has given rise to various pandemics throughout history, which is confirmed both in archaeological finds and in written sources. Regarding the latter, however, it should immediately be clarified that what the ancients would call *plague* did not necessarily refer specifically to infection by *Y. pestis*. The Latin word *pestis*, for example (as well as the corresponding terms that derive from it in many European languages) is in fact very often used to generally designate a misfortune, a calamity, a ruin, or a generic epidemic. Similarly, *plaga* (like the Greek πληγή), which gave rise to the corresponding Italian word *piaga* and the English *plague*, designates a serious damage, a scourge or a calamity; in the case of diseases, it does not specifically indicate what type of calamity [10]. Less vague, in the sense that it indicated a contagious infectious disease, is the term *pestilentia*, introduced in the late Roman Republican age and used for example by Julius Caesar (100-44 BC) to define the epidemic that broke out in Marseille, which forced the inhabitants to surrender. The use of *pestilentia* in these contexts is influenced by the miasmatic theory and is therefore frequently connected to the climatic and orographic conditions that accompany epidemics and endemics and is a sign of the progressive affirmation of the rationalistic interpretation of epidemics to the detriment of the long-standing tendency prevalent, to consider them – not knowing the pathogens – as catastrophic events to be attributed to supernatural intervention [11].
A striking example is given by the 'plague' (νοῦσος) narrated at the opening of the *Iliad* (I.10), caused by Apollo to punish the Achaeans and their supreme leader Agamemnon. The latter had refused to return the young Chryseis, his war prey, to her father Chryses, priest of the god, chasing him away in a bad way. Chryses, having set out towards the sea, then stopped to pray to Apollo, reminding him of the many opulent sacrifices made to him and imploring her revenge:

> *the old man prayed to the lord Apollo, whom fair-haired Leto bore: "Hear me, god of the silver bow, who stand over Chryse and holy Cilla, and rule mightily over Tenedos, Sminthian god, if ever I roofed over a temple to your pleasing, or if ever I burned to you fat thigh-pieces of bulls and goats, fulfill this prayer for me: let the Danaans pay for my tears by your arrows" So he spoke in prayer, and Phoebus Apollo heard him. Down from the peaks of Olympus he strode, angered at heart, bearing on his shoulders his bow and covered quiver. The arrows rattled on the shoulders of the angry god as he moved, and his coming was like the night. Then he sat down apart from the ships and let fly an arrow: terrible was the twang of the silver bow. The mules he assailed first and the swift dogs, but then on the men themselves he let fly his stinging shafts.* [Iliad I. 35-52] [12]

The plague that appears in the Greek camp therefore serves to punish the arrogance (ὕβρις) of Agamemnon, who had dared to challenge the gods by rejecting the request of one of their priests. The same equation plague = divine punishment is present other times in Greek literature, for example in Sophocles' *Oedipus Rex* [vv. 25-30, 168-187] (around 430-420 BC). In the prologue it is narrated how the Thebans, devastated by the plague, beg the wise king Oedipus to intervene to stop the spread of the disease. In both the *Iliad* and *Oedipus Rex*, no description is made of the disease. What matters is only to underline how it is caused by the supernatural intervention of the gods, in the first case by Apollo, triggered by the wicked action of man. The symptoms of νοῦσος as well as its course are also ignored, making it impossible to exactly identify the type. The only useful detail provided by the poetic account of the Iliad, namely that it affects mules first, then dogs and finally men, corresponds to the 'classic' scheme of zoonoses, favored by promiscuity. No mention is made even of prophylaxis: the only precaution to contain the contagion seems to be the elimination of the corpses through cremation, while for the rest the Achaean camp remains totally exposed as well as its occupants, defenseless and submissive to the unraveling of the events.
Just like the cause, the remedy is also, in both cases, linked solely to the supernatural sphere. In the Iliad, the soothsayer Calchas reveals what caused the plague, who will say that it broke out because of Apollo's anger at the mistreatment of his priest; in Sophocles' tragedy, however, the cause revealed by the oracle of Delphi is the killing, which went unpunished, of the previous sovereign Laius. Both human attitudes have caused the balance to be broken, and to remedy it will be necessary to restore it by returning, respectively, Chryseis to her father and identifying and punishing Laius' murderer. The 'didactic' message conveyed by both episodes is therefore very clear: only respect for the will of the gods guarantees order and the *status quo*; on the contrary, the lack of respect towards the deities and the infringement of the rules triggers chaos and the epidemic, which is a symbolic manifestation of it.
Among the plagues mentioned in ancient sources, only very few can be attributed with certainty to *Y. pestis*. Biblical descriptions, for example, are very vague to allow for certain identification. The *Book of Samuel* [1 Sam 5] narrates the plague of the Philistines (ca. 11th century BC), sent by God as punishment for having stolen the ark of the covenant from the defeated Israelites. The disease manifests itself through 'buboes', and the people' groans, 'rose to heaven'.
Another alleged plague account relates to the siege of Jerusalem by Sennacherib's Assyrian army (701 BC). The biblical source [2 Kings 19:3] limits itself to asserting that one morning the besieged awoke to discover that during the night an angel of the Lord had killed all their enemies; however Herodotus, who also cites the episode, adds that 'when they arrived, the enemies suffered an invasion of field mice at night that gnawed at their quivers and bows and shield straps, so

Fig. 1. Tucidide (Θουκυδίδης) (Athens, 460 BC - Athens, after 404 or 399 BC) (Adapted by the authors) (Wikipedia Commons - public domain).

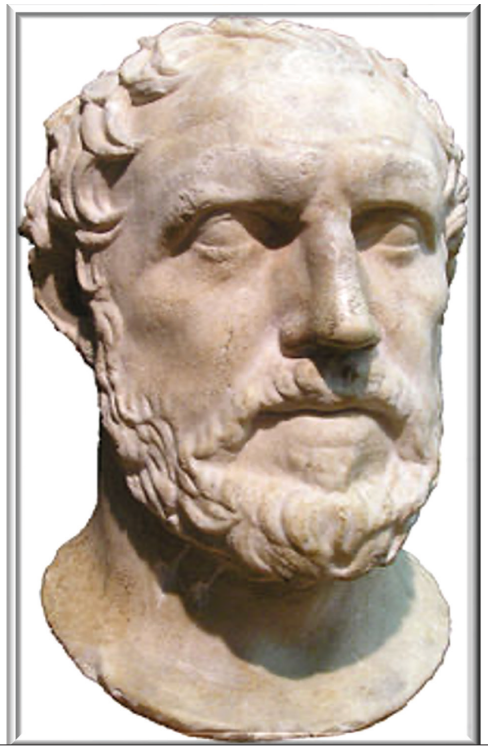

Fig. 2. The angel of death striking a door during the plague of Rome: an engraving by Levasseur after Jules-Elie Delaunay (1894) (Wikipedia Commons -public domain).

that the next day, left defenseless, they fled and fell in great numbers' [Herodotus II, 2.141] The only clue to a possible plague epidemic is the presence of rodents in large numbers, but the hint is too vague to be conclusive. As for the famous plague of Athens (430 BC), it was narrated in detail by Thucydides [*History of the Peloponnesian War* II.2, 47-54]. [13] Ever since the beginning of written evidence, it had always been supposed that a person who had recovered from a certain disease became immune to contracting it again. Indeed, some 2,500 years ago, Thucydides (460 BC-404 or 399 BC; Fig. 1), in his description of an epidemic that hit Athens, observed that "No one has ever been affected a second time, or at least fatally" [14, 15].

The plague arrived in Athens through the port at Piraeus shortly after the beginning of the Second Peloponnesian War (431-404 BC) fought between Athens and Sparta. The symptoms described have, over time, suggested its identification as typhus, Ebola or haemorrhagic fever; more likely, however, it was typhoid fever, given that its pathogen, *Salmonella enterica serovar Typhi*, was found in DNA extracted from the dental pulp of three teeth recovered from the Athenian cemetery of Kerameikos [16]. Thucydides reports the following symptoms of the disease: headache, red eyes, red throat, bad breath, sneezing, hoarseness, coughing, vomiting, convulsions, body blisters, fever, thirst, restlessness, sleeplessness, bowel ulcers, diarrhea, gangrene, memory loss.

Other plagues reported by sources also do not appear to be caused by *Y. pestis* but by other pathogens. Moreover, it was not easy for the ancients to distinguish diseases only based on symptoms, so pathologies such as measles, chickenpox and smallpox were often confused with each other and with 'plague' itself [17].

This is the case, for example, of the Antonine Plague (165–180 AD) during the reign of *Marcus Aurelius* also known as the Plague of Galen (after Galen, the Greek physician who described it) (Figure 2).

Galen knew the plague and had direct experience because he was in Rome when the plague reached the city in AD 166 and also during an outbreak among troops stationed at Aquileia during the winter of AD 168-169.

His suggestions, notes and remarks to the plague are scattered and often brief but they are interesting and enough to identify and recognize the plague as smallpox [18]. His description of the exanthema is fairly typical of the smallpox rash; the symptoms described by Galen in the *Methodus medendi* while observing the troops stationed in Aquileia – fever, diarrhea, inflammation of the pharynx and eruptions on the skin, both dry or purulent, which manifested themselves around the ninth day of illness - rather indicate a smallpox pandemic with devastating consequences [17] (Fig. 3).

The Antonine Plague was a terrible, long, and destructive epidemic that had a terrible impact on the entire Roman Empire; it felled ten thousand people in first-century Rome; it began in Mesopotamia in late AD 165 or early AD 166 during Verus' Parthian campaign, and quickly spread to Rome. It was possibly contracted and spread by soldiers who were returning from the exhausting and challenging campaigns of war in the Near East.

It lasted at least until the death of Marcus Aurelius in AD 180. This pandemic then spread across the Empire to North Africa, Western Asia and other parts of Europe; it is believed to have caused five million deaths.

In the same way, the Plague of Cyprian (around 250-266 AD) (Fig. 4), which arrived in Rome after having devastated Africa and reached Britain, touching the *Vallum Hadriani*, favored by rapid emptying of cities. The disease

Fig. 3. Galen (Κλαύδιος Γαληνός). An 18th-century engraving by Georg P. Busch (Wikipedia Commons -public domain).

Fig. 4. 16th-century painting of Saint Cyprian, who documented the plague in his writings (Wikipedia commons - public domain).

takes its name from Archbishop Cyprian of Carthage, who described it in *De mortalitate* [Chapter 14]:

> *Now the fact that the belly, gripped by cramps, disperses the body's strength in an uncontrolled dysentery, that deep within the bones the infection flares up causing sores in the throat and to expand by boiling, that the intestines are shaken by continuous vomiting, that the eyes burn with bloodshot, that the feet or other limbs have to be amputated due to the contagion of the unhealthy gangrene, which due to this loss or damage to parts of the body, while weakness creeps in everywhere, the step becomes uncertain, the hearing fades, the sight becomes dark, all this is useful to show our true faith.*

As we can see, however, these symptoms, recently rediscussed by Harper, would seem to point in the direction of a hemorrhagic fever like Ebola rather than the plague [19].

No doubt however for the well-known epidemic that raged in the Byzantine Empire, especially in Constantinople, between 541 and 542 during the reign of Justinian I (527-565) and which we know well from the detailed account given by Procopius of Caesarea (490-565) [Bellum Persicum 2.22] and other authors such as Gregory of Tours and Paul the Deacon [20].

Considered the first plague pandemic in history [21], the Plague of Justinian caused a very high number of victims – almost 100 million according to Procopius – contributing to the decline of what remained of Roman Empire and the definitive transition between the Classical world and the Middle Ages. The *Y. pestis* bacillus responsible for the disease was found in some skeletons buried in Sens (France) and Aschheim, Bavaria (6th century); the analyzes conducted in 2014 by a team of scholars on the DNA extracted from the teeth of two individuals (A120 and A76) buried in the latter burial ground also demonstrated that the genomes belonged to a pathogen form a now extinct strain [22].

From the 6th century until around the year 1000, no major plagues or plagues occurred in Europe except for leprosy or scrofula [23]. However, around the turn of the millennium a milder climate (especially in the continental West), together with the recovery of trade

and the introduction of various technological innovations improved the quantity and quality of crops. The richer diet and the growth in individual living standards, combined with the sense of greater security conferred by the progressive stabilization of political structures, led to a progressive increase in the population which, however, in the long run led to the growth of urban development, with consequent overcrowding of the cities and deterioration of general hygienic conditions. Climatic conditions worsened again in the 14th century, when temperatures increased rains and the drop in temperature corresponded to a contraction in agricultural production which gave rise to various episodes of famine, leaving the population exhausted. The conditions were ideal for the outbreak of the second plague pandemic caused, once again by *Y. pestis*, the infamous Black Death which reached its peak in Europe from 1347 to 1351 causing about 15 to 25 million deaths.

The Black Death or bubonic plague

The bacillus appeared around the 1320s in Asia and reached the Crimea through the Russian steppes. Here the Tatar khan Ganī Bek occupied in the siege of Caffa (today's Fedosia, Crimea) ordered the corpses of the infected dead to be thrown inside the city walls as an *ante-litteram* 'bacteriological weapon'. From Caffa, a Genoese colony at the time, the plague was brought to Constantinople by Ligurian ships, finally landing in Europe from the ports of Genoa, Messina and Marseille to spread throughout the continent until reaching, in the space of three years, the extreme north and the Scandinavian peninsula.

Accounts of the time show that, as in ancient times, the disease was considered a divine punishment which desperately attempted to be remedied through prayers, penances, processions and pilgrimages. The medicine of the time ignored the aetiology of the disease and proved completely powerless in containing the pandemic. A report compiled at the University of Paris, for example, attributed the blame for the plague to some unknown and inscrutable celestial event:

> *An astral conjunction, together with other conjunctions and eclipses, is the real cause of the gravely deadly corruption of the air around us, source of mortality and famine [...]. We believe that the present epidemic or plague comes directly from the air corrupted in its substance, and not only from the alteration of its qualities. This fact must be understood in this way: since the air is, in fact, by its nature pure and clear, it does not putrefy and does not become corrupt unless evil vapors are mixed with it, following any cause.*
>
> *Many corrupt vapors, at the time of the said conjunctions and by their own virtue, rose from the land and the sea and spread into the air itself; many of those vapors, under the influence of the frequent blowing of hot and humid and violent southerly winds, owing to the damp and strange vapors which those winds carried with them, have corrupted the air in its very substance. Consequently, this air, thus corrupted, necessarily penetrating the lungs, attracted by breathing, corrupts the gaseous substance that is found in it and, due to the humidity, causes everything that is close to it to putrefy. This is where the fevers arise from nature, which corrupt the principle of life [...]. We cannot hide the fact that, when the epidemic proceeds from divine will, we have no other advice to give than to humbly entrust ourselves to this will, without abandoning the doctor's prescriptions'* – (translation of the quoted passage by the Authors) [24].

In the impossibility of identifying a certain cause, scapegoats were sought for, identified, as often happens in similar cases, in the 'weakest' and most marginal categories of society, especially women and Jews.

As for prophylaxis, it was almost non-existent: doctors examined patients wearing a sort of beak-shaped mask - the use of which was perfected in the seventeenth century, an experienced French physician named Charles de Lorme (1584–1678), (who practiced in various regions of Europe during the 17th century) and was court doctor of Louis XIII (1601-1643) [25].

In 1619, the bubonic plague erupted in Paris, and Delorme created the "plague preventive costume" (Fig. 5), which consisted of a long overclothing garment which went from the neck all the way down to the ankle; the gist was that the air could not penetrate. The outfit also contained gloves, boots, and a hat; the hat was made of waxed leather. The hat was not really part of the costume; it was more of a symbol of the physician's position as a medical practitioner. There was also a mask which had a nose half a foot long, shaped like a beak, filled with perfume with only two holes, one on each side near the nostrils; it could suffice to breathe and to carry along with the air one breathes the impression of the drugs enclosed further along in the beak. The mask is filled with aromatic herbs to help the wearer bear unpleasant smell. The eyes were also covered and protected with specs.

The doctor also has a stick to examine patients without touching them. With this complete set of equipment, Delorme and other physicians could assist patients who required their help [26].

During the 1619 French plague, Delorme was seen as a star, assisting numerous people struck by the plague. His clothing received many grants, and he was much appreciated; his name was associated with the term 'the beak doctor'.

Alternatively, those who could (like the Pope in Avignon) practiced fumigation with herbs and aromatic substances to purify the air [27].

The Black Death took around four years to make its way along the Silk Road from the Steppes of Central Asia, via Crimea, to the Western most parts of Europe, the Middle East and North Africa. The Black Death had epochal consequences on late medieval European society, triggering an economic recession that caused revolts by peasants in various parts of Europe, such as

Fig. 5. Copper engraving of a plague doctor of 17th-century Rome. (Wikipedia commons - public domain).

the jacquerie in France and England, and in Florence the riot of the Ciompi (wool workers), as well as the strengthening of the feudal system in Eastern Europe. In the long run, however, the demographic collapse imposed a redistribution of assets and incomes, creating new, better-paid jobs, while the shortage of labor led to the cultivation of only the most profitable and fertile land and stimulated new technological inventions. Those who survived therefore experienced a well-being that they had never achieved before. Even from a cultural point of view, the epochal tragedy represented a break with respect to values that had remained unchanged for centuries. Having called into question religious certainties, the man who escaped the scourge had to find a new role for himself within a universe in which everything was more precarious and he himself now appeared to be the direct architect of his own destiny. Despite its tremendous burden of mourning, the Black Death projected Europe into Humanism, closing the Middle Ages and starting a new era. A rough estimate is that 25 million people in Europe died from plague during the Black Death. By the end of the 1800s, developments in bacteriology and infection control meant that medical researchers were able to observe and investigate the disease in detail for the first time. Three types of vaccines [28, 29] namely killed whole-cell (KWC) vaccines, live attenuated vaccines (EV76), and recombinant subunit vaccines, have been developed against plague.

Although KWC and EV76 vaccines provide protection against plague in animal models, both have side effects and need repeated immunizations for developing immunity in humans. Analysis of centuries-old DNA from both victims and survivors of the Black Death has identified key genetic differences that helped people survive the plague. Evidence has been put forward that a gene variant that helped people survive the Black Death also significantly lessens the impact of COVID-19 [30]. The recent COVID-19 (2020) pandemic has brought the global population back to confront a world unprepared to deal with a health emergency of such magnitude, despite the fact that over time the cinema and media have helped shape the collective perception of pandemics, playing an educational role but also fueling myths and beliefs [31]. The contribution of health professionals, particularly WHO physicians [32], has been crucial, especially with the experience gained during the 2003 SARS outbreak that cost Dr. Carlo Urbani his life [33]. Early recognition of the disease and its systemic implications [34], in fact, coupled with the implementation of preventive measures, proved essential to improve treatments and limit damage. Historical containment measures such as quarantine and curfews have proven their relevance [35] in stemming the spread of infection as much as possible, while highlighting the need to prioritize preventive medicine during health crises rather than allowing it to be influenced by political considerations [36].

Pandemics are not only health emergencies, but also events with profound social, political, and systemic implications. Historical experience and preventive medicine remain central to managing and preventing future health crises, while international collaboration and science must guide global responses.

Concluding remarks

Our essential review of the major epidemics of the ancient world and the Middle Ages allows us to draw the following general conclusions: 1. Psychological mechanisms shared by world populations and ancestral nature have always characterized the way in which the human species has tried to 'rationalize' sudden epidemic phenomena and has tried to counter them. 2. The application of a historical-medical, archaeological and paleopathological approach to these problems not only allows scholars to reconstruct the origin and evolutionary path of infectious diseases, but also complements historical research in the strict sense, determining the global changes level of communities and societies shocked by the infectious phenomenon. 3. Epidemics have always represented a powerful catalyst in history. 4. A multidisciplinary approach to past epidemics can provide an interesting and useful key to understanding the pandemic events that characterize contemporary times. The next pandemic could be imminent, driven by factors such as urbanisation, climate change, global travel and zoonotic diseases; notwithstanding the enlightening insights gained from the recent outbreak, the medical community and the global population at large continue to exhibit deficiencies in their preparedness for future virus-based crises [37]. A review of the historical records of plague [38] and SARS [39] reveals that pandemics have a significant impact not only on public health but also on social and political dynamics [40]. It

is evident that innovation in health responses and global collaboration are vital to prevent and contain future epidemic threats [41]. The eradication of a pandemic is a complex process that necessitates a multidisciplinary approach, encompassing the eradication of infectious diseases and the utilisation of novel technologies [42, 43]. The effective management of infectious diseases requires a multidimensional approach that integrates innovation, global collaboration, and historical analysis [44-46].

Note

A preliminary version of this research was presented at the congress *Schemata, la città oltre la forma.* Università degli studi di Catania & Università degli studi della Campania "Luigi Vanvitelli", Siracusa (Italy), 26-28 February, 2020. Moreover, apart from reference [8], for which a direct quotation was inserted, all other citations of classical sources were limited to reporting the relevant passage without giving a full bibliographic reference.

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Informed consent statement

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Data availability statement

Not applicable.

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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

FMG, EV, EP, LI, DR: designed the study; FMG, EV, EP, LI, DR: conceived the manuscript; FMG, EV, EP, LI, DR: drafted the manuscript; VV, LI, MV, MM, DR: revised the manuscript; LI, MM, MV, DR, EV: performed a search of the literature; DR, MV, EV,VV: critically revised the manuscript; FMG, EV, EP, LI, DR: conceptualization, and methodology; FMG, EV, EP, LI, DR, MM, MV: investigation and data curation; FMG, EV, EP: original draft preparation; MV, MM, VV: editing. All authors have read and approved the latest version of the paper for publication.

References

[1] Worldometers. COVID-19 coronavirus pandemic. Available at: https://www.worldometers.info/coronavirus/#google_vignette (Accessed on: 8 August 2024).

[2] Galassi FM, Pate FD, You W, Gurr A, Lucas T, Antunes-Ferreira N, Varotto E, Habicht ME. Pandemic realism as the indispensable political precondition for global disease eradication, Public Health 2022;212:55-7. https://doi.org/10.1016/j.puhe.2022.08.016.

[3] Galassi FM, Varotto E. Sinophobia as the disease and palaeopathology as the cure: response to Adja et al. Public Health 2020;187:189-90. https://doi.org/10.1016/j.puhe.2020.06.058.

[4] 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.

[5] Raoult D, Mouffok N, Bitam I, Piarroux R, Drancourt M. Plague: history and contemporary analysis. J Infect 2013;66:18-26. https://doi.org/10.1016/j.jinf.2012.09.010.

[6] Wang W, Li X, Wu J, Fu X, Li B. Imaging analysis of pneumonic plague infection in Xizang, China: a case report and literature review. BMC Pulm Med 2024;24:378. https://doi.org/10.1186/s12890-024-03187-3.

[7] Butler T. Plague into the 21st century. Clin Infect Dis 2009;49:736e42. https://doi.org/10.1086/604718.

[8] Wong D, Wild MA, Walburger MA, Higgins CL, Callahan M, Czarnecki LA, et al. Primary pneumonic plague contracted from a mountain lion carcass. Clin Infect Dis 2009;49:e33e8. https://doi.org/10.1086/600818.

[9] Wong JD, Barash JR, Sandfort RF, Janda JM. Susceptibilities of Yersinia pestis strains to 12 antimicrobial agents. Antimicrob Agents Chemother 2000;44:1995e6. https://doi.org/10.1128/AAC.44.7.1995-1996.2000.

[10] Online Etymology Dictionary, sub voce 'plague', online. Available at: https://www.etymonline.com/word/plague (Accessed on: 8 August 2024).

[11] Stock F. Il lessico del contagio. In: Radici Colace P, Zumbo A, editors. Letteratura scientifica e tecnica greca. Atti del Seminario internazionale di studi. Messina: EDAS 2000, pp. 55-59.

[12] Homer. The Iliad with an English (translation by A.T. Murray). Cambridge, MA: Harvard University Press; London: William Heinemann, Ltd 1924. Online at: https://www.perseus.tufts.edu/hopper/text?doc=Perseus%3Atext%3A1999.01.0134%3Abook%3D1%3Acard%3D33 (Accessed on:8 August 2024).

[13] Tucidide. La guerra del Peloponneso. In: Canfora L, ed. Torino: Einaudi-Gallimard 1996.

[14] 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-E104. https://doi.org/10.15167/2421-4248/jpmh2024.65.1.3229.

[15] Orsini D, Martini M. From inoculation to vaccination: the fight against smallpox in Siena in the 18th and 19th centuries. Infez Med 2020;28:634-41.

[16] Olson PE, Hames CS, Benenson AS, Genovese EN. The Thucydides syndrome: Ebola déjà vu? (or Ebola reemergent?). Emerg Infect Dis 1996;2:155-56. https://doi.org/10.3201/eid0202.960220.

[17] McNeill WC. Plagues and Peoples. New York: Anchor Books Doubleda 1976.

[18] Haas C. The Antonine plague. Bull Acad Natl Med 2006;190:1093-8.

[19] Harper K. Pandemics and passages to late antiquity: rethinking the plague of c. 249-270 described by Cyprian. JRA 2015;28:223-60.

[20] Sabbatani S, Manfredi R, Fiorino S. La peste di Giustiniano (prima parte). Infez Med 2012;20:125-39.

[21] Naphy W, Spicer A. La peste in Europa. Bologna: Il Mulino; 2006.

[22] Wagner DM, Klunk J, Harbeck M, Devault A, Waglechner N, Sahl JW, Enk J, Birdsell DN, Kuch M, Lumibao C, Poinar D, Pearson T, Fourment M, Golding B, Riehm JM, Earn DJ, Dewitte S, Rouillard JM, Grupe G, Wiechmann I, Bliska JB, Keim PS, Scholz HC, Holmes EC, Poinar H. Yersinia pestis and the plague of Justinian 541-543 AD: a genomic analysis. Lancet Infect Dis 2014;14:319-26. https://doi.org/10.1016/S1473-3099(13)70323-2.

[23] Nanni P. Per un quadro ambientale e biologico: il periodo caldo medievale e la variabilità climatica. In: Franceschi F, ed. La crescita economica dell'Occidente medievale. Un tema storico non ancora esaurito. Atti del XXV Convegno Internazionale di studi. Roma: Viella 2017, pp. 69-91.

[24] Guénin G, Novillac J. Lectures Historiques. Paris: Hachette 1926.

[25] Pizon P. Charles de Lorme - médecin des bains de Bourbon – L'Archambault (1584-1678). Presse Med 1953;61:1786-8.

[26] Mattie HJ. Men in Tights: Charles De Lorme (1584-1678) and the First Plague Costume. European Journal for the History of Medicine and Health 2023;81:1-13. https://doi.org/10.1163/26667711-bja10033.

[27] Lippi D, Varotto E, Boccalini S, Bechini A, Donell ST, Galassi FM. Face Masks to Prevent Infectious Diseases: An Historico-Anthropological Perspective in the Light of the Recent Pandemic. Anthropologie (Brno) 2023;61:211-15. https://doi.org/10.26720/anthro.23.06.12.2.

[28] Merlin M. Vaccination antipesteuse : le passé et les perspectives d'avenir. Bul Soc Pathol Exot 1999;92:427-31.

[29] Rosenzweig JA, Chopra AK. The future of plague vaccines: hopes raised by a surrogate, live-attenuated recombinant vaccine candidate. Expert Rev Vaccines 2012;11:659-61. https://doi.org/10.1586/erv.12.34.

[30] Klunk J, Vilgalys TP, Demeure CE, Cheng X, Shiratori M, Madej J, Beau R, Elli D, Patino MI, Redfern R, DeWitte SN, Gamble JA, Boldsen JL, Carmichael A, Varlik N, Eaton K, Grenier JC, Golding GB, Devault A, Rouillard JM, Yotova V, Sindeaux R, Ye CJ, Bikaran M, Dumaine A, Brinkworth JF, Missiakas D, Rouleau GA, Steinrücken M, Pizarro-Cerdá J, Poinar HN, Barreiro LB. Evolution of immune genes is associated with the Black Death. Nature 2022;611:312-9. https://doi.org/10.1038/s41586-022-05349-x.

[31] Simonetti O, Zatta M, Monticelli J, Orsini D, Martini, M. Filmdemics: The History of Modern Pandemics Through the Lens of Cinema. Medicina nei Secoli 2023,35:111-30. https://doi.org/10.13133/2531-7288/2823.

[32] Martini M. WHO Doctor and Hero of SARS in 2003. Emerg Infect Dis 2023;29:1933-36. https://doi.org/10.3201/eid2909.212412.

[33] Martini M. SARS-CoV-2 (Covid-19) and the teaching of Carlo Urbani in Vietnam: a lesson from history almost 20 years after SARS. J Prev Med Hyg 2021;62(Suppl. 1):E584-E6. https://doi.org/https://doi.org/10.15167%2F2421-4248%2Fjpmh2021.62.1S3.2134.

[34] Grassi T, Varotto E, Galassi FM. COVID-19, a viral endocrinological disease? Eur J Intern Med 2020;77:156-7. https://doi.org/10.1016/j.ejim.2020.06.003.

[35] Galassi FM, Habicht ME, Pate FD, Varotto E. Flying higher than politics: The goal of preventive medicine at the time of the COVID-19 pandemic. Eur J Intern Med 2021;86:102-3. https://doi.org/10.1016/j.ejim.2020.12.021.

[36] Galassi FM, Cofone L, Pindinello I, Ribatti D, Smith DL, Vaccarezza M, Varotto, E. The curfew bell and the COVID-19 pandemic: a historical-medical perspective based on the Italian case. Int J Infect Dis 2024;147:107217. https://doi.org/10.1016/j.ijid.2024.107217.

[37] Sky news. Available at: https://news.sky.com/story/next-pandemic-is-around-the-corner-expert-warns-but-would-lockdown-ever-happen-again-13097693 (Accessed on: 22 September 2024).

[38] Varlık N. The plague that never left: Restoring the Second Pandemic to Ottoman and Turkish history in the time of COVID-19. New Perspect Turk 2020;63:176-89.

[39] Smith R. Did we eradicate SARS? Lessons learned and the way forward. Am J Biomed Sci Res 2019;6:152-5.

[40] Prince R. Pandemic publics: how epidemics transform social and political collectives of public health. In: Kelly A, Keck F, Lynteris C, eds. The anthropology of epidemics. London: Routledge 2019, pp. 135-53.

[41] Dowdle W, Hopkins D. The eradication of infectious diseases: Report of the Dahlem Workshop on the Eradication of Infectious Diseases, Berlin, March 16-22, 1997. Chichester, England: Wiley.

[42] White A. How pandemics end: Learning the lessons of history. World Politics Review (Nov 2020). Retrieved from: https://www.worldpoliticsreview.com/articles/29188/how-pandemics-end-learning-the-lessons-of-history.

[43] Fryer B, Quick JD. End of Epidemics: The Looming Threat to Humanity and How to Stop It. New York: St. Martin's Press 2018.

[44] Appleby A. The disappearance of plague: a continuing puzzle. Econ Hist Rev 1980;33:161-73.

[45] Vallès X, Stenseth NC, Demeure C, Horby P, Mead PS, Cabanillas O, Ratsitorahina M, Rajerison M, Andrianaivoarimanana V, Ramasindrazana B, Pizarro-Cerda J, Scholz HC, Girod R, Joseph Hinnebusch B, Vigan-Womas I, Fontanet A, Wagner DM, Telfer S, Yazdanpanah Y, Tortosa P, Carrara G, Deuve J, Belmain SR, D'ortenzio E, Baril L. Human plague: an old scourge that needs new answers. PLOS Negl Trop Dis 2020;14:e0008251. https://doi.org/10.1371/journal.pntd.0008251.

[46] Peckham R. Where has SARS gone? The strange case of the disappearing coronavirus. Somatosphere; 2016. Available at: http://somatosphere.net/2016/where-has-sars-gone-the-strange-case-of-the-disappearing-coronavirus.html (Accessed on: 22 September 2024).

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HISTORY OF MEDICINE AND ETHICS

War and Health: the devastating impact of conflict on Wellbeing and Humanitarian Crises

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Keywords

War • Infectious Diseases • Vaccine Hesitanc • Herd Immunity • Epidemiology • Public Health

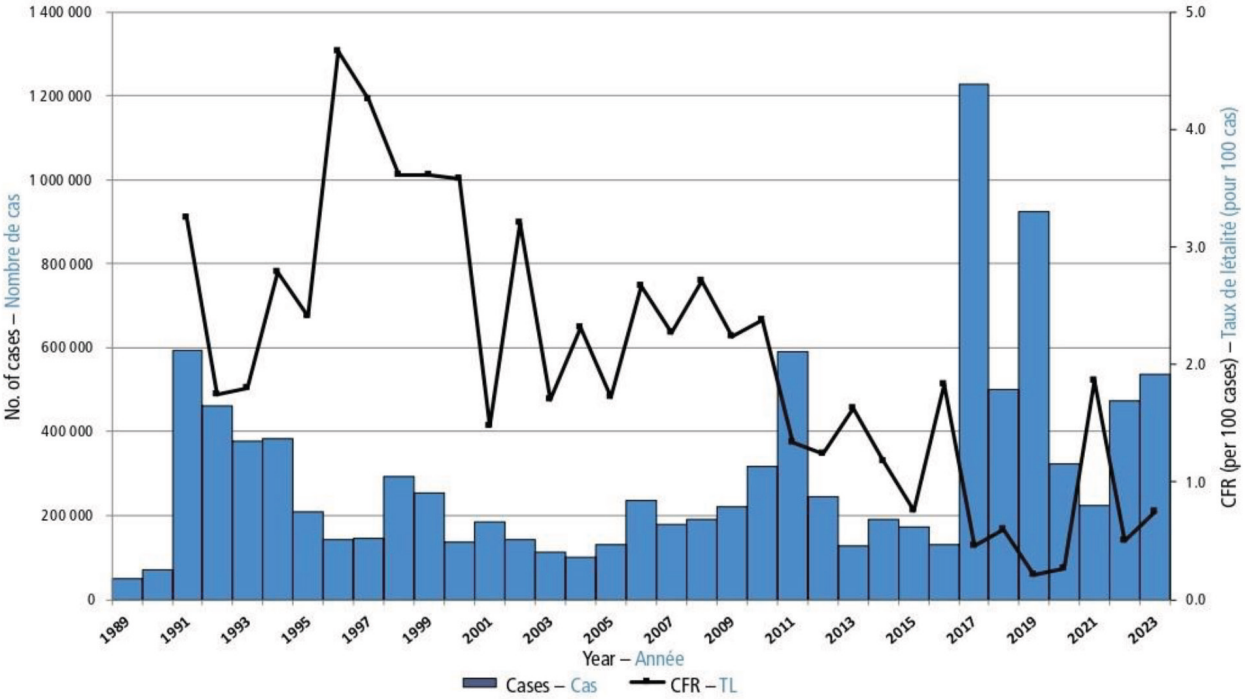
Summary

Health is a precious asset, essential for both individuals and communities. The wars that have affected various parts of the world in recent years have had a detrimental impact on health, leading to malnutrition and an increased vulnerability to epidemic diseases among the population, especially the poorest.
Hospitals and healthcare facilities themselves have become primary strategic targets in many war zones. The destruction of infrastructure and hospitals, along with challenges in obtaining clean water and access to medicines, has contributed to the resurgence of epidemic diseases in countries where they had been eradicated. Additionally, the difficulty in ensuring vaccination programs for children raises the risk of these diseases spreading to areas typically free from them.
The authors reflect on the consequences of wars on the health of populations and the close link between health and peace, presenting the latest data on ongoing epidemics in countries affected by war.

The diseases caused by the conflicts that have been raging in many parts of the world in recent years demonstrate once again the close link between health and peace.
Health is a precious asset, one that is fundamental for both the individual and the community. Unfortunately, however, war has a deleterious effect on health, causing malnutrition and a predisposition to epidemic diseases in the population, especially among its poorest members [1]. Even hospitals and health facilities have become major strategic targets in many theatres of war [2], despite the fact that the Geneva Conventions clearly state that in no case can healthcare facilities and personnel be targeted by military operations [3].
People's health is constantly endangered by wars, as well as by the famines and infectious diseases that follow. For instance, in 2022, cholera broke out again in Syria [4], a country that has been the scene of a bloody war for almost 15 years, and was further devastated by a destructive earthquake in February 2023.
Massive displacements of people have undermined sanitation and waste management systems. Compounding this issue are the significant reductions in functioning health facilities, which are becoming increasingly overcrowded, a shortage of medical supplies and a lack of healthcare personnel. Water resources are increasingly scarce and the population is very often forced to drink unsafe water [5].
A similar situation has emerged in Sudan, although this country remains almost entirely absent from global news and debate, partly because the U.S. and European nations are preoccupied with the conflicts in Ukraine and Gaza, which are consuming their political and military resources. As a result, in Sudan there has been little international assistance, and healthcare facilities, around 70% of which are not operating at full capacity, are severely under-resourced [6].
Due to the civil war that broke out in April 2023, 14 million children in Sudan have been left to fend for themselves. As the war rages on, famine and disease are on the rise [7].
The World Health Organization has reported that yet another cholera epidemic was officially declared by the Federal Ministry of Health (FMoH) on 12 August 2024, following a new wave of cholera cases was documented on 22 July 2024. The previous epidemic had technically ended in June 2024. Between 22 July and 1 September, a total of 2,895 cholera cases were reported, resulting in 112 associated deaths and a case fatality rate (CFR) of 3.9% [8].
Unfortunately, cholera cases in the world have been significantly increasing over the past three years, with conflicts and the destruction of infrastructure contributing to this rise, as shown by data from the Weekly epidemiological record, published on September 6, 2024 [9] (Fig. 1).
Similarly, in the spotlight of the international media, the lives of the Ukrainian people are at risk not only due to attacks by the Russian armed forces, but also because of the destruction of many infrastructures and hospitals, as well as the difficulty of obtaining medicines and vaccinating children. In this scenario, the population

https://doi.org/10.15167/2421-4248/jpmh2024.65.3.3412

Fig. 1. Annual cholera cases and case fatality rate (CFR) reported by year, 1989-2023 (Data World Health Organization. Weekly epidemiological record n. 36/2024).



is in constant danger of the spread of epidemic diseases such as measles [10], poliomyelitis [11] and tuberculosis [12].

Another country to consider is Yemen. After a decade of conflict, it is in economic collapse, with poverty, mass population displacement and a destroyed healthcare and social system.

In Yemen, measles and rubella are the main causes of child mortality and congenital disabilities, yet both diseases can be prevented and avoided through vaccines.

A huge number of children are unvaccinated; Save the Children data published in June 2024 shows that the percentage of children who have never had a routine vaccination - defined as "zero-dose" children - is three times higher in conflict zones (22.7%) than elsewhere around the world (7.1%) [13].

In countries such as Sudan, Yemen and Syria there are almost 87% of the total "zero dose" children.

At the end of November 2023, according to the World Health Organization (WHO) 50,795 suspected cases of measles and rubella were reported in Yemen, associated with more than 560 deaths: a strong increase compared to the 27,000 suspected cases and 220 deaths recorded in 2022 [14].

According to WHO and UNICEF data, the number of children worldwide who received three doses of diphtheria, tetanus, and pertussis (DTP) vaccine in 2023 – a key indicator for global immunization coverage – amounted at 84% (108 million).

At the same time, the number of children who did not receive a single dose of vaccine increased from 13.9 million in 2022 to 14.5 million in 2023 [15]. The latest trends show that many countries don't vaccinate the children because several parents have doubts about the effectiveness and safety of vaccines so many children not vaccinated can transmit vaccine- preventable diseases at schools and in the community.

This is hands down a dangerous situation for the children; we also point out that half of the unvaccinated children in the world live in 31 countries affected by conflict, and in those geographical areas they are at risk of contracting some preventable diseases due to the lack of food and health services for the population [16].

Among the numerous ongoing conflicts, the disastrous situation in the Gaza and the West Bank must warrants attention. The Israeli-Palestinian conflict has been marked by repeated violations of international human rights. An investigation by The Guardian newspaper, Amnesty International and the Human Rights Watch documented as early as 2009 the exploitation of Gaza's civilian population as human shields and the use of white phosphorus in military operations [17].

As of today, 1.9 million people in Gaza, out of a total population of 2 million, are displaced. They live in makeshift shelters and overcrowded refugee camps, which they are often forced to abandon to avoid being targeted by Israeli bombings. In the Gaza Strip, 31 out of 36 hospitals have been damaged or destroyed due to Israeli attacks. The region's_infrastructure has been completely devastated, with the waste and sewage disposal network demolished, and access to drinking water is critically limited.

Fig. 2. Polio cases detected worldwide as of August 2024 (data "Global Wild Poliovirus 2017 - 2024". Global Polio Eradication Initiative GPEI. 24 August 2024).

Country	Wild cases	Circulating vaccine-derived cases	Transmission status	Type
Afghanistan	18	0	endemic	WPV1
Pakistan	16	0	endemic	WPV1
Nigeria	0	49	cVDPV only	cVDPV2
Yemen	0	33	cVDPV only	cVDPV2
DRC	0	5 9	cVDPV only	cVDPV1 cVDPV2
Ethiopia	0	11	cVDPV only	cVDPV2
Niger	0	9	cVDPV only	cVDPV2
South Sudan	0	8	cVDPV only	cVDPV2
Chad	0	8	cVDPV only	cVDPV2
Indonesia	0	7	cVDPV only	cVDPV2
Angola	0	6	cVDPV only	cVDPV2
Guinea	0	5	cVDPV only	cVDPV2
Somalia	0	3	cVDPV only	cVDPV2
Liberia	0	1	cVDPV only	cVDPV2
Mali	0	1	cVDPV only	cVDPV2
Benin	0	1	cVDPV only	cVDPV2
Mozambique	0	1	cVDPV only	cVDPV1
Palestine	0	1	cVDPV only	cVDPV2
Total	34	158		

A similar scenario is now being seen in Lebanon, where approximately 346,000 people have been forced to leave their homes due to the ongoing violence stemming from Israeli strikes and attacks. Moreover, the government states that this number could grow to 1 million, with a significant portion of those displaced being women and children. Once again, the humanitarian situation is alarming, as displaced families struggle with inadequate access to basic needs such as food, water, and healthcare. Women and children, in particular, face heightened risks of exploitation and abuse in such chaotic environments [18].

In July 2024, the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) reported the high risk of the spread of polio in Gaza, following the detection of viral traces in six wastewater samples in the central part of Gaza in June. Moreover, *o*n August 23, polio was confirmed in an 11-month-old boy, who was left paralyzed. In this situation, tens of thousands of children under five years old are now at risk of contracting polio; indeed, 50,000 children have been born in Gaza alone since October 2023, and thus are without vaccination coverage.

From the latest data provided in August 2024 by the Global Polio Eradication Initiative (GPEI), it is evident that polio tends to recur constantly. In addition to the two countries where it remains endemic, Afghanistan and Pakistan, polio is also present in those countries that are characterized by conditions of extreme poverty due to environmental phenomena and wars (Fig. 2).

Despite these challenges, an agreement was reached that allowed for more than 640,000 children under the age of 10 to begin receiving the new oral polio vaccine type 2 (nOPV2), starting from the 1st of September. During the first round of an emergency vaccination campaign conducted in three phases from September 1 to 12, 2024, approximately 560,000 children under ten were vaccinated against polio in the Gaza Strip [19].

This urgent, temporary humanitarian response aimed at preventing the spread of polio, which has resurfaced in Gaza after 25 years with the circulating variant of poliovirus type 2 (cVDPV2). All parties are respecting this humanitarian pause, and there is hope from various stakeholders that this positive momentum will continue. This will not only facilitate the vaccination of children against polio but also to prevent or treat the many other infectious diseases that can spread at any moment in this devastated land.

However, for a polio vaccination campaign to be effective, it must be able to reach at least 95% of children, and it is clear that such a percentage is difficult to achieve in any country at war. Furthermore, it is evident that vaccines alone can only be part of the effort to stop the spread of the virus. To prevent future epidemics, whether in Gaza, Ukraine, Sudan or Lebanon peace and health equality must be restored.

Only by restoring peace can we guarantee access to healthcare, vaccines, and medicines for the entire population. Ensuring access to safe, clean and treated water, along with adequate hygiene facilities, is essential for preventing the spread of infectious diseases.

Any ceasefire or pause in hostilities will be crucial, such in the case of Gaza, is crucial for enabling full humanitarian access, not only to vaccines but also to the full range of assistance necessary to support the basic needs of civilians.

Moreover, to ensure safe and sustainable access to healthcare, advocating for peace and finding solutions to ongoing conflicts must remain an absolute priority. It is essential to allocate resources to healthcare aid and personnel. Only in this way can we effectively control epidemic outbreaks that could otherwise escalate severely at any moment.

Support for peace is therefore essential from a healthcare perspective to limit epidemics and save a significant number of lives. It is clear that peace is equally crucial in preventing these epidemics from spreading to countries—such as those in Europe—that seem secure. In these regions, outbreaks could have serious health consequences for the population, partly due to declining vaccination rates. Over the past 15 years, the great clinical success of vaccinations has, in a way, also created its paradoxical limitation. In

wealthy, developed Western countries like the United States and those of Western Europe, the disappearance or significant reduction of infectious diseases has diminished the perceived importance of vaccination. At the same time, the increased use of the internet and social media as sources of information has contributed to spreading news sometimes lacking any scientific basis. In addition to misinformation, there is the attitude of those who, in the face of the highly unlikely risk of an adverse vaccine reaction, overlook the clear benefits of immunization against disease, allowing doubts and suspicions to guide them. This fuels vaccine hesitancy, which, as history shows, has existed since Edward Jenner's discovery of the vaccine in the late 18th century [20]. Today, however, it is reaching levels that threaten herd immunity.

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Authors' contributions

DO: designed the study. MM e DO: conceived the manuscript. MM e DO: drafted the manuscript. LV, RP: preliminary revision of the manuscript. MM, DO, LV, EM: performed a search of the literature. LV, EM, RP: critically revised the manuscript. LV, EM, RP: conceptualization, and methodology. LV e EM: investigation and data curation. MM e DO: original draft preparation. LV e EM: editing. All authors have read and approved the latest version of the paper for publication.

References

[1] Levy BS. From Horror to Hope. Recognizing and Preventing the Health Impacts of War. New York: Oxford University Press 2021, pp. 124-6.

[2] Dentico N. Una pace integrale, per cambiare il clima della storia. In: Fateh-Moghadam P, ed. Guerra o salute. Dalle evidenze scientifiche alla promozione della pace. Roma: Il Pensiero Scientifico Editore 2023.

[3] The Lancet. Russia's invasion of Ukraine: an attack on health. Lancet 2023;401:617. https://doi.org/10.1016/S0140-6736(23)00387-2

[4] Orsini D, Martini M. The insidious return of cholera in the Eastern Mediterranean Region, Lebanon and Syria: a worrying signal! Past, present, and future forthcoming. J Prev Med Hyg. 2023;64:E27-E33. https://doi.org/10.15167/2421-4248/jpmh2023.64.1.2910.

[5] Alhaffar MBA, Gomez MDMM, Sigua JA, Eriksson A. The cholera outbreak in Syria: a call for urgent actions. IJID Reg 2023;8:71-4. https://doi.org/10.1016/j.ijregi.2023.06.005.

[6] United Nations. The world must 'wake up and help Sudan out of the nightmare of conflict', says WHO's Tedros. Available at: https://news.un.org/en/story/2024/09/1154056 (Accessed on: 03/10/2024).

[7] Martini M, Orsini D. The ghost of polio haunts us once again. The appeal of the scientific community is clear: "Vaccinate your kids today!". Vaccine 2023;41:5338-41. https://doi.org/10.1016/j.vaccine.2023.07.029.

[8] OCHA (United Nations Office for the Coordination of Humanitarian Affairs. Sudan Humanitarian Update (1 September 2024). Available at: https://www.unocha.org/publications/report/sudan/sudan-humanitarian-update-1-september-2024 (Accessed on: 16/09/2024).

[9] World Health Organization. Weekly Epidemiological Record 2024;99:479-96.

[10] Orsini D, Martini M. Measles: a new danger for Ukraine's children! The need for an effective and timely vaccination prevention campaign for an insidious disease that comes from afar. J Prev Med Hyg 2023;64:E204-8. https://doi.org/10.15167/2421-4248/jpmh2023.64.2.2996.

[11] Martini M, Orsini D. Armed conflict in the world threatens the eradication of Poliomyelitis: risks of humanitarian crises. Pathog Glob Health 2022;116:267-8. https://doi.org/10.1080/20477724.2022.2081785.

[12] Holt E. Tuberculosis services disrupted by war in Ukraine. Lancet Infect Dis 2022;22:e129. https://doi.org/10.1016/S1473-3099(22)00214-6.

[13] Save the Children. Infanzia: la percentuale di bambini non vaccinati è tre volte superiore nelle zone di conflitto rispetto al resto del mondo. 18 giugno 2024. Available at: https://www.savethechildren.it/press/infanzia-la-percentuale-di-bambini-non-vaccinati-e-tre-volte-superiore-nelle-zone-di (Accessed on: 08/10/2024).

[14] World Health Organization WHO. Yemen Health Emergency. Available at: https://www.who.int/emergencies/situations/yemen-crisis (Accessed on: 08/10/2024).

[15] The Map Report. Nel 2023 più di 14 milioni di bambini nel mondo non sono stati vaccinati. Available at: https://www.themapreport.com/2024/07/16/nel-2023-piu-di-14-milioni-di-bambini-nel-mondo-non-sono-stati-vaccinati/ (Accessed on: 08/10/2024).

[16] Allarme Onu: troppi bambini non vaccinati. Avvenire 15 luglio 2024. Available at: https://www.avvenire.it/mondo/pagine/allarme-onu-troppi-bambini-non-vaccinati (Accessed on: 08/10/2024).

[17] Chassay C, Borger J. Guardian investigation uncovers evidence of alleged Israeli war crimes in Gaza. The Guardian 24 marzo 2009.

[18] United Nations. Avoid 'All Out War' in Lebanon, Stop 'Tit-for-Tat Violence' Engulfing Middle East, Secretary-General Tells Security Council. Available at: https://press.un.org/en/2024/sgsm22400.doc.htm (Accessed on: 03/10/2024).

[19] World Health Organization WHO. Around 560 000 children vaccinated in first round of polio campaign in Gaza. Available at: https://www.who.int/news/item/13-09-2024-around-560-

000-children-vaccinated-in-first-round-of-polio-campaign-in-gaza (Accessed on: 16/09/2024).

[20] 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.

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