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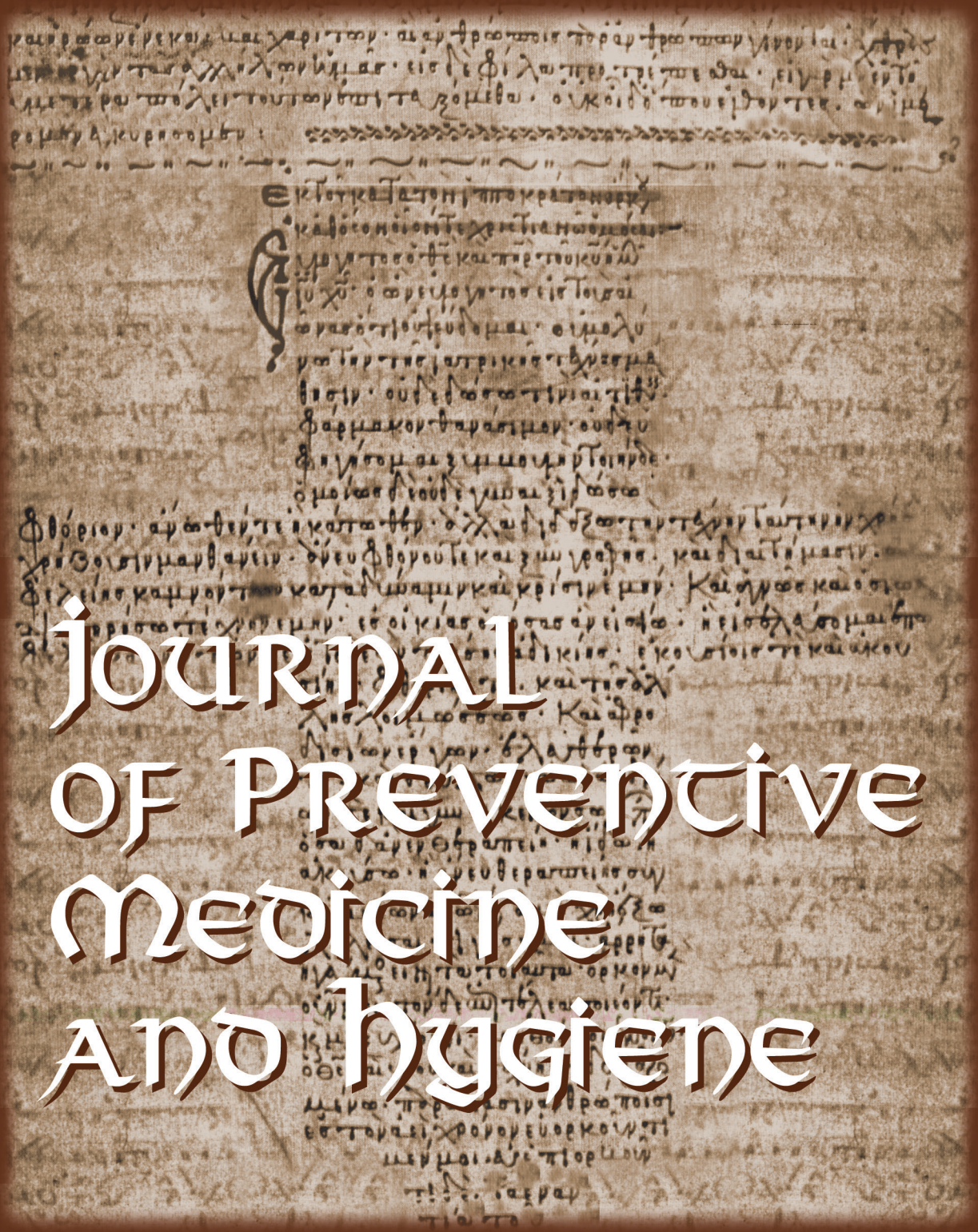

The original document of Hippocrates' oath

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Consensus paper

# Hexavalent vaccines: characteristics of available products and practical considerations from a panel of Italian experts

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Keywords

Hexavalent vaccines • Combination vaccines • Vaccine manufacturing • Safety • Co-administration

Summary

*Combination vaccines represent a valuable technological innovation in the field of infectious disease prevention and public health, because of their great health and economic value from the individual, societal, and healthcare system perspectives.*
*In order to increase parents' and healthcare professionals' confidence in the vaccination programs and maintain their benefits to society, more information about the benefits of innovative vaccination tools such as combination vaccines is needed.*
*Purpose of this work is an examination of available hexavalent vaccines, that protect against Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B and Haemophilus influenzae type b infections. From the epidemiological updates of vaccine preventable diseases to the vaccine development cycle, from the immunogenicity of antigenic components to the safety and co-administration with other vaccines, several aspects of available hexavalent vaccines are discussed and deepened.*
*Also a number of practical considerations on schedules, age of employment, strategies for vaccination recovery, vaccination in at-risk births are issued, based on the recommendations of Italian Ministry of Health, Italian Society of Pharmacology (SIF), Italian Society for Pediatrics (SIP), Italian Federation of Family Paediatricians (FIMP) and Italian Society of Hygiene, Preventive Medicine and Public Health (SItI).*

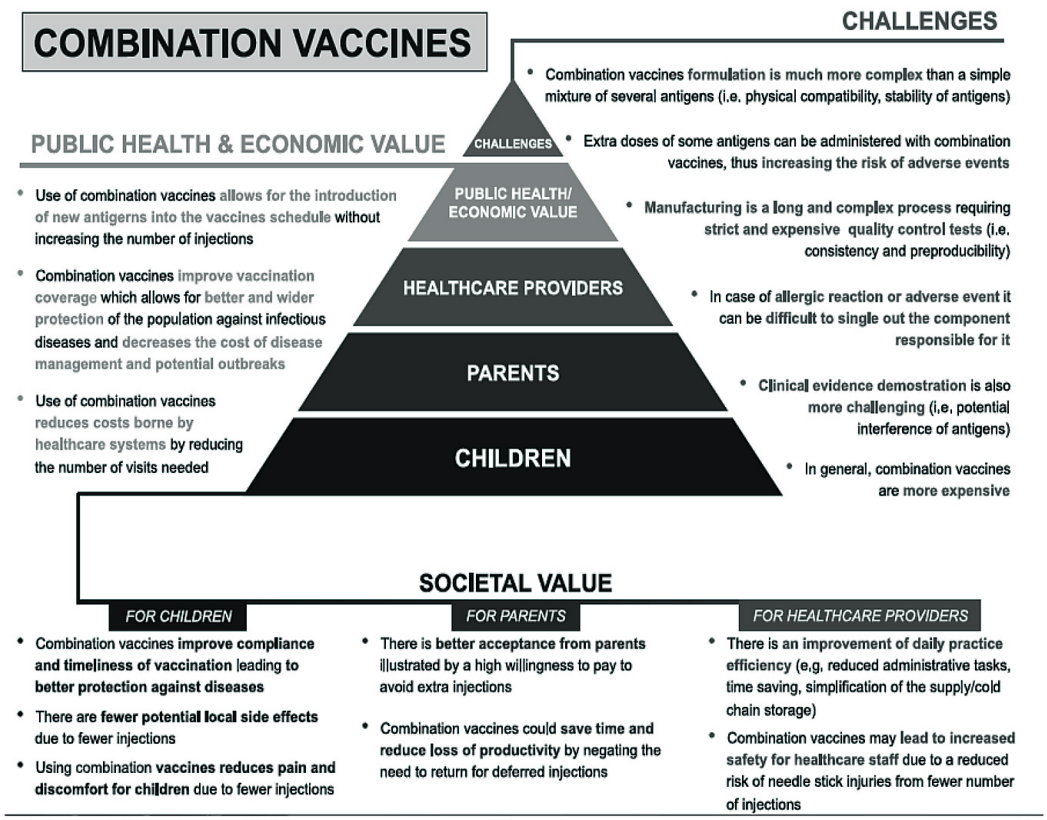
## Introduction

Since the very early vaccines formulation, increasingly important targets have been reached in prevention area. Nowadays, vaccinations are one of the most relevant resource in Public Health, providing prevention against diseases once cause of epidemics [1].
Recently, thanks to combination vaccines usage, other important targets have been achieved. In fact, combination vaccines ensure in a single injection a multiple immunization [2]. Reduction in the number of administrations leads to a decrease in ambulatory accesses and to a better safety profile of vaccinations programs, given the fact that a significant proportion of adverse events following immunization (AEFI) results from the act of injection. Combination vaccines availability is therefore an important tool in achieving a safe and successful protection against numerous pathogens, simplifying prospective introduction of new vaccines in a less crowded vaccine schedule [3, 4].
Combination vaccines usage provides a relevant value to health, with positive effects in the people health with a social and economic saving (Fig. 1) [5].
Purpose of this work is an examination of hexavalent vaccines, that protect against Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B and *Haemophilus influenzae* type b (Hib) infections.

## Hexavalent vaccines development cycle: from manufacturing to delivery

Hexavalent vaccines development is time-consuming and complex, and passes through the production of singles vaccines providing Diphtheria, Tetanus and Pertussis antigens (dTaP). Several quality controls are applied in every development cycle phase, so that efficacy and safety profiles have been raising over the years. The first phase is 12-years-long on average and includes the pre-clinical and clinical stages, the regulatory agencies

Fig. 1. Combination vaccines usage: a public health, economic and social value.




registration, and the discharge of the first approved and deliverable vaccine batch; within this time vaccine formulation are continually tested in order to provide the definitive composition and to develop adequate production systems. The second phase is no more than 36-months-long for the hexavalent vaccines development, and includes the production stage; up to 70% of this time is devoted to quality controls; the remaining time is required for antigens, carriers and adjuvants processing and combination, to the achievement of the hexavalent composition. Hence the hexavalent vaccine is in accordance with the highest standards in pharmaceutical industry, in terms of efficacy and safety [6, 7].

During the vaccine development cycle, that is long and elaborate, it's possible a vaccine batch doesn't pass quality control check; this may due, for example, to inadequate antigenic concentrations or to an unstable formulation. In this scenario, the whole hexavalent combination is stopped and not utilized, even if the quality control check failure is related only to a single antigen. Hence, it could be necessary a 2-years-long time to restore the production standards, with the consequence of supplies delivery deficiencies. Pharmaceutical factories are dealing with those challenges: if we consider the production stages timing, it's necessary that supplies variations and vaccines demands will ideally be made with a 3-years advance in order to maintain an adequate availability [6, 7].

Details about antigens preparation processing and timing, and about their formulation in the hexavalent vaccines, are described in Figure 2.

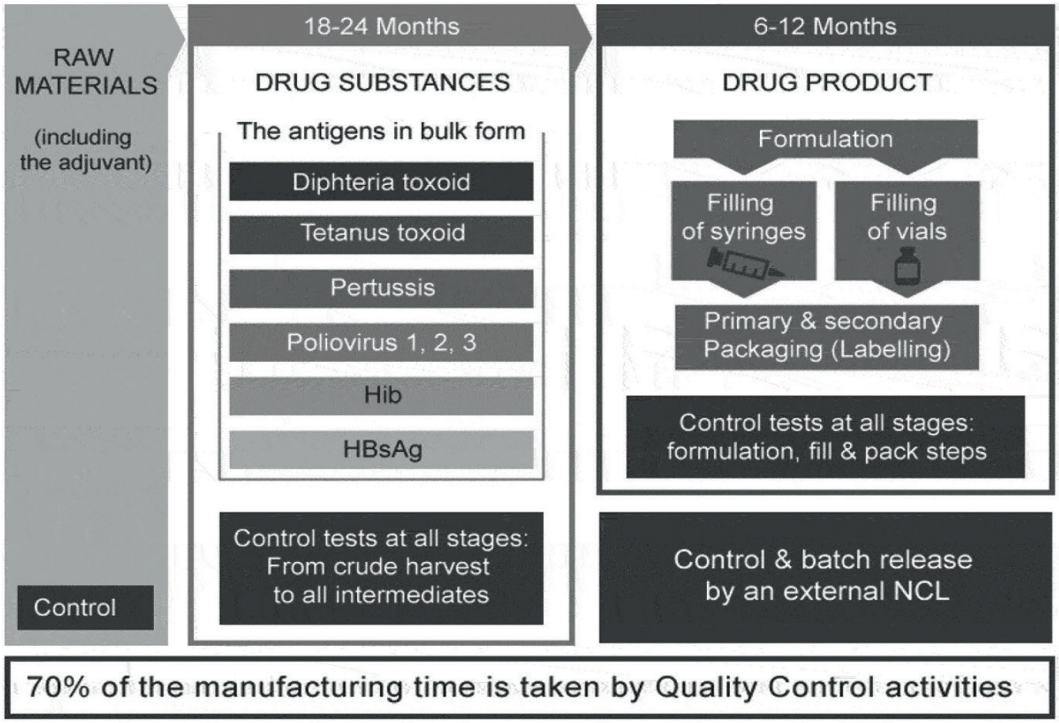
In addition to quality assessment, complexity and heterogeneity of different regulatory systems amongst countries is another relevant challenge in vaccines production, since it dictates another time delay to the final vaccines availability. Particularly, marketing and import authorization of vaccines lots are main critical issues in this context [6, 7].

## Hexavalent vaccine preventable diseases: epidemiological notions

Due to vaccinations introduction, a considerable number of diseases have been controlled and avoided. Those diseases comprehend Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B and Hib infections, for whom immunization can be reached in a single vaccine administration, hexavalent vaccine [8].

In order to get the best control and prevention of four of these diseases (Diphtheria, Tetanus, Pertussis and Poliomyelitis), booster vaccinations are necessary, as

Fig. 2. Quality controls performed within the different hexavalent vaccines production stages.




required by 2017-2019 Italian National Vaccine Prevention Plan (PNPV) [9]: (i) dTaP-IPV vaccination (pediatric vaccine with a full antigenic amount) in 6-years-old children; (ii) dTap-IPV vaccination (adult vaccine with a low antigenic amount) in 12 to 19-years-old subjects and (iii) dTap vaccination (adult vaccine with a low antigenic amount) every 10 years in adult age.
Thanks to such strategies, a significant reduction in epidemiological trends of these diseases have been reached (Tab. I).

## Diphtheria

An increasing reduction in Diphtheria cases in Europe, from 42/100000 population in 2008 to less than 0.1/100000 population in 2015, is documented in last ECDC Report [10]. Two cases of Diphtheria were nonetheless reported in Spain and Belgium [11].
In Italy, Diphtheria incidence had a dramatically reduction, up to 0 events in the 2010-2013 period. In the 2015-2017 period, nonetheless, 8 Diphtheria cases were reported. In particular, one C. Diphtheriae strain was a toxin-producer, responsible of cutaneous diphtheria, while other cases were caused by a non-toxin producer strain [12].
Even in countries where diphtheria is not endemic, thanks to high vaccination coverages, risk should not be underestimated. Some C. Diphtheriae toxin-gene-free strains can colonize nasopharynx and then cause pharyngitis, bacteraemias, endocarditis, septic arthritis, abscesses and pneumonia. The presence of non-toxigenic

Tab. I. Italian epidemiology of hexavalent vaccine preventable diseases: a comparison before and after vaccine introduction [16].

| Disease | Notified case number (on average) every year, before vaccinations | Notified case number (on average) in the period 2010-2013 | % Reduction |
|---|---|---|---|
| Diphtheria | 7000 | 0 | 100% |
| Tetanus | 700 | 60 | – 91.4% |
| Pertussis | 21000 | 509 | – 97.6% |
| Poliomyelitis | 2000 | 0 | 100% |
| Hepatitis B | 3000 | 419 | – 86.0% |
| Haemophilus influenzae type b | 69 | 6 | – 91.3% |

C. Diphtheriae strains has been recently documented in United States and in Europe, Italy included. Uncommonly, some of these strains are armed with toxin genes and could start producing the toxin through spontaneous reversion to toxigen strain or homologous recombination among different corynebacteriophages [13, 14].

### Tetanus

Even though Tetanus is a preventable disease, several cases occur in Italy each year, with the highest notification and hospitalization rates compared to other European countries and other high-income countries. In 2014, in the last ECDC Report, 84 events were reported in Europe, of which 48 confirmed in the laboratory. 35 events (45% of total cases) were reported in Italy, with an incidence of 0.02/100000 population [15].
In 2010-2013 period, 60 cases/year (with 20 deaths/year) were notified in Italy. Mostly belonged to unvaccinated elderly or to elderly that did not performed booster, with a reduction of 91.4% compared to pre-vaccine era [16]. Lack of pediatric vaccination or booster dosages has been related to the higher disease incidence in population aged > 64 years. Anti-Tetanus vaccination basal cycle is followed by multiple boosters to the adult age, when a booster dosage must be repeated every 10 years. The importance of boosters against Tetanus is due to antibodies levels decline over years and to the time needed for antibodies production in the period between infection and death [17].
In 2001-2010 period 2 cases of pediatric Tetanus (age < 14 years) were notified; successively no pediatric cases were reported until June 2017, when 2 cases were notified, the first in Sardinia and the second in Piedmont; both child were not immunized [18].

### Pertussis

Pertussis is a very contagious disease that can occur in every ages, but it's more serious in newborns and infants [19]. Within this age, hospitalization rates due to complications as apnea, seizures and pulmonary hypertension are higher; fatality rate can reach 1%. Complications and death risks are higher in pre-term born compared to term-born [20, 21].
Currently, Pertussis is the vaccine-preventable infectious disease most frequent in high-income countries. Its real impact is hardly evaluable and scarcely perceived by population and even by health workers [22].
From 1999 to 2009 in Italy a decrease in Pertussis cases trend was reported, thanks to high vaccine coverage. However, Pertussis is probably underestimated, especially in adolescents and young adults, due to the milder clinical presentation and the scarce usage of laboratory testing. Among those subjects, parents represent the main source of infection for children, in which the disease can be more severe [23, 24].
In Italy, about 500 cases/year have been notified from 2011 to 2015 [25]. Hence, compared to the pre-vaccine era, Pertussis incidence has a 97.6% reduction; this result was also achieved thanks to hexavalent vaccine containing Pertussis antigens (Tab. I).

Since both natural and vaccine-acquired immunization period against Pertussis is time-limited, it's pivotal to per-form booster dosages in the two cases. In fact, although clinical manifestations are milder as individuals grow, every subject can infect newborns, in a time before their acquired immunity reaches protective levels. Consequently, as planned in the PNPV paper, it's essential to provide a booster with DTaP-IPV in pre-school age, a booster with dTap-IPV in adolescence age and a booster with dTap every 10 years in adult age [26].
Cocoon strategy was proposed in order to reduce newborns infections. It consists of a booster administration in every potential newborn contacts.
Recent recommendations made by Italian experts, in accordance with WHO, and based on scientific studies, demonstrate that the best cost-effective intervention in newborns Pertussis prevention is the vaccination with dTap vaccine in the pregnant woman, ideally in the third trimester: doing so, maternal antibodies will be transmitted to the fetus and can protect the newborn in the window time from the birth to the first vaccination [27].

### Poliomyelitis

Poliomyelitis (polio) is an infectious disease burdened with a severe prognosis. The main risk in polio is a nonreversible flaccid paralysis, affecting especially pediatric population. The sole option to prevent Poliomyelitis consequences is vaccination. The Global Polio Eradication Initiative contributed to reduce over 99% of the global Poliomyelitis incidence. Europe was declared polio-free in 2002. The last case of polio was reported in Turkey in 1978, while 3 cases of polio were reported in Bulgaria in 2001, belonging to Rom children from India; in that last context, autochthonous transmission was stopped [28].
In Italy, thanks to vaccination (mandatory from 1966), the last Poliomyelitis case was reported in 1982. Still, in order to reach Poliomyelitis eradication, it's pivotal to carry on the IPV (Inactivated Poliovirus Vaccine) vaccination program, since as long as a single infected child is present, every child in the world is potentially susceptible [29-31]. In fact, even now it's important to maintain high antibodies levels since the risk of importation, and the consequent transmission, is present: Poliomyelitis is still endemic in Afghanistan and Pakistan [32].

### Hepatitis B

Worldwide, 257 million people are Hepatitis B virus (HBV) chronic carriers. Chronicity risk is greater especially if the HBV infection is precocious: risk rate is 90% in birth-infected children, 30-50% in infected children less than 4 years old, 1-10% in the population of age > 4 years [33].
Most European countries provide vaccination against HBV infection. Italy was a paradigm since in 1991 it established anti-HBV vaccination as mandatory for every new born and for 12-years-old children [34, 35].
Trends' analysis concerning case numbers in the period 1985-2016 shows a significant decline from 1991. Inci-

dence decline was related especially to age 15-24 years, due to newborns and 12-years-old children vaccination [36]. Thanks to this intervention, Hepatitis B incidence had a 86% reduction and chronic carriers prevalence had a reduction from 3% to less than 1% [16, 37]. This decline is extremely important, since Hepatitis B is one of the leading cause of liver cirrhosis and liver cancer, whose diagnosis is 10 years late after infection. At a distance of 20 years from the introduction of the anti-HBV vaccination, a significant decline in the case numbers of Hepatitis B associated liver cirrhosis and liver cancer is evident [38].
Over the past five years, 19% of HBV acute infections regarded non-Italian subjects arriving from HBV endemic regions, as East Europe (9% of overall HBV notified cases to the Italian Integrated Epidemiological System of Acute Viral Hepatitis [SEIEVA]) and Africa (4,9% of cases) [39].

#### *Haemophilus influenzae* type b

Hib could be cause of severe and invasive diseases as meningitis, sepsis, pneumonia. Hib epidemiology is not easy to define, since in several cases a timely laboratory confirmation is not made [40]. In 2007-2014 period 0.6 cases/100000 population/year were notified in Europe. Most of these cases was related to younger subjects: incidence was 23.4 cases/100000 newborns [41]. In Italy, the introduction of the vaccination against Hib led to 91.3% disease incidence reduction compared to pre-vaccine era. Also hospitalization rates due to Hib-disease halved compared to pre-vaccine era, as described in a recent Italian study [42]. Nevertheless, concomitantly with vaccination coverage decline, severe invasive Hib disease occurred recently in children less than 2 years old [42-44].

## Currently available hexavalent vaccines

The first combined vaccines were bivalent, with Diphtheria and Tetanus antigen (DT o dT); later Pertussis antigens were included thus forming the trivalent DTwP and dTaP vaccines, containing the inactivated Bordetella Pertussis and acellular antigenic components. Hexavalent combined vaccines, obtained with the antigens mentioned above and in addition polio, Hepatitis B, Hib antigens, are available for over 15 years. In Italy, as other countries in Europe, hexavalent vaccines are the most frequently used vaccine for the immunization of infants and toddlers against Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis and disease caused by Hib [45, 49].
Currently in Italy, three hexavalent combination vaccines are available: Infanrix Hexa®, used since 2000; Hexyon®, since 2013; and Vaxelis®, recently authorized. Their characteristics, described in the Summary of Product Characteristics (SPC) documents, are summarized in Table II [46-48].

#### Immunogenicity of antigenic components: focus on Pertussis, Hepatitis B, Hib

Although different in composition, the three vaccines have comparable immune response, resulting protective against the 6 target diseases. The immunogenicity of hexavalent vaccines has been extensively studied and comparative clinical trials have been carried out: in particular, the studies conducted with the 2 + 1 schedule reproduce a vaccination scheme similar to the one in current vaccination schedule of the PNPV, both for the age of use both for the co-administration with anti-pneumococcal and anti-rotavirus vaccines [49, 50].
In these studies, the responses to each antigen were evaluated using pre-established standard seroprotection correlates as concentration and antibody titers to be achieved in order to assert that the vaccine has determined antibody protection (seroprotection).
In the case of Pertussis antigens, for which a seroprotection indicator is not available, the response to the vaccine is evaluated considering the concentrations of specific antibodies produced after vaccination that are higher than those present before vaccination.
The results demonstrate the high immunogenicity of all the antigens included in the three hexavalent products, with high percentages of children with seroprotection and similar values for each antibody response. Specifically, the percentage of seroprotected children who responded to the hexavalent vaccines was non-inferior for all anti-body concentrations compared to those of children immunized with monovalent or fewer components (e.g. dTaP) [3, 4].
Also clinical data of safety, immune response and effectiveness are available. The results of the follow-up of clinical studies confirmed the presence of protective antibody titers. Effective protection up to the age of the dTaP-IPV booster has been demonstrated, for Hepatitis B antibody titers were at protective levels up to the age of pre-adolescence, guaranteeing protection against the risk of transmission in adolescents and adults. In addition, epidemiological surveillance programs conducted in several countries such as Sweden, Denmark and Germany, on pathologies such as Pertussis and Hib, have confirmed the effectiveness of hexavalent vaccines.
These information are reported in the SPC of the two long-standing hexavalents authorized, Infanrix Hexa® and Hexyon®, and will be available in a few years for Vaxelis®, that have the most recent authorization.

#### Pertussis

All vaccines combined with acellular components (aP acellular Pertussis) contain Pertussis toxoid (PT). The other antigenic components of Bordetella Pertussis, sometimes included, are: filamentous haemagglutinin (FHA), pertactin (PRN) and fimbriae types 2 and 3 (FIM). Pertussis vaccines are different in the formulation, combination and concentration in micrograms of the individual components, and also in the production methods used, such as the detoxification and purification. Therefore, the comparison between different aP vaccines cannot be based only on the number of antigen-

**Tab. II.** Summary of currently available hexavalent vaccines characteristics.

| | Infanrix Hexa® [46] | Hexyon® [47] | Vaxelis® [48] |
|---|---|---|---|
| Hib -PRP | 10 µg<br>Conjugated to Tetanus toxoid | 12 µg<br>Conjugated to Tetanus toxoid | 3 µg<br>Conjugated to Meningococcal protein |
| Pertussis | PT 25 µg<br>FHA 25 µg<br>PRN 8 µg | PT 25 µg<br>FHA 25 µg | PT 20 µg<br>FHA 20 µg;<br>PRN3 µg<br>FIM type 2,3: 5 µg |
| Diphtheria toxoid | Not less than 30 UI<br>*mean value | Not less than 20 UI<br>*lower limit CI 95% | Not less than 20 UI<br>*lower limit CI 95% |
| Tetanus toxoid | Not less than 40 UI | Not less than 40 UI | Not less than 40 UI |
| IPV Polio | Poliovirus inactivated<br>type 1, 2, 3 | Poliovirus inactivated<br>type 1, 2, 3 | Poliovirus inactivated<br>type 1, 2, 3 |
| Hepatitis B - HBsAg produced in | Saccharomyces cerevisiae | Hansenula polymorpha | Saccharomyces cerevisiae |
| Ready to use | No | Yes | Yes |
| Co-administration | Yes | Yes | Yes |
| Preterm | Yes | Yes | Yes |
| Minimum age | Not specified | 6 weeks | 6 weeks |
| Maximum age | No limits | No limits | No limits |
| Follow-up studies of antibodies persistence | Yes | Yes | Not available |
| Effectiveness results | Yes | Yes | Not available |

ic components contained, also because the contribution to immune protection by each anti-gen is not completely clear [26].

The essential component is PT, present in all aP vaccines, and directly responsible for the development of a protective immune response following vaccination.

The FHA it is the antigen that over time is less mutated genetically, unlike the PRN whose mutations led to the diffusion of pertactin-resistant strains.

There is no evidence on the contribution of immune protection given by the fimbriae in the newborn, while it seems they may play a role when contained in the booster vaccines for the adult [26].

Moreover, it is well known that even the natural infection with Pertussis, which obviously contains "all the components", is able to induce permanent immunity [24, 26].

Although no Pertussis or serologic protection indicator is available for Pertussis, all aP vaccine antigens present in hexavalent vaccines have shown high immunogenicity in comparative clinical studies (both between hexavalent and both combined vaccines with fewer components) in terms of the presence of higher antibody levels after vaccination compared to the pre-vaccination serological test [51].

Several evidences have clearly shown how prevention and control of Pertussis are based on the adoption of a vaccination schedule that includes, in addition to primary vaccination in the newborn, booster in childhood, adolescence and adulthood (every 10 years), and on reaching and maintaining high coverage, regardless of the employed aP vaccine and the number of components contained. In particular, in Denmark, where an aP vaccine with only PT component has been used for over 15 years, the disease has been well controlled and no outbreaks have occurred [52, 53]. Also in Sweden, after 19 years of epidemiological surveillance, Pertussis is effectively controlled throughout the nation, regardless of the type of vaccine used, with one or more components [54].

As underlined by the WHO Pertussis technical group (WHO SAGE Pertussis Working Group), the key point in the control of the pathology is the achievement of high vaccination coverage and a schedule with adequate timing for the childhood and booster in adulthood [55]. The same consideration are described by the American Society of Pediatrics and the CDC in the 12th edition of the Pink Book, as well as in the last WHO Pertussis Vaccines Position paper 2015: a summary of recommendations and evidences of use of the aP vaccines is reported in Table III.

## Hepatitis B

The current Hepatitis B vaccines, both monovalent and combined, contain the HBV virus surface antigen (HBs), produced in yeast cells by recombinant DNA technology. In the case of hexavalent vaccines, the yeast cells used are Hansenula polimorpha and Saccharomyces cerevisiae: all HBs antigens have been shown to be highly immunogenic, although the production processes differ in the cell line used.

In the registered clinical trials, high seroprotection rates were detected in vaccinated children, with overlapping results in the comparison between hexavalent vaccines and monovalent anti-Hepatitis B vaccine (anti-HBs titre ≥ 10 mIU/mL) [49, 50]. Furthermore, in the clinical trials follow-up up to pre-adolescence age, anti-Hepatitis B antibodies result at highly protective levels in response to the administration of a challenge dose, with important implications for long-term memory and protection against possible future infections [46, 47, 59]. Further

studies on vaccinations for Hepatitis B have shown that, after the primary vaccination during the first year of life, protective antibody levels are maintained until adolescence age. Therefore, thanks to the vaccines used up to now, including the hexavalents, it is not necessary to administer a booster for Hepatitis B in the general population, while a booster dose may be necessary in those at risk and in non-responders [60, 61].

### *Haemophilus influenzae* type b

In the currently available hexavalent vaccines registration studies, the immunogenicity of the Hib vaccine was assessed by measuring serum IgG antibodies against the PRP capsular antigen. The thresholds set for short- and long-term protection are, respectively, ≥ 0.15 μg/mL and ≥ 1 μg/mL. Considering these as reference values, the responses against the PRP antigen of Hib have recorded high levels of seroprotection in children vaccinated with the hexavalents in use [49, 50].
Furthermore, the efficacy of the Hib vaccine is supported by various evidences deriving from national surveillance systems that monitor the incidence of cases of Hib disease and evaluate the trends before and after introduction of vaccination. In Germany, a population-based system that integrated hospital admissions surveillance and molecular laboratory diagnosis allowed to assess the impact of anti-Hib vaccination after the introduction of tetravalent and pentavalent products, respectively in 1996 and 1998. The first surveillance data for the two-year period 1998-1999 showed that the number of cases of Hib disease in children aged 0-5 ranged from 28 to 13 [62]. Subsequently, data related to a longer period (August 2000 - December 2004) made it possible to estimate the efficacy of the vaccine in relation to the doses administered: the effectiveness of the Hib vaccine was 96.7% (95% CI: 87.7-99.1) for the cycle complete primary, and 98.5% (95% CI: 94.5 to 99.6) for the booster dose. Estimates of efficacy of the anti-Hib component in hexavalent vaccines did not show significant differences compared to combined tetra and pentavalent vaccines [63].
Regarding Italian region, before the introduction of universal vaccination against Hib, the incidence of invasive disease caused by Hib in children aged less than 5 years increased from 2.5/100.000 in 1994 to 4.5/100.000 in 1998, a trend most likely due to the implementation of active surveillance for the invasive disease from Hib based on laboratory data, implemented at that time in some Italian regions. Since 1999, after the introduction of anti-Hib vaccination with 2 + 1 schedule, an excellent control of the disease has been registered, underlined by the reduction in hospitalization rates due to invasive disease [42].

## Co-administration with other vaccines

The safety and immunogenicity of hexavalent vaccines do not change significantly when co-administered with other vaccines included in the child's vaccination schedule [64]. Clinical studies of the three hexavalent products demonstrated elevated immunogenicity and safety standards of the 2 + 1 hexavalent schedule co-administered with anti-pneumococcal and anti-rotavirus vaccines [6, 48, 49]. Further clinical studies have also confirmed the co-administration with vaccines such as anti-meningococcal conjugate, anti-measles, mumps, rubella and anti-varicella vaccines. The indications for all possible co-administrations are reported in the relative SPC [46-48].
In general, as recommended in the CDC guide on co-administrations, all vaccines may be administered in the same session, without any limitation in the number of vaccines administered (alternating sites for subsequent injections), unless reported in SPC [65, 66].

**Tab. III.** Summary of recommendations and evidences of use of the aP vaccines.

| | |
|---|---|
| Plotkin S et al. 2013 [56] | Surveillance programs demonstrate the efficacy of each aP vaccine in achieving excellent pPertussis control |
| WHO 2016 [57] | Long-term national surveillance studies conducted in Sweden and Denmark, where 10 2-component vaccines are also used, showed high levels of effectiveness in preventing Pertussis regardless of the antigenic content of the various aP vaccines used. All polyvalent aP vaccines showed high levels of effectiveness in preventing pertussis independently of aP in these contents |
| WHO SAGE Working Group 2014 [55] | There is no evidence to conclude that one type of aP vaccine is superior to others. The available data reinforce the importance of achieving and maintaining high coverage and implementing appropriate vaccination schedules |
| CDC Pink Book 2015 [19] | The efficacy of the vaccines aP it's variable between 80% and 85%, the respective confidence intervals of these overlap each other, suggesting that none of the aP vaccines is significantly more effective than other |
| American Academy of Pediatrics 1997 [58] | Although the different aP vaccines available differ in their formulation of Pertussis antigens, their efficacy is similar |
| Gabutti et al. 2015 [26] | The use of the current polyvalent vaccines with aP allowed the achievement and maintenance of high vaccine coverage that, regardless of the type of vaccine and the number of AP in these contents, is the key factor for successful vaccination interventions against Pertussis |

## Safety of hexavalent vaccines

Vaccines can be considered among the most controlled and safe pharmaceutical products. Before marketing authorization and introduction into immunization programs, they are subjected to different stages of safety and efficacy assessment. Once authorized, the production processes are subject to accurate and continuous checks and the presumed adverse events are constantly monitored and analyzed, in order to guarantee to the population safe and high quality vaccines. Furthermore, the production of vaccines is controlled in compliance with standards indicated by international organizations such as the European Medicines Agency (EMA) and the WHO.

Although the vaccines currently used in immunization programs are safe and effective, they, like all drugs, are not exempt from possible adverse events, although rare, after vaccination. An AEFI is defined as any adverse clinical event that occurs following the administration of a vaccine and which does not necessarily have a causal relationship with the use of the vaccine [67].

The results of the safety reports analyzes collected in the clinical studies on hexavalent products showed good tolerability of these vaccines, confirmed both by the study follow-up and by the phase IV post-marketing surveillance systems. The results of the safety of hexavalent vaccines are included in the relative SPC [46-48].

In general, a higher but not clinically significant rate of fever and local symptoms (from mild to moderate, and in any case transient) was recorded compared to vaccines with fewer components. However, the use of combined hexavalent vaccines is overall safer because, by subjecting the child to a single injection instead of six, the total frequency of these reactions is reduced, which also occurs for co-administration with other vaccines for children [5, 68, 69].

Detailed data on post-marketing surveillance of vaccines in Italy derive from the latest AIFA report, which summarizes the post-marketing surveillance activities on vaccines conducted in Italy in 2016 [70]. Reports of suspected ad-verse reactions to hexavalent vaccine, collected through the National Pharmacovigilance Network in 2016 were 1'127, of which 670 (59.4%) occurred in the period from January 1 to December 31, 2016. The serious reactions were 188, 16.7% of suspected reports included in the National Pharmacovigilance Network. Most reports (No. 845, 75%) refer to the simultaneous administration of hexavalent and other vaccines (in particular the pneumococcal vaccine), following the co-administration provided by the vaccination schedule.

As with other vaccines, most reactions are mild and transient. The ten reactions more frequently reported after hexavalent vaccine in 2016 in Italy are described in Table IV.

As regard to Sudden Infant Death Syndrome (SIDS), the Report states that there is no evidence of causal relationship between exposure to vaccines and SIDS, and that the incidence of this is the same both in the presence and both in the absence of vaccination. A short distance between the SIDS and the vaccination does not imply, therefore, any cause-effect relationship.

Further support for the safe use of vaccines is the Guide to contraindications to vaccinations, including the hexavalent one, in which the real contraindications are distinguished from the false ones [71] (Tab. V).

## Practical considerations

### Summary of Product Characteristics: clarifications on terminology

The terminology used in the summary of product characteristics, that is sometimes a source of interpretative confusion, has been recently deepened and clarified in a document of the "Calendario per la Vita" Italian board, a panel of experts belonging to the main scientific society engaged in vaccination and public health [72].

One of the key points is the paragraph 4.1 which establishes indications of the use of the vaccine, even with a medical point of view. Section 4.2 indicates the dosage and method of administration of the vaccines. The other sections contain specifications on population groups in which efficacy and safety studies were performed, data on interactions with other drugs (section 4.5) and pharmacodynamic properties (section 5.1). The information contained in these paragraphs should not be confused with the indications of the vaccine1. For example, with regard to the age of employment, hexavalent vaccines are given "starting at 6 weeks of life", without an upper limit of use. Considering that they contain a dose of "pediatric" antigens, even if this indication is not included in the technical data sheet, their use is recommended up to 7 years of age. Obviously, both the vaccines and the drugs used in the therapeutic field are usually studied in the age groups where their greatest use is expected. However, the fact that a vaccine has safety studies up to 24/36 months, for example, does not preclude its use in older age groups, as it is also reported in the indications for hexavalent vaccines and appropriately specified also by the European Medicines Agency (EMA).

**Tab. IV.** First ten reactions reported in order of frequency after administration of hexavalent vaccine in 2016 in Italy.

| Type of reaction | Frequency (No.) |
|---|---|
| Fever | 618 |
| Hyperpyrexia | 146 |
| Cry | 124 |
| Irritability | 100 |
| Drowsiness | 91 |
| Swallow at the time of vaccination | 55 |
| Erythema at the time of vaccination | 51 |
| Pain at the time of vaccination | 49 |
| Agitation | 41 |
| Diarrhea | 40 |

Tab. V. Contraindication (true or false) and precautions for the use of hexavalent vaccine.

| Contraindications | Precautions | False contraindications |
|---|---|---|
| Severe allergic reaction (anaphylaxis) after administration of a previous dose<br>Severe allergic reaction (anaphylaxis) to a component of the vaccine<br><br>*Temporary contraindications*<br>Encephalopathy not attributable to another cause within seven days of administration of a previous dose of hexavalent until clarification of the cause or stable disease | Encephalopathies and encephalopathies with seizure of unknown aetiology, including West syndrome<br>Guillain-Barré Syndrome and related syndromes within 6 weeks of administration of a previous dose of vaccine<br>Severe or moderate acute illness, with or without fever<br>Peripheral neuritis after the administration of a previous dose<br>Immediate generalized urticaria after the administration of a previous dose<br>Extreme prematurity<br>Severe latex allergic reaction (for products containing latex in the syringe)<br>Immunocomplexing (arthus) after administration of a previous dose | Positive anamnesis for febrile seizure<br>Neurological disorders (well-controlled seizures, cerebral palsy, developmental delay)<br>Episode of hypotonia-hyporesponsiveness within 48 hours after administration of a previous dose of hexavalent<br>Hyperpyrexia after a previous dose of hexavalent<br>Persistent and uncontrolled crying for more than 3 hours after previous administration of hexavalent<br>Family history of SIDS<br>Non-extreme prematurity<br>History of local reaction extended after previous dose<br>Clinical history of pertussis<br>Family history of convulsions<br>Family history of adverse events after administration of aP or wP |

A further example regards the employment in particular groups of children, such as preterm births. In this case, although there is no specific indication in paragraph 4.1, the administrability is confirmed both by the absence of relative contraindications (section 4.3), and by the presence of specific precautions regarding very premature births (section 4.4).
Furthermore, as indicated by AIFA in the Drugs Information Bulletin, the use in clinical practice of drugs, or even vaccines, already registered but used in a manner not in accordance with the summary of the characteristics of the drug is defined "off-label" authorized product [73]. Therefore, also taking into account the current legislation that regulates the off-label use of medical products and compliance with the authorized therapeutic indications (Article 3 of Legislative Decree 17 February 1998, converted into Law of 8 April 1998), we can conclude that all and three hexavalent vaccines can be used up to 7 years of age and can be used in premature babies [74]. In essence, the use of hexavalents in premature babies and in all subjects up to 7 years is to be considered as "on-label" use, adequate to what is prescribed in the summary of product characteristics.

### Schedule and specific dosage

The results obtained in the studies conducted with 2 + 1 schedule, with administrations at the 3$^{rd}$, 5$^{th}$ and 11$^{th}$ -13$^{th}$ month of age, showed that the antibody responses reach high levels of seroprotection for all the antigens of the three hexavalents [49, 50].
The two long-standing hexavalents authorized and used with 2 + 1 schedule have been shown to prevent the six diseases for which they determine immunity, feedback obtained from the follow-up of clinical studies and the anal-ysis of epidemiological surveillance programs [46-48].

### Age of employment and recovery of defaulters

All hexavalent vaccines are indicated in all children from 6 weeks of age and, as described in the summary of product characteristics, there is no limit of upper age. The recommendations of the "Calendario per la Vita" board for the recovery of vaccinations in non-compliant children have been reiterated by the Ministry of Health: the use of hexavalent vaccines is recommended up to 7 years of age. Both the board and the Ministry of Health recommend to the healthcare workers to propose to the parents, as the first choice, the administration of the hexavalent vaccine, as it allows to reduce to a minimum the number of sessions and the number of administrations and to minimize the possible side effects [72, 75].
The recommendations of the board and the Ministry of Health are in line with those contained in the vaccination position paper of the Italian Society of Pharmacology (SIF), drawn up together with the Italian Society of Pediatrics (SIP), with the Italian Society of Preventive Medicine and Public Health (SITI), wih the Federation of Family Pediatricians (FIMP) and with the General Practitioners (FIMMG). The document, approved by the National Institute of Health, recommends the use of vaccines containing antigens in pediatric concentration up to 7 years, such as hexavalent vaccines.
The ECDC and the WHO also recommend the use of pediatric vaccines, such as hexavalents, in older children, in line with EMA indications on these type of vaccines [76, 77].
Therefore, the use of hexavalent vaccines is supported by: (i) the evidence of the registration studies (efficacy and safety studies) conducted in the population groups that include the age groups in which their greatest use is expected; (ii) the experience of vaccines combined with similar formulation, such as tetravalents, already studied and indicated up to higher ages (DTaP-IPV up to 12 years of age); (iii) pharmacovigilance studies and

post-marketing surveillance; (iv) the recommendations of scientific societies, international organizations and the Ministry of Health.

### Vaccination in preterm births

The WHO defines as a preterm the child born before the 37th week of gestation; moreover, prematurity is distinguished in mild, medium and severe according to the gestational age at birth [78].
In the vaccination schedule of the PNPV, no difference is made between term and premature births, indicating that all children are vaccinated with hexavalent from the 3rd month of life [9].
The results of a recent literature review have confirmed that all monovalent and combined vaccinations give sufficient protection guarantee when administered in preterm births, with the only exception of the monovalent Hepatitis B vaccine which, when given at birth (born from HBsAg positive mothers), gives a lower immune response and should be repeated at one month of life to obtain adequate protection. Sufficient and protective anti-HBs concentrations are produced by preterm infants at the completion of the hexavalent vaccination schedule at 9-12 months of age [79].
Furthermore, the results of epidemiological surveillance of invasive Hib disease in Tuscany in 2007-2017, the period in which Infanrix Hexa® was first used and after Hexyon® in all children, including preterm births, have shown that both hexavalent vaccines are safe and effective, since no case of illness was registered among the children vaccinated in the study period (except for a child with a congenital antibody defect, unable to produce antibodies to protective levels) [80].
The three hexavalent vaccines do not have a specific indication in point 4.1 of the summary of product characteristics relating to preterm births. Infanrix Hexa® and Vaxelis® summary of product characteristics report clinical data on premature delivery, although on a limited number of newborns. Hexyon® does not have specific data on preterm births in the data sheet, but data on use and effectiveness were collected in an epidemiological surveillance program in Tuscany.
As proof of the fact that the use of the three hexavalent vaccines fully respect the authorized therapeutic indications, the summary of products characteristics of the three vaccines show the same information on the "very preterm" born in point 4.4 (Special warnings and precautions for use), born before the 28th week and with a history of respiratory failure. In these children, in fact, considering the potential risk of apnoea onset, it is necessary to monitor the respiration in the hospital for 48-72 hours after administration. Because the benefit of vaccination is high in this group of newborns, vaccination should not be stopped or postponed [46-48].
These precautions are valid for all pediatric vaccines that can be administered in newborns and for which preterm use, including very premature ones, is also expected.
Therefore, all hexavalent vaccines can be used in preterm births, with a 2 + 1 schedule and respecting the same timing of term births, without delaying immunization.

### Vaccination in the births of a positive HBsAg mother

The available hexavalent vaccines report in the summary of product characteristics the possibility of use in children born to HBsAg positive mothers [46-48]. The 2017-2019 PNPV schedule includes monovalent vaccination for Hepatitis B at birth and at 30 days of life. In these children, the vaccination series continues with the 2 + 1 schedule of the hexavalent [9]. As demonstrated by a review of clinical trials, this scheme ensures the production of protective antibody concentrations in all children, including preterm births [79].

### Interchangeability

Given the existence of combined vaccines containing slightly different components, practitioners often ask them-selves how to continue the cycle if the previous vaccine given is unknown or is no longer available at the time of the next dose.
In general, it is preferable to continue the vaccination schedule with the same product with which immunization was started [81]. Although it is possible, if not explicitly contraindicated in the data sheet, to use a hexavalent vaccine different from that used in the previous dose of the schedule, it is appropriate that safety and efficacy data are available, and that this mode of use is described in summary of products characteristics [5, 46-48].
Actually, only the hexavalent Hexyon® possesses these requirements, and the related methods of use are described in summary of products characteristics.

### Preparation method: pre-filled syringe or to be reconstituted

While Hexyon® and Vaxelis® are available in fully-liquid formulation, in pre-filled and ready-to-use syringe, Infanrix Hexa® requires, prior to the administration, the reconstitution in the main syringe of the Hib antigen, contained in-stead in a vial [46-48].
Several studies have compared these types of vaccines, with results of a reduction of about 5 times the risk of possible errors in the preparation and halving of the time of administration for those in formulation in pre-filled syringe compared to vaccines that require a reconstitution process [82-85].

## Conclusions

In consideration of what has been described and evoked by the literature and by the registration studies of the hexavalent vaccines, together with the recent recommendations on their use of the "Calendario per la Vita" board, it can be concluded that: (i) combined vaccines reduce the number of administrations and therefore the frequency of local reactions to the injection site and of

crying, as well as reducing the number of visits and access necessary for completing the vaccination schedule; (ii) clinical studies have shown that the three hexavalent vaccines have a high immunogenicity and safety profile; (iii) hexavalent vaccines may be co-administered in the same vaccination session with pneumococcal and anti-rotavirus vaccines, as foreseen in the PNPV calendar; (iv) hexavalent vaccines can be administered in preterm births with a 2 + 1 schedule, without delaying the start of the immunization cycle; moreover, for the very preterm births (ie born before the 28th week of gestation) and with respiratory insufficiency, the precautions for use described in the summary of product characteristics must be followed; (v) two hexavalent vaccines have antibody persistence data in summary of product characteristics, demonstrated by follow-up of clinical trials (up to 9-11 years for anti-HBs antibodies) and efficacy data from epidemiological surveillance programs. For the third vaccine, with the most recent authorization, the same data will be available in a few years; (vi) all hexavalents are highly effective in preventing Pertussis, as demonstrated by related surveillance programs; the vaccination of the mother during pregnancy is the most effective intervention for the prevention of the disease in the first months of life; (vii) there are no differences in immunogenicity between different antigen formulations; (viii) it is preferable to continue the schedule with the same vaccine with which it was started, or that specific modalities are reported in the summary of product characteristics; (ix) the formulation in pre-filled syringe reduces the risk of possible errors and time of preparation and administration.

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## Authors' contributions

All Authors have made a substantial contribution to the conception, design, analysis and interpretation of data, drafting the article and revising it critically for intellectual content; all Authors approve the final version submitted to the *Journal of Preventive Medicine and Hygiene*.

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ORIGINAL ARTICLE

# Impact of vaccination programs against measles, varicella and meningococcus C in Italy and in Tuscany and public health policies in the last decades

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Keywords

Vaccination program • Measles • Varicella • Neisseria meningitidis type C • Italy

Summary

*The World Health Organization (WHO) has established specific targets for control, elimination or eradication of some vaccine preventable infectious diseases, which were periodically updated. In Italy, WHO recommendations have been endorsed and implemented over time, through the national and regional health prevention plans. The aim of the study was to assess the impact of the immunization practices against measles, varicella and Neisseria meningitidis type C (Men C) in Italy and in Tuscany Region, during the last decades, by analyzing national and regional surveillance databases. Benefits of vaccination strategies were discussed from different points of view (clinical, epidemiological, economic, ethical, social and communicative). The implementation of measles, varicella and Men C vaccination, caused a considerable decrease of incidence rates over the years in Italy and in Tuscany too. However, in the last years, notifications of measles and Men C cases in subjects not targeted by immunization campaigns, in Italy and in Tuscany, are a cause for concern for public health and for the achievement of the elimination goals. Achieving and maintaining high vaccine coverage guarantees a decrease in the incidence of serious diseases and their clinical and economic consequences, but it is necessary to strengthen surveillance system of infectious diseases in order to monitor epidemiological trends. Moreover, outreach campaigns are necessary to raise awareness in the general population and create the culture of prevention with the same nationwide health goals for all.*

## Introduction

Vaccination is one of the most successful health interventions ever introduced in the history of medicine and, together with the modern hygiene practices and the use of antibiotics, has contributed significantly to decrease infectious diseases. All over the world, introduction of universal vaccination resulted in an overall net reduction of infectious diseases, the main cause of mortality in children in the past and, currently, in developing countries. Indeed, the World Health Organization (WHO) estimates that 1.5 million deaths each year could be averted thanks to vaccinations that provide protection against infectious diseases. However, in 2013 nearly 22 million children missed out the opportunity to be adequately protected against vaccine preventable diseases, resulting in a significant infant mortality, particularly in developing countries. Globally, under-five mortality rate has decreased by 53%: it has dropped from 91 deaths per 1000 live births in 1990 to 43 deaths per 1000 live births in 2015 [1, 2]. According to the "Global Vaccine Action Plan 2011-2020" published by WHO, vaccines will prevent 25 million deaths during the current decade [3]. However, transmission of infectious diseases could be reduced, only achieving and maintaining high level of vaccination coverage (VC). The WHO has set specific targets for the control, elimination or eradication of different infectious diseases (i.e. measles and polio), which were periodically updated.

In Italy, these targets have been included in all the National Health Plans approved in the last decade. In particular, in the National Plan for Vaccine Prevention 2017-2019, specific goals for immunization against Measles, Varicella and Meningococcal C diseases were defined [4]:

- achieving and maintaining VC for one dose of MMR (measles, mumps, rubella) ≥ 95% within 2 years of age and two doses of MMR ≥ 95% in children aged 5-6 years and adolescents (11-18 years);
- achieving and maintaining VC ≥ 95% for meningococcal C vaccination in newborns and adolescents (11-18 years) within 2 years of age;
- achieving and maintaining VC ≥ 95% for one dose of varicella vaccination within 2 years of age and two doses of varicella vaccination ≥ 95% in children of 5-6 years of age.

In Tuscany, health authorities adopted specific vaccination strategies against measles, *Neisseria meningitidis* C (Men C) and varicella, in different times, in order to reduce the burden of those diseases at regional level and contribute to the achievement of national objectives.

The aim of this study was to assess the impact of the regional vaccination program in Italy and in Tuscany by analyzing and comparing national and regional inci-

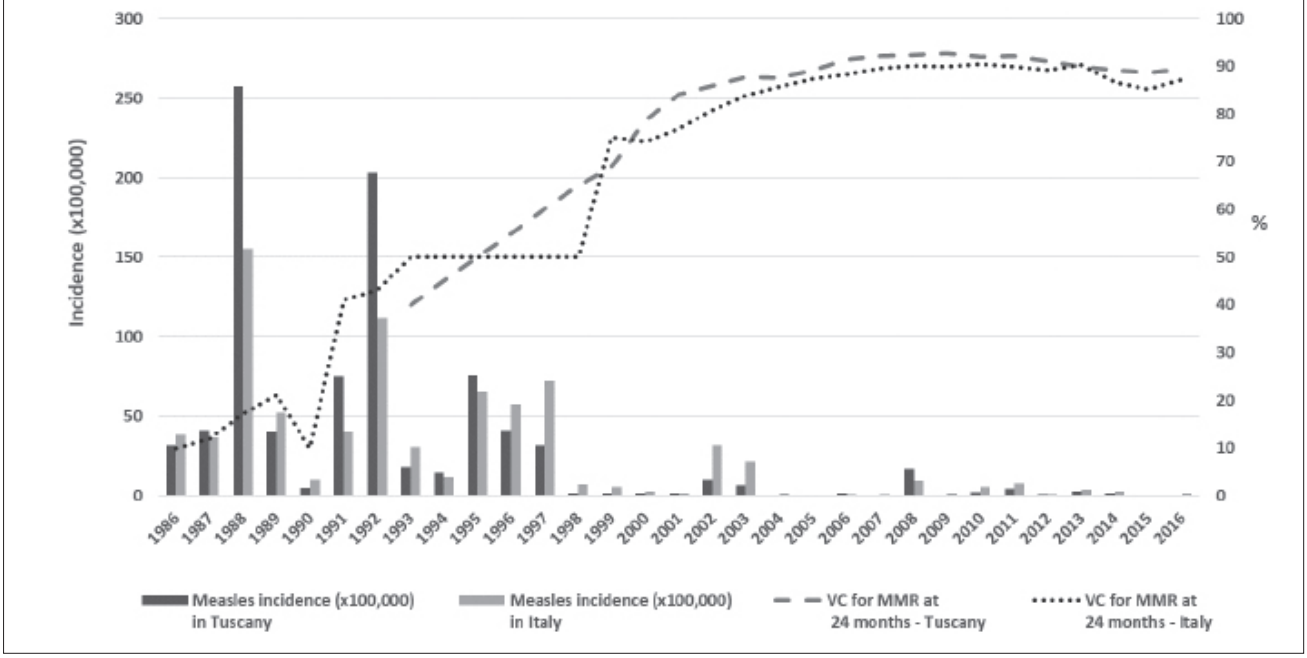
dence data on measles, Men C and varicella before and after the introduction of the specific recommendations for immunization up to 2010. Moreover, we added some considerations on the current epidemiological data of measles and Men C cases observed in the last years at the regional and national level.
Benefits of vaccination practices in the field of public health were discussed from different points of view: clinical, epidemiological, economic, ethical, social and communicative.
The impact of vaccination programs was assessed by analyzing epidemiological surveillance data of these three infectious diseases in Italy and in Tuscany. The discussion is supported by specific searches carried out on "PubMed" database. A consultation of national and international official websites (WHO, UNICEF, Ministry of Health, National Institute of Health - ISS Epicentro) was also performed in order to retrieve recommendations on vaccines and vaccination policy in other Italian regions or EU countries.

## Evaluation of the impact of vaccination in Tuscany and in Italy: the clinical-epidemiological value

### Measles

In Italy, the introduction of measles (M) and measles-mumps-rubella (MMR) vaccination determined a significant decrease in the number of cases and deaths due to MMR over time. Figure 1 shows the trend of measles incidence in Tuscany and Italy from 1986 to 2016 and VC for one dose of measles-containing vaccines within two years of age. Noteworthy, the increase of immunization coverage at 24 months of age, that reached in 2010 the value of 91% and 92% in Italy and in Tuscany, respectively, corresponds to a drastic decrease in the number of measles cases and of incidence rates too (1.4 and 0.7 per 100,000 in Italy and Tuscany, respectively in 2010). Moreover, in 2010 MMR immunization coverage with 2 doses reached almost 70% at 6, 12 and 15 years of age [5]. According to the ICONA study 2008, vaccination coverage in Italian adolescents (16 years) was 91% for 1 dose of MMR and 75% for 2 doses [6], in line with the Tuscan VC data.
The incidence of measles in Italy in 2005 reached a historic low of 0.2 cases per 100,000 inhabitants (108 cases). In the period 2003-2007 there was an improvement in immunization coverage for the first dose of MMR within 24 months (from 84% in 2003 to 90% in 2007), and a special surveillance system for measles and rubella cases was established at regional and national level, in order to laboratory confirm suspected cases. Moreover, in the same period, the second dose of MMR vaccine at 5-6 years was definitively introduced. However, in Italy outbreaks of measles still occur and serious complications (such as pneumonia, encephalitis and deaths) are reported [7, 8]. From July 2009 to September 2010 the incidence of measles was 3.6 cases per 100,000 inhabitants, with 2,151 cases in 15 regions (of which 42% laboratory-confirmed). The average age of cases was 18 years and 92% of the cases involved unvaccinated people. A large percentage of subjects (36%) required hospitalization [9].
The trends of measles incidence rates in Tuscany reflect the national one. The VC for MMR in children aged 24 months in Tuscany gradually increased since 2000 and

Fig. 1. Measles incidence (x100,000) in Tuscany and Italy from 1986 to 2016 and VC for one dose of measles-containing vaccines within two years of age, starting from 1986 for Italy and 1993 for Tuscany, respectively. [Source of Italian data: Ministry of Health available from: http://www.salute.gov.it/portale/temi/datidefconsMalattie.jsp; Source of Tuscan data: Tuscany Region health authority].



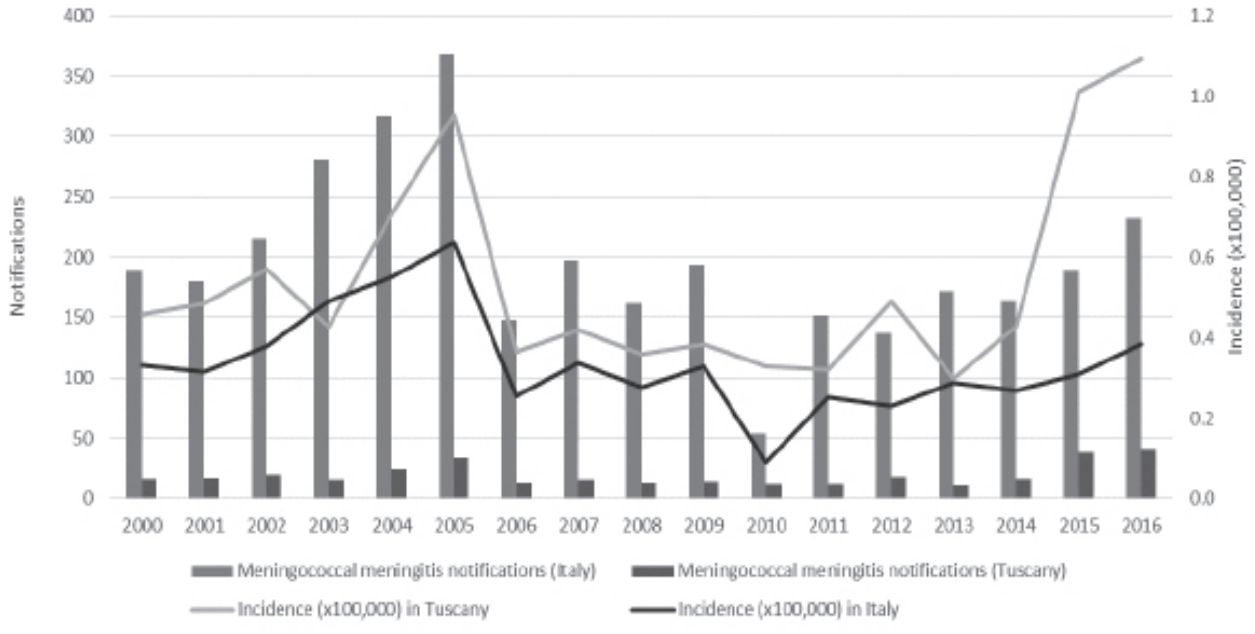
the 2002-03 epidemic of measles occurred in Italy, had a less impact in Tuscany than into the other Italian regions. In fact, only 330 and 218 cases were notified in 2002 and in 2003, respectively [10]. In the following years, a marked reduction in incidence was still observed, with only 3-55 cases reported in 2007 and 2006, but a peak of 600 cases occurred in 2008 (16.3 cases/100,000). The age group most affected was that of young adults (75%), confirming the achievement of optimal vaccination coverage in younger subjects, target of the vaccination program. Moreover, in the last years, a high susceptibility to measles in young adults in Tuscany was discovered [5]. In 2017, an epidemic of measles occurred in Italy and in Tuscany too. At national level 4,885 cases and 4 deaths were reported from 1 January 2017, including infants and adults (median age: 27 years). It involved especially unvaccinated subjects (88%) or subjects vaccinated with a single dose (6%), causing a high percentage of complications (35%) and a large number of hospitalizations (44%). Moreover, 315 cases occurred among health care workers [8]. From January 1 to April 30, 2018, 18 regions have reported to the national integrated measles and rubella surveillance system 1,258 cases of measles, including 4 deaths [11]. These evidences reflect the expected epidemiological shift of the mean age of infection towards older age groups caused by the missed goals of vaccination coverage in childhood. Improvement of vaccination coverage can be reached through additional vaccination strategies in hard-to-reach subjects (adolescents or adults) who are not included in the routine vaccination offer [12].

### Neisseria meningitidis type C

Although Italy, in the period 1994-2012, faced the lowest incidence rates for invasive meningococcal diseases (IMD) compared to other European countries, 3,929 cases of IMD have been notified to the surveillance system of Invasive Bacterial Diseases (MIB), and 2,280 cases (58.0%) were typed. Serogroup B has always been the most common, accounting for 60.3% (1,375 cases) of cases typed, followed by serogroup C (33%, 760 cases) [13]. On the other hand, serogroup C isolates progressively increased from 1994 to 2005 at national level [14, 15]. Figure 2 shows meningococcal meningitis notifications and incidence in Tuscany and Italy from 2000 to 2016.

In Tuscany, since 2006 a clear reduction in the number of Men C cases was observed, probably related to the introduction of conjugate vaccines against Men C in the regional immunization program. Since 2003, monovalent polysaccharide conjugate vaccination against Men C in Tuscany was offered to subjects at risk of all ages and it was accessible to all the other people in co-payment. Tuscany was the first Italian region to include Men C vaccination in the universal immunization program. Since 2005, three doses of vaccine were offered free of charge to children at 3, 5 and 13 months of age and one catch-up dose for children up to 6 years of age. Starting from 2008, the vaccination schedule was amended, and a single dose at 13 months of age to all infants was recommended [16]. In 2010, the goal of the Tuscany Region was to achieve a vaccination coverage of 80% [17]. Immunization coverage at 24 months of age, with monovalent vaccine against meningococcal C, progressively increased year after year, from 68% in 2006 to 90.5% in 2011. In 2006 vaccination coverage by birth cohort was 49% for children born in 2001 and 68% for children born in 2004, similarly in 2009 vaccination coverage was 61% for children born in 2000 and 87% for children

Fig. 2. Meningococcal meningitis notifications and incidence (x 100,000) in Tuscany and Italy from 2000 to 2016. [Source of Italian data: Ministry of Health available from: http://www.salute.gov.it/portale/temi/datidefconsMalattie.jsp. Source of Tuscan data: Tuscany Region health authority].



born in 2006 [14]. All cases of Men C observed from 2006 to 2011 occurred in unvaccinated subjects [15]. However, in 2015-2016 the incidence of IMD in Tuscany increased, and some cases occurred in subjects vaccinated 8 years before the symptoms onset [18]. For this reason, the Tuscany Region adopted a new vaccination strategy, to give protection to all adolescents already vaccinated and adults. Tuscany Region will monitor the epidemiological situation and the impact of this campaign will be visible in the coming years [19].

### Varicella

In Italy, according to the National Plan for Vaccine Prevention 2012-2014, the decision to recommend the universal vaccination varicella (UVV) in children has been postponed to 2015, for the 2014 birth cohort, when surveillance data on the impact of vaccination programs, already active in some Italian Regions, including Tuscany, will be available [4].

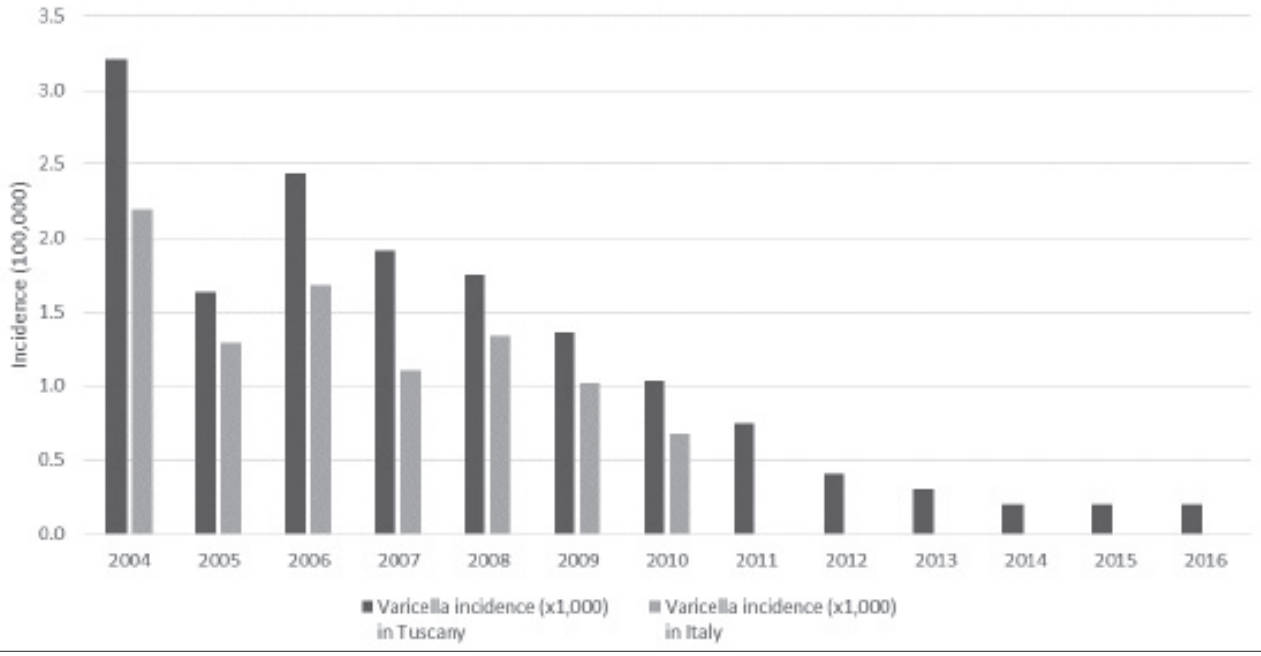
In Tuscany, UVV with two doses of quadrivalent Measles-Mumps-Rubella-Varicella (MMRV) vaccine is recommended for children 13-15 months and 5-6 years old since July 2008 [15]. UVV, was also endorsed by the 2010 and 2014 regional immunization schedules [20-21]. The introduction of UVV in Tuscany and in other seven Italian Regions in two doses for all newborns achieved remarkable results up to 2014 [22]. The high immunization coverage at 24 months of age (84% with one dose in 2012) was rapidly achieved in Tuscany, thanks to the drawing effect of the trivalent MMR vaccine coverage, close to 90%. Data on VC for varicella in 2016 was about 30% at the national level, because there was not a national recommendation since the launch of the new National Prevention Plan (2017-2019). While in the regions which have already introduced UVV, VC reached values between 65% and 86% [23]. Incidence rates of varicella cases decreased in the period 2004-2016 in Tuscany in all age groups (Fig. 3).

The degree of varicella underreporting in Italy, in individuals from 6 months to 20 years of age, in 2002 was 7.7 (95% CI 7.4-7.9). Underreporting was greater in older age groups and in southern Italy [24]. In Italian Central regions the underreporting rate is lower than in the South (about 5.4), this could explain the higher incidence values registered in Tuscany compared to the national average rate, from 2004 to 2010. National varicella notification data from 2011 to 2016 are not available in the surveillance system. (Fig. 3). Even at European level, existing surveillance systems are affected by underreporting and under-ascertainment [25].

Noteworthy, in Tuscany UVV has had a remarkable impact both in clinical-epidemiological and economic aspect. The introduction of universal varicella vaccination with MMRV in Tuscany has also resulted in a significant reduction of varicella-related hospitalisations, especially in subjects under 15 years of age and a total reduction of related costs. The UVV in Tuscany led to savings amounting to Euro 613,121 (Euro 153,280/year) already after four years of UVV implementation [26].

In the years 2009-2011 vaccination has had an overall rate of reported adverse reactions of 6/10,000 doses administered (45 cases out of 77,938 doses). Only 15 cases of adverse reactions were classified as serious, but without permanent damage [27]. Future UVV adoption in all Italian regions should be monitored with attention in order to avoid a possible shift of cases to adolescence or adulthood.

**Figure 3.** Varicella incidence in Tuscany from 2004 to 2016 and in Italy in the period 2004-2010. [Source of Italian data: Notification data 2004-2007: http://www.epicentro.iss.it/problemi/varicella/epid.asp and notification data 2008-2010: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=812&area=Malattie%20infettive&menu=vuoto; Source of Tuscan data: Tuscany Region health authority].



## Evaluation of the impact of vaccination: economic, ethical, social and communicative aspects

Immunization programs are different between Italian Regions, and sometimes these differences occur even into the same regional territories, resulting in a great heterogeneity of prevention practices at national level. In the most recent years Italian Regions have started to move towards a common strategy, but on open debate on health prevention policies to be adopted, is still going on.

Concerning the previous mentioned example of measles in Tuscany, increased vaccination coverage in children reduces the risk to contract the disease. In fact, vaccination coverage at 24 months of age has greatly improved in recent years at the national level; although, VC targets have not yet reached, differences in VC between Italian Regions are reducing. The increasing susceptibility to measles in young adults suggests the importance to establish vaccine strategies focused on this age group [12]. Moreover, in 2017 measles cases occurred in health care workers in Italy. In this professional group, immunization status to measles (and to other infectious diseases, such as rubella and varicella or pertussis) should be monitored. Not only for their direct protection, but also for the protection of the patients they care during their work; in particular in case of patients at risk of complications (i.e. pregnant women, newborns or immunocompromised subjects). It is fundamental to assess the impact of the immunization programs, through the monitoring of the VC trends and incidence rates. However, further efforts are needed to collect coverage and notification data in a standardized way in all regions, in order to obtain reliable surveillance figures and to plan and evaluate immunization programs.

High level of immunization coverage and disease incidence reduction have also been obtained in Tuscany with the extended use of monovalent meningococcal C conjugate vaccine (MCV). However, recent cases of meningococcal C meningitis occurred in Tuscany even in vaccinated subjects, highlighting the need to re-evaluate the current vaccination policies for all adolescent. Regional health authorities recommended the administration of a second dose of meningococcal C vaccine between 6 and 9 years, to counter the loss of immunity conferred by the first dose of vaccine, administered in the second year of life [28, 29], and a third dose of MCV was recommended even in adolescence [19].

Previous results about the UVV in Tuscany shown the social importance of vaccination as a preventive method, which can advantage not only the individual, but also the entire community. For many vaccines is possible to obtain a herd protection through the achievement of high immunization coverage in the target population to protect susceptible or vulnerable people inside the community, this represents the additional social value of vaccination [30]. Indeed, immunization allows the control and containment of circulation of microorganisms responsible of many infectious diseases. Vaccination has the advantage of providing protection to the whole community, resulting in a significant impact on the population's health in terms of infectious diseases control and reduction of disease burden (morbidity, mortality, use of medical care, hospitalizations), as well as on the decrease of costs attributed to the infectious diseases themselves [31]. In Tuscany the high level of varicella VC (84% in 2012) resulted in a significant decline in varicella notifications, from 33,114 (2004–2007) to 13,184 cases (2009–2012), and also of hospitalisations, from 584 (pre-vaccination period) to 325 (vaccination period). The hospitalisation rate was 4.1 per 100,000 before the introduction of vaccination, which dropped to 2.2 per 100,000 in the vaccination period [26]. These results obtained in Tuscany with UVV are similar to those achieved in other Italian regions. Sicily, which was the first Italian Region to offer free UVV to children at 15 months of life and to all susceptible adolescents in the twelfth year of age, since January 2003, quickly reached a rate of vaccination coverage equal to 65.5% in children (12-23 months) and 12.1% in adolescents (11-12 years) after 2 years. In the same period, the incidence rate of varicella decreased from 95.7 / 1,000 person-years in 2004 to 9.0 / 1,000 person-years in 2007 in pediatric population (0-13 years) [32, 33]. Since January 2005, Veneto Region has offered free UVV to children at 14 months of age, a second dose to 6 years old children and a catch-up program for 12-year-old children. Moreover, three years after the adoption of the varicella vaccination program in Veneto, an increase in vaccination coverage (78.6% in the cohort of 2008) and a clear decrease in the incidence of varicella in children (0-14 years) has been observed [34-36]. In the general population, the number of varicella cases in 2011 reduced by almost 85% compared to 2006 (from 13,700 cases to about 2,090 cases) [37]. Vaccination strategies can be implemented differently in each Regions depending on their needs, infrastructure and healthcare budget. However, ensuring high coverage remains the critical success factor for significant prevention of varicella when introducing varicella vaccination in the national immunisation programme [38].

More generally, the reduction over time of the incidence of vaccine-preventable diseases thanks to the increase of the immunization coverage and the loss of risk perception related to damages caused by infectious diseases in the general population, has fostered a tendency to question the real need of vaccines [39]. Moreover, in recent years refusal to vaccinations based on ideological and cultural convictions has gradually emerged [40], sometimes it is associated with a high (and often unfounded) perception of the risk of possible vaccination consequences (side effects, adverse reactions). The doubts and beliefs that often lead to the choice to vaccinate or not to vaccinate should be discussed with health professionals, in order to establish a trusting relationship and provide accurate, clear, complete, and up to date information. Therefore, counseling is the best strategy to guarantee that adherence or non-adherence to vaccination result from an aware choice [41]. Evidence suggests that personalized and targeted counseling, combined with a

good health service delivery, could increase vaccination coverage even among adults [42].
The decrease of the burden of disease due to vaccination strategies corresponded in Tuscany to an overall reduction of hospitalizations and consequently a decrease in the health costs related to hospitalizations and to the management of patients. Different Italian studies report that in case of a varicella hospitalization, the average cost per patient is around 2,050 euros. Azzari et al. in their study shown that the real hospitalization costs due to varicella are about 30-40% higher than those calculated with the Diagnosed Related Group (DRG) [43]. Vaccinations have also a significant economic impact that is higher than the costs supported by the National Health Service related to treatment, and included indirect costs generated for the whole society (loss of work days for the assistance to an infectious person). A good vaccination strategy could contribute to create a healthy population which is able to determine the classic engines of economic growth: a better education, a more qualified employment and technological progress, as well as international appraisal [44].
According to the latest estimates of the WHO-UNICEF, even if immunization coverage for childhood diseases is over 94% in the European Region, globally at least 24 million of children are not protected by vaccinations and in each country, there are high risk groups of population that continue to be susceptible to some diseases despite the obvious advantages of vaccinations. In the 2008-2009 measles outbreaks occurred in some European countries (Austria, Bosnia-Herzegovina, Bulgaria, France, Germany, Italy, Poland and Spain), the majority of cases were reported in people who had not been vaccinated for philosophical reasons or who were part of migrant groups with limited access to immunization services. Inequalities in the access to vaccination services are due to the different socio-economic conditions between countries or even inside a single country. However, even in countries with high Gross National Product (GNP) and high investment on health services and opportunities, there were large outbreaks with a high incidence of vaccine preventable diseases, mostly due to the influence in the general population of anti-vaccination movements, which often, are the cause of the limited vaccination acceptance. For example, in 2009, for the first time, 95% of measles reported cases were from people residing in EU countries with high socio-economic level (65% from Western Europe) [45].
The harmonization process of vaccination practices at national level should take into account an equal accessibility to healthcare services, territorial differences, the effectiveness of vaccinations strategies, moreover communicative solutions to contrast the overcome resistance in the population should be proposed and realized. The achievement and maintenance of high vaccination coverage, including high risk people, can guarantee a decrease in the incidence rates of infectious diseases and of their complications. For this reason it is important to sensitize the entire population implementing extraordinary immunization campaigns; trying to overcome territorial differences; strengthening all types of surveillance, making communication campaigns both for the population and for health professionals, involving health professionals in the empowerment process of the general population.

## Conclusions

In conclusion, all the evidences reported in this study confirm that public health vaccination policies, such as the ones adopted in Tuscany for the prevention of measles, meningococcal C diseases and varicella, have a high clinical, epidemiological, economic and ethical impact on the society. Vaccination programs should be constantly monitored and updated to reach high protective level of immunity inside the community, with particular attention to susceptible subjects or high risk groups.

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## Authors' contributions

AB, MC, EP, ET, CL, GB, PB, SB. All authors contributed equally to this paper.

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ORIGINAL ARTICLE

# Knowledge and attitudes on influenza vaccination among Italian physicians specialized in respiratory infections: an Italian Respiratory Society (SIP/IRS) web-based survey

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Keywords

Influenza • Influenza vaccination • Health-care workers

Summary

**Introduction.** *Influenza epidemics are one of the main causes of morbidity and mortality worldwide. Influenza vaccination is considered the most important public health intervention to prevent seasonal influenza infection. European health authority policies focus on patient protection by vaccinating both these subjects and their care-givers, including health-care workers (HCWs). The aim of this survey is to investigate knowledge about influenza vaccination and intention to get vaccinated among Italian HCWs who take care patients with respiratory disease.*
**Methods.** *An anonymous web-based survey was addressed to members of the Italian Respiratory Society (IRS).*
**Results.** *Among the 1,776 IRS members who have been invited to the survey, 144 (8.1%) completed the survey (97 men; median age 59 years; 85.4% Respiratory Disease). The vast majority recommended vaccination to all their patients (81%). More than two thirds of respondents considered influenza vaccination safe for immunocompromised patients. More than 50% of respondents underwent seasonal influenza vaccination in 2015 and 68% declared the intention to undergo vaccination in 2016 epidemic season. Reasons for having vaccination mainly referred to 'protect oneself from influenza' (63%), 'protect patients' (31%) or household members' (6%). The main reasons for vaccination refusal were 'lack of time' (45%), 'concerns about side effects' (22%), 'do not get influenza easily and/or not afraid of influenza infection' (22%) and 'disagreement with indication of vaccination for HCWs' (9%).*
**Conclusions.** *The promotion of better knowledge and attitude towards influenza vaccination among Italian specialists remains an unmet goal and should be addressed by appropriate multifaceted interventions.*

## Introduction

Influenza is one of the main causes of morbidity and mortality worldwide, especially among elderly and patients with chronic medical conditions [1]. Influenza epidemics represent a public health problem in Europe causing an increase in lost productivity and health-related costs due to complications especially among high risk patients [2, 3]. Influenza vaccination is considered the most important public health intervention to prevent seasonal influenza transmission and infection [2]. European guidelines and health authority policies for influenza focus on protecting high risk patients vaccinating both these subjects and their care-givers, including health-care workers (HCWs) [4].
A recent meta-analysis confirmed that influenza vaccination among HCWs is effective in preventing mortality and influenza spread [5]. Despite several efforts have been made over the past decade to promote influenza vaccination programs, vaccination levels among HCWs are still unsatisfactory worldwide [6]. For this reason, we aimed at investigating knowledge about seasonal influenza vaccination among Italian physicians who take care patients with respiratory disease, as well as intention to get vaccinated themselves and prevalence of vaccination in HCWs population.

## Methods

An anonymous web-based survey was designed by a task-force of the Italian Respiratory Society (IRS) including respiratory diseases and infectious diseases specialists. The questionnaire was available through web link pages and included multiple-choice questions (Tab. I). Respondents were allowed to give their reasons for having or not seasonal influenza vaccination as free additional text. The results are reported as mean ± IQR or proportion (%). Fisher's exact test was employed to compare categorical variables and continuous variables between groups, respectively. IBM SPSS software was used to statistical analyses.

**Tab. I.** Web-based survey questionnaire and results.

| | |
|---|---|
| **1. Demographics** | |
| Male | 97 (67.4%) |
| Median age | 59 (47 – 66) |
| Respiratory disease | 123 (85.4%) |
| Internal medicine | 12 (8.3%) |
| Infectious disease | 9 (6.3%) |
| Employed at academic institutions | 30 (20.8%) |
| **2. Working place and Italian region where the activity takes place** | |
| Northern Italy | 53 (36.8%) |
| Central Italy | 31 (21.5%) |
| Southern Italy | 60 (41.7%) |
| **3. What is the percentage of time that you spend in contact with patients?** | |
| More than 50% | 117 (81.2%) |
| Less than 50% | 27 (18.8%) |
| **4. Did you undergo influenza vaccination last year (2015-2016)?** | |
| Yes | 79 (54.9%) |
| No | 65 (45.1%) |
| **5. Are you planning to have vaccination or have you already did it this year (2016-2017)?** | |
| Yes | 99 (68.7%) |
| No | 45 (31.3%) |
| **6. Do you incur the risk to get influenza by vaccination?** | |
| Yes | 29 (20.1%) |
| No | 115 (79.9%) |
| **7. Is it safe for immunosuppressed patients to undergo vaccination?** | |
| Yes | 120 (83.3%) |
| No | 24 (16.7%) |
| **8. Can influenza vaccination be dispensed in association with anti-pneumococcal?** | |
| Yes | 142 (98.6%) |
| **9. What kinds of influenza vaccinations are available in your countries?** | |
| Trivalent injectable influenza vaccine | 59 (40.1%) |
| Quadrivalent injectable influenza vaccine | 70 (48.6%) |
| Others | 15 (11.3%) |
| **10. Is influenza vaccination mandatory at your jobsite?** | |
| Yes | 7 (4.9%) |
| No | 137 (95.1%) |
| **11. How do you consider communication about influenza vaccination from your hospital or institution?** | |
| Excellent | 19 (13.2%) |
| Good | 62 (43.0%) |
| Not sufficient | 63 (43.8%) |
| **12. Do you recommend influenza vaccination to all your patients at the right time?** | |
| Yes, I recommend vaccination to all my patients without contra-indications | 117 (81.2%) |
| No, I recommend influenza vaccination only to high risk patients | 27 (18.8%) |
| **13. What is the main reason for you to have influenza vaccination?** *NB. Only 104 respondents (72.2%)* | |
| Protect oneself 63% | 63 (60.6%) |
| Protect my patients 31% | 32 (30.8%) |
| Protect household members 6% | 6 (5.8%) |
| Others | 3 (2.8%) |
| **14. What is the main reason for you to refuse to have influenza vaccination?** *NB. Only 31 respondents (21.5%)* | |
| Lack of time | 14 (45.2%) |
| Concerns about side effects | 7 (22.6%) |
| No fear of influenza infection | 7 (22.6%) |
| Disagreement with indication of vaccination for health-care workers | 3 (9.6%) |

## Results

Among the 1,776 IRS members who have been invited to participate to the study, 144 (8.1%) completed the survey (97 men; median age 59 years, IQR 47 - 66). A total of 19 out of 20 Italian regions were covered. Among the respondents, 123 were respiratory diseases, 12 internal medicine and 9 infectious diseases specialists. Thirty respondents (20.8%) were employed at academic institutions. The majority of the respondents reported to recommend influenza vaccination to all their patients who do not have contra-indications (81%), while the remaining (19%) reported to advice on vaccination only high-risk patients. More than two thirds of respondents considered influenza vaccination safe even for immunocompromised/immunosuppressed patients. A total of 29 (20%) participants affirmed that vaccination can cause influenza. Co-administration of pneumococcal and influenza vaccine was considered a reasonable strategy for almost all respondents (99%) and 49% of respondents were aware of quadrivalente vaccine availability in Italy. More than 50% of respondents underwent seasonal influenza vaccination in 2015 and 68% declared the intention to undergo vaccination in current epidemic season. Reasons for having vaccination were reported by 72% of the vaccinated respondents and mainly refer to 'protect oneself from influenza' (63%), 'protect patients' (31%) and 'protect household members' (6%). The main reasons for vaccination refusal were 'lack of time' (45%), 'concerns about side effects' (22%), 'do not get influenza easily and/or not afraid of influenza infection' (22%) and 'disagreement with indication of vaccination for HCWs' (9%).

## Discussion

The present survey shows a general good understanding of the indications for influenza vaccination among Italian physicians taking care patients with respiratory diseases. However, a subgroup of respondents showed inadequate understanding on important issues, as vaccination safety. Lack of knowledge and concerns about safety may affect vaccination rate. Despite these limitations, vaccination rate in this population is higher than previously reported.

The response rate of this survey was lower than expected and, despite the target population was mainly made of specialists dealing with respiratory infections, our assumption is that the issue being addressed might not be of interest for most of the invitees. This scenario is even more alarming in consideration of the large amount of efforts spent by health authorities to change the attitude of HCWs and the public toward influenza vaccination [7].

The survey highlights that influenza vaccination is a common recommendation, at least for high risk groups of patients. The relatively high rate of respondents affirming that vaccination can cause influenza reveals that unreasonable concerns about side effects are common even among specialists. No difference between this group and other respondents was observed in term of age, working place and vaccination rate. A further statistical description was not possible due to the small sample size. Inadequate knowledge among HCWs on such an important issue as vaccine safety may result in false information to patients, thus possibly affecting the success of vaccination campaigns [8]. These results emphasize the strong need to target HCWs with an appropriate training which has been missed in Italy over the past decades. Specific information and proper tailored educational programs need to be improved by health authorities and institution in consideration that almost 44% of participants rated communication strategies about influenza vaccination as rather unsatisfactory. The 2016 statement for the prevention of influenza edited by the Italian public health authority strongly recommends influenza vaccination among HCWs as a cost-effective measure to reduce infection among medical personnel and prevent morbidity and mortality among high risk group of patients [9]. Despite these recommendations, vaccination coverage rates seem to be very low in Italy and across Europe [10]. A cross-sectional survey carried during two 2007/2008 influenza seasons in several European countries confirmed that the coverage rates among HCWs were generally low, ranging from the lowest rate of 6.4% in Poland to 26.3% in Czech Republic; in Italy, the vaccination coverage rate among HCWs was about 12% [10]. Differently, in this survey more than the half of participants had seasonal influenza vaccination in 2016 resulting in a coverage level far better than previously reported. Consistently with this report, the majority of respondents declared the intention to undergo vaccination in that season and up to 90% would recommend it to colleagues. Vaccination coverage rate presented here is still suboptimal but higher than the rate reported by previous experiences [10, 11]. As already noted by Blasi and colleagues in a similar experience, this may be due to the high prevalence of pulmonologists in this population [12]. Specialists dealing with respiratory infections may be more sensitized towards influenza vaccination than other colleagues.

The generalizability of the study should be carefully considered under the light of several limitations. First, as discussed above, the response rate is lower than expected affecting the reproducibility of the results on a larger scale. Secondly, self-reporting may affect the quality of data presented here. Thirdly, the proportion of the vaccinated physicians among the non-respondents is impossible to be assessed. Fourthly, physicians choosing to answer the questionnaire may have been more motivated towards vaccination, so that a selection bias cannot be ruled out. Finally, the collection of data might miss a part of the vaccination season due to the point-prevalence design of the study. On the other hand, this survey provides a real-life snapshot on the lack of interest among HCWs toward seasonal influenza vaccination. In addition, our analysis has suggested a subgroup among specialists with inadequate knowledge about vaccination safety. A further characterization should be needed in or-

der to provide this population with targeted educational interventions.

## Conclusions

The promotion of better knowledge and proper attitude for Italian specialists towards influenza vaccination remains an unmet goal and should be addressed by a multifaceted intervention, including appropriate training and the promotion of proactive attitudes.

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## Authors' contributions

Conception and design: FB and AG. Analysis and interpretation: SA, MM, FB and AG. Drafting the manuscript: AG. All authors participated in writing and revising the article prior to submission. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

# A *Clostridium difficile* outbreak in an Italian hospital: the efficacy of the multi-disciplinary and multifaceted approach

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Keywords

*C. difficile* • Outbreak • Infection control practices • Implementation

Summary

**Introduction**. *We described an outbreak of C. difficile that occurred in the Internal Medicine department of an Italian hospital and assessed the efficacy of the measures adopted to manage the outbreak.*

**Methods**. *The outbreak involved 15 patients and was identified by means of continuous integrated microbiological surveillance, starting with laboratory data (alert organism surveillance). Diarrheal fecal samples from patients with suspected infection by C. difficile underwent rapid membrane immuno-enzymatic testing, which detects both the presence of the glutamate dehydrogenase antigen and the presence of the A and B toxins. Extensive microbiological sampling was carried out both before and after sanitation of the environment, in order to assess the efficacy of the sanitation procedure.*

**Results**. *The outbreak lasted one and a half month, during which time the Committee for the Prevention of Hospital Infections ordered the implementation of multiple interventions, which enabled the outbreak to be controlled and the occurrence of new cases to be progressively prevented. The strategies adopted mainly involved patient isolation, reinforcement of proper hand hygiene techniques, antimicrobial stewardship and environmental decontamination by means of chlorine-based products. Moreover, the multifaceted management of the outbreak involved numerous sessions of instruction/training for nursing staff and socio-sanitary operatives during the outbreak. Sampling of environmental surfaces enabled two sites contaminated by C. difficile to be identified.*

**Conclusions**. *Joint planning of multiple infection control practices, together with effective communication and collaboration between the Hospital Infections Committee and the ward involved proved to be successful in controlling the outbreak.*

## Introduction

*C. difficile* is a Gram-positive anaerobic bacterium. Its vegetative cells are capable of forming spores, which confer resistance to heating, drying and chemical agents, including disinfectants. The pathogenic strains of *C. difficile* produce large exotoxin proteins, toxin A (TcdA) and toxin B (TcdB), which constitute the principal virulence factors of the microorganism [1, 2].

Disease caused by *C. difficile* can range in severity from mild diarrhea to fulminant pseudomembranous colitis and, without suitable treatment, toxic megacolon and death [3]. A recent prevalence survey of healthcare-associated infections (HAI) conducted in 183 hospitals determined that *C. difficile* was the most frequently reported infectious agent, being responsible for 12.1% of all HAI [4, 5].

*Clostridium difficile* has increased in prevalence since 2000, and has caused outbreaks of nosocomial diarrhea worldwide [6]. The main cause of most outbreaks of *Clostridium difficile* infection is NAP1/BI/027: a more virulent ribotype that has been associated with significantly higher morbidity and mortality as a result of more severe complications [7]. It is characterized by an *in vitro* overproduction of toxins A and B and by the production of binary toxins [2].

The principal risk factor in *Clostridium difficile* infection (CDI) is antibiotic use, and antibiotics from almost all classes have been associated with infection [7]. Other well-described risk factors are: advanced age, extensive comorbidity, and prolonged hospital stay leading to asymptomatic carriage, recurrent diarrhea, pseudomembranous colitis, or death [7-10].

Patients suffering from *C. difficile* infection shed large amounts of spores that are resistant to disinfectants and regular cleaning procedures, contaminating their surroundings and the hands of nurses, medical staff and others who come into contact with them; hence, contaminated environmental surfaces play a major role in the transmission of *C. difficile* in hospitals [11, 12].

The mortality associated with CDI is high, particularly in older adults with comorbid conditions, severe disease and illness caused by the NAP1 strain of *C. difficile* [13]. Mortality is at least 6% within 3 months of diagnosis and 13% in patients >80 years of age [14].

The economic impact of CDI on the healthcare system is significant, as it doubles the average length of hospitalization and increases the cost of treatment [6, 15]. Nosocomial transmission highlights the importance of rigorous infection control practices for preventing the spread of *C. difficile* [14, 16].

The aims of the present study were to describe an outbreak of *C. difficile* that occurred from 29 December 2015 to 15 February 2016 in the Internal Medicine department of an Italian hospital and to assess the efficacy of the measures adopted to manage the outbreak.

## Methods

The outbreak occurred in a nationally renowned, highly specialized hospital in northern Italy, organized in accordance with treatment intensity. The facility is composed of separate pavilions with a total of 431 beds. The ward directly involved was female internal medicine, which has 26 beds.

Hospital infection cases were defined as patients with positive toxin assays > 48 hours after hospital admission. The outbreak, which involved 15 patients from 29 December 2015 to 15 February 2016, was identified by means of continuous integrated microbiological surveillance, starting with laboratory data (alert organism surveillance). Following laboratory identification of an epidemiologically important microorganism, the dedicated software of the surveillance system automatically e-mails the data to all the members of the Hospital Infections Committee (made up of members of the hospital's healthcare administration, physicians, microbiologists, infectious disease specialists, epidemiologists), who then implement the interventions deemed necessary, with particular regard to the application of isolation measures. A validated report is simultaneously sent through the laboratory information system to the hospital facility involved.

For patients with a diagnosis of *Clostridium difficile*, information on age, history of hospitalizations, antibiotic treatments, duration of hospitalization and outcome were collected.

### Microbiological analysis

Diarrheal fecal samples from patients with suspected infection by *C. difficile* underwent rapid membrane immuno-enzymatic testing by means of the TECHLAB C. diff Chek Quick Complete® (Alere™) kit, which detects both the presence of the glutamate dehydrogenase (GDH) antigen, as a means of screening for *C. difficile*, and the presence of the A and B toxins.

### Environmental investigation

Extensive microbiological sampling was carried out both before and after sanitation of the environment, in order to assess the efficacy of the sanitation procedure. Sampling was carried out at 14 sites of high-frequency contact; the sampling points were selected in accordance with the checklist of the CDCs reported in the APIC guidelines "Guide to Preventing *Clostridium difficile* Infections" [17], which specifies the critical points to be examined in the event of an outbreak. Monitoring therefore included critical surfaces in proximity to the patient's bed (e.g. personal light switch and call button) and other surfaces at high risk of contact with hospital personnel (e.g. medicine trolley, light switch, curtains between the beds, etc) or patients.

In accordance with the methods of Best et al. [18] and Ali et al. [19], specimens were taken by using 25-cm$^2$ sponge swabs pre-moistened with neutralizing solution (Medical Wire & Equipment, England). The swabs were then placed aseptically into sterile Stomacher bags containing 50 ml of Ringer solution (Oxoid) and homogenized manually by vigorously massaging the bag between the fingertips for 1 min. Liquid from the bag was passed through a 0.45-μm filter (Millipore), which was then placed aseptically onto Brazier's *Clostridium difficile* selective agar (Oxoid). Plates were then incubated at 37°C under anaerobic conditions for 48 h prior to reading.

*C. difficile* was initially identified on the basis of the macroscopic appearance of colonies and microscopic characteristics, and confirmed to be *C. difficile* by means of latex agglutination testing (Oxoid *C. difficile* Test kit).

## Results

### Description of the outbreak

Following the analysis of patients' records, a possible index case was identified: an 86-year-old woman hospitalized on 16 December 2015 in the ward where the outbreak originated. This patient had already been admitted to the same hospital in the previous month (geriatric ward) for bronchopneumopathy.

On 12 December she was taken to the Emergency Department with bruising to the pelvis after a fall at home. A bilateral pleural effusion and respiratory insufficiency were diagnosed. She was therefore hospitalized in the Sub-intensive Care Unit and, after being stabilized, was transferred to the Internal Medicine Department three days later.

Table I reports the characteristics of the patients involved in the outbreak. Their mean age was 82.13 years (range 70-90 years), the mean Charlson index was 7 (range 4-13) and the mean duration of hospitalization before the first isolation of *C. difficile* was 16 days (range 4-34 days). With regard to outcome, 5 patients died (4 attributable to *C. difficile*), 6 were transferred to other healthcare facilities and/or wards, and 4 were discharged.

In 86.67% of cases, the *C. difficile* strain responsible for the infection produced both toxin A and toxin B; in the remaining cases, weak positivity to the immuno-enzymatic test was recorded. The patients were treated with metronidazole and, in the event of failure, vancomycin.

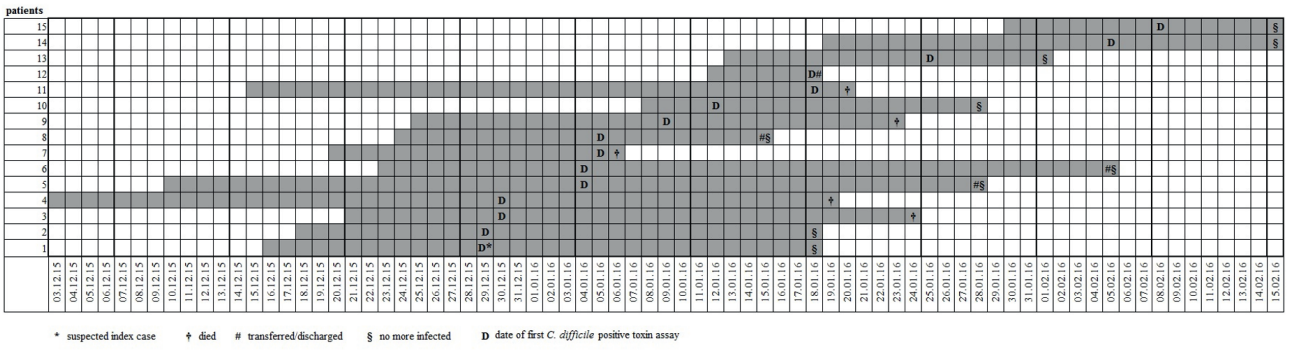
Figure 1 describes distribution of *Clostridium difficile* infected patients as a function of time

**Tab. I.** Characteristics of patients involved in the outbreak

| Patient | *Clostridium difficile* toxins | Days of hospitalization | Age | Charlson index | Bed | Outcome |
|---|---|---|---|---|---|---|
| 1* | A and B | 16 | 85 | 7 | 23 | Transferred |
| 2 | A and B | 11 | 80 | 7 | 24 | Transferred |
| 3 | A and B | 9 | 70 | 12 | 6 | Died |
| 4 | A and B | 27 | 88 | 6 | 5 | Died |
| 5 | A and B | 26 | 79 | 4 | 8 | Discharged |
| 6 | Weak positivity | 13 | 84 | 6 | 9 | Discharged |
| 7 | A and B | 16 | 75 | 7 | 1 | Died |
| 8 | A and B | 12 | 85 | 5 | 10 | Discharged |
| 9 | A and B | 15 | 90 | 8 | 7 | Died |
| 10 | A and B | 4 | 84 | 5 | 1 | Discharged |
| 11 | A and B | 34 | 80 | 6 | 14 | Died |
| 12 | A and B | 16 | 77 | 4 | 23 | Transferred |
| 13 | Weak positivity | 12 | 80 | 7 | 10 | Transferred |
| 14 | A and B | 17 | 88 | 6 | 6 | Transferred |
| 15 | A and B | 12 | 87 | 13 | 26 | Transferred |

*Suspected index case

**Fig. 1.** Distribution of *Clostridium difficile* infected patients as a function of time.



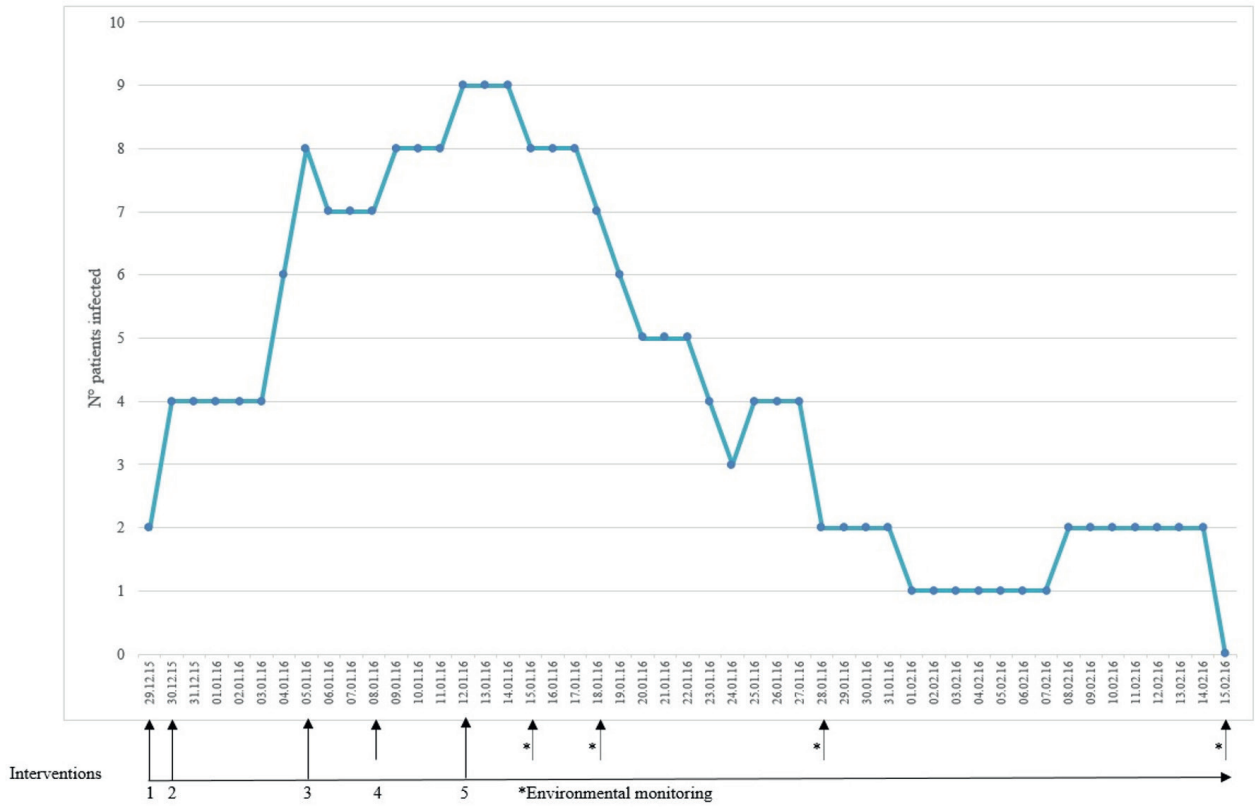

## Infection control practices during the outbreak

Figure 2 shows the epidemic curve of the outbreak from 29 December 2015 to 15 February 2016. The timescale of the interventions implemented by the Committee for the Prevention of Hospital Infections is also indicated. From the moment when the first two cases of infection were diagnosed an antimicrobial stewardship program and the following interventions were implemented:

**Intervention 1**: from 29 December 2015:

- Specification of the measures to be taken in order to contain risk of infection by *Clostridium difficile,* considering all patients to be potentially infected; written instructions delivered to all healthcare personnel involved.
- Testing for *C. difficile* toxins in all symptomatic patients.
- Isolation in cohorts of infected patients; assistance to cohorts (dedicated operators); use of dedicated small devices (e.g. oximeter, hemoglucotest device, etc) for infected patients.
- *Ad hoc* environmental sanitation for *Clostridium difficile* in the entire department (with 20% concentrations of chlorine-based detergent), including decontamination of telephones and computer keyboards and screens (ready-to-use sodium hypochlorite solution). In order to facilitate adequate daily sanitation, bedside tables were kept clear of all but indispensable objects (bottle of water and glass).
- Checking to ensure that healthcare personnel complied with hand hygiene protocols. In addition, the hands of all non-self-sufficient patients were washed more frequently and self-sufficient patients were instructed on how to wash their hands properly.
- Checking to ensure that gloves were used properly and were changed after assisting each individual patient, and that hands were washed immediately after the removal of gloves.
- Operators involved in direct assistance were instructed to change their overalls daily and were encouraged to use microfiber overalls, which are more protective of the hygiene of infected patients, and disposable nonwoven gowns.
- Staff were forbidden to use personal mobile phones while assisting infected patients.

**Fig. 2.** Epidemic curve of the *C. difficile* outbreak and the timescale of the interventions implemented.




- Correct patient hygiene practices were emphasized; soiled underwear was placed in an impermeable bag labeled with the patient's name, which was then placed in a dedicated container inside the room/cubicle. If a patient lift was used, the sling cover was changed for each patient and sent for disinfection as if it were certainly infected; the same approach was adopted towards minor aids, for which disposable protective covers were also used.
- The number of visitors was reduced, and a specific information leaflet concerning the behavior of visitors to infected patients was distributed; this provided instructions on hand washing and interpersonal contact.

The day after implementation of intervention 1, another two cases of infection were discovered. Following a meeting to update and instruct nursing staff and social/healthcare workers, the second phase of intervention was implemented.

**Intervention 2**: from 30 December 2015:
- Simulation of donning and removing personal protection devices (PPD).
- Reiteration of procedures for the proper sanitation of stands for i.v. drips, commode chairs, infusion pumps, PCs and telephones.
- Meals served in heat-sealed containers for all patients.
- Checking of proper isolation of infected patients (e.g. collocation of the patient, supply of hand-washing requisites, availability of disposable overalls, materials and dedicated devices, etc.); this revealed the need to supply some types of medical devices for dedicated use (e.g. stethoscope and sphigmomanometer).
- Urgent processing of fecal samples for culture tests; prompt telephone communication of positive reports to the expert consultants of the Committee for the Prevention of Hospital Infections, for immediate application of the necessary measures.
- Periodic checks on compliance with the measures recommended.

**Intervention 3**: from 5 January 2016
- Ward staff increased on both day shifts and night shifts.

**Intervention 4**: 8 January 2016
- Review of cases following the administration of antibiotic treatment and implementation of the control measures; assessment of the need to institute further briefings/training for medical and nursing staff.

**Intervention 5**: from 12 January 2016
- Structural, logistical and organizational segregation of infected patients (left side of the ward) from unin-

fected patients (right side), and consequent reorganization of the activities of sanitation and assistance.
- Direct observation to ensure proper implementation of the measures to contain the risk of infection, and institution of "on the job" staff training with regard to: donning and removal of personal protection devices; the hygiene of infected patients, with particular regard to the hands; decontamination of the patient-unit; use of personalized devices for each patient; decontamination of the environment, materials and medical devices; functional isolation of cohorts; institution of a differential pathway from "clean" to "dirty"; proper collection and conservation of fecal samples prior to analysis; application of medication to CVC with maintenance of asepsis in infected patients; healthcare education of visitors, with simulation of hand hygiene.

From this date onwards, thanks to the set of control measures adopted, the number of cases of infection progressively diminished, and the last two cases recorded on 8 February 2016 were resolved.

#### Environmental monitoring

The microbiological results of environmental monitoring conducted on 15 January 2016 revealed contamination by *Clostridium difficile* on the curtain separating two beds that had been occupied by patients involved in the outbreak (beds 23 and 24) and on the call button of bed 24. The curtain was promptly removed and disposed of, and the entire environment was thoroughly disinfected. Subsequent monitorings, carried out after environmental sanitation, revealed no contamination by *C. difficile*.

## Discussion

Several reports suggest that the incidence and severity of *C. difficile* infection have been increasing in recent years across the United States, Canada and Europe. Recent data from 28 community hospitals in the southern United States suggest that *C. difficile* has replaced methicillin-resistant *Staphylococcus aureus* as the most common cause of healthcare-associated infection [20, 21]. The burden of healthcare-associated CDIs in acute-care hospitals in the EU/EEA has been estimated at 123,997 cases annually. In the ECDC point prevalence survey of healthcare-associated infections in European acute-care hospitals 2011-2012, *C. difficile* was the 8th most frequently detected microorganism among HAIs [22].

In the present study, we documented the occurrence of 15 cases of *C. difficile* infection in an internal medicine department in an Italian hospital. During the outbreak the Committee for the Prevention of Hospital Infections ordered the implementation of multiple interventions, which enabled the outbreak to be controlled and the occurrence of new cases to be progressively prevented.

The outbreak described in this paper started and finished in a single ward, involved a relatively small number of patients, and lasted one and a half month. Wong-McClure et al. [23] described an outbreak due to *C. difficile* that involved three wards and 389 patients, and which lasted for several months. More recently, van Beurden et al. [6] described an outbreak that involved 19 wards and 72 patients, and which lasted for a year.

As pointed out by several studies, there may not be a single method that is effective in minimizing exposure to *C. difficile*, and a multifaceted approach is usually required [24]. Indeed, the management of CDI in hospitals requires just such a multidisciplinary approach, which begins with infection prevention. A previous study by Weiss et al. [25] showed that a multi-pronged intervention strategy is most effective in reducing the rate of healthcare CDI.

Strategies for the prevention and control of *C. difficile* infections are aimed at promptly identifying, isolating and efficaciously treating patients affected by CDI (in order to reduce the dissemination of spores and prevent secondary cases) and at minimizing preventable risk factors through the implementation of protocols of behavior, environmental sanitation and antibiotic stewardship [26].

In accordance with this approach, the strategies adopted for the control of the *Clostridium difficile* outbreak described here mainly involved patient isolation, reinforcement of proper hand hygiene techniques, antimicrobial stewardship and environmental decontamination by means of chlorine-based products.

Indeed, the presence of other patients with infection, hand carriage on the part of healthcare personnel and contaminated environmental surfaces are considered to be major factors in the transmission of pathogens in hospitals [27-29], including *C. difficile*.

When there is an infected patient in hospital, the hospital environment is contaminated by spores within a few hours of the onset of diarrhea; other patients may therefore be infected and the patient himself/herself may be reinfected. Moreover, *C. difficile* spores are highly resistant to many commonly used disinfectants and may persist for months in hospital environments [30].

Environmental contamination with *C. difficile* spores occurs at as many as 34-58% of sites, despite cleaning, with surfaces of fomites being most frequently contaminated [18].

Frequenly touched surfaces in near patient areas are rapidly contaminated by the microorganisms disseminated by the infected patient occupying the room, and may remain contaminated for extended periods of time [31]. Consequently, *C. difficile* can be found on hospital floors, on bedrails, windowsills, commodes, toilets, call buttons, blood pressure cuffs, electronic thermometers, bedsheets and anything that comes into contact with contaminated hands [32]. Thus, thorough disinfection of the contaminated hospital environment is essential in order to prevent the transmission of this nosocomial pathogen, and the choice of hospital decontamination protocols can markedly affect the prevalence and environmental distribution of *C. difficile* contamination [33].

The scientific evidence supports the use of detergents containing chlorine (at least 1000 ppm of active chlo-

rine) in endemic situations or during epidemic outbreaks [1]. A study by Fawley et al. [33] compared the efficacy of five different cleaning agents against epidemic and non-epidemic *C. difficile* strains. They found that only chlorine-based germicides were able to inactivate *C. difficile* spores.

Contamination of the hands of healthcare staff and patients with *C. difficile* is a major route of transmission of the infection, and there is a close correlation between hand contamination and the degree of environmental contamination. For this reason, proper hand hygiene is crucial to preventing the transmission of *C. difficile* in the hospital setting [32].

During the outbreak described in this paper, various interventions were undertaken in order to ensure adherence to hand hygiene protocols on the part of healthcare staff and patients; those visiting infected patients were also taught to wash their hands and to limit contact only to the patient being visited. Indeed, checking the staff's compliance with hand hygiene has been deemed a more effective strategy than microbiological testing of the hands by means of sampling.

A recommendation common to many guidelines on the prevention and control of healthcare-related infections concerns the training of healthcare personnel, visitors, caregivers and patients themselves. The multifaceted management of the outbreak described here involved numerous sessions of instruction/training for nursing staff and socio-sanitary operatives during the course of the epidemic. By modifying risk behaviors, these interventions certainly helped to control the outbreak.

Equally important was environmental monitoring. Limited to times of outbreak, rather than being part of routine practice, this can provide a valuable estimate of the level of contamination on surfaces such as walls, work surfaces, floors and equipment [34] and is currently recommended by the Centers for Disease Control and Prevention [35]. In the present case, sampling of environmental surfaces enabled two sites contaminated by *C. difficile* to be identified, one of which was a soft plastic-coated curtain separating two beds that had previously been occupied by infected patients. As this curtain would have been very difficult to disinfect, it was removed and disposed of immediately after the detection of contamination; this measure may well have enabled an environmental reservoir of the microorganism to be eliminated, a hypothesis that is also supported by the trend in the epidemic curve after the implementation of environmental monitoring.

In conclusion, joint planning of multiple infection control practices, together with effective communication and collaboration between the Hospital Infections Committee and the ward involved proved to be successful in controlling the outbreak.

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All authors declare that there is no conflict of interest.

## Authors' contributions

MLC conceived and designed the study. AB collected data. BC performed the data quality control. ES performed environmental controls. MS validating and analysing the data. MLC and AMS wrote the paper. GLP revised the manuscript. All Authors revised the manuscript and gave their contribution to improve the paper. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

# Hospital discharge in patients at risk of surgical site infection: antimicrobial stewardship at Ferrara University Hospital, Italy

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## Keywords

Antimicrobial stewardship • Surgical patients • Hospital discharge • Surgical site infections

## Summary

**Introduction.** *The appropriate use of antibiotics is a global priority in order to avoid antibiotic resistance. Up to 50% of antibiotics usage in hospital is inappropriate (e.g. prolonged surgical prophylaxis, "defensive medicine" approach). In 2015, at the Ferrara University Hospital, an antimicrobial stewardship intervention to reduce antimicrobial prescription at the time of hospital discharge in patients at risk of surgical site infection was implemented. This programme included: update meetings for health professionals, focused meetings for critical wards, reviews of some surgical prophylaxis protocols, recommendations to reduce broad-spectrum antimicrobials use, and planning of an audit. The purpose of this study has been to evaluate the effect of this antimicrobial stewardship programme.*

**Methods.** *To evaluate the effect of this intervention, a study has been carried out including inpatients in surveillance for surgical site infection who had surgery during the last quarter of 2014 (pre-intervention group; 461 patients) and of 2015 (post-intervention group; 532 patients).*

**Results.** *The proportion of patients with prescription of at least one antimicrobial at discharge decreased from 33% to 24.4% ($p = 0.002$). The most prescribed categories of antimicrobials in both groups were the combination of penicillins with beta-lactamase inhibitors (with prescription rate reduced from 21.9% to 18%; $p = 0.13$) and fluoroquinolones (from 8.2% to 3.2%; $p < 0.001$).*

**Conclusions.** *This statistically significant reduction in antimicrobial prescription after the intervention was registered without a change in surgical site infections rate (from 3.5% to 3.2%; $p = 0.08$). Therefore, this intervention was effective in reducing the antimicrobial prescription at discharge, without affecting patients' safety.*

## Introduction

The rapid worldwide antibiotic-resistant bacteria spread is affecting the efficacy of antibiotics [1, 2]. Antibiotic resistance mainly results from the excessive and inappropriate use of antibiotics [1, 3]. The consumption of antibiotics is globally increasing every year, creating the preconditions of a global public health emergency [4].

Antibiotic resistance causes an increase in morbidity and mortality as well as an increase in hospitalizations and costs [5, 6]. In Europe, infections sustained by antimicrobial resistant germs cause about 25,000 deaths every year and a cost of at least 1.5 billion euros [6, 7].

Appropriate use of antibiotics can help to counteract bacteria-resistance development and to preserve drug's efficacy for the use in the future [8]. Since a long time, the international scientific community has underlined the need to hinder this phenomenon and to sustain the proper use of antibiotics, that is their targeted, rational and moderate use [9]. Despite these international guidelines, it is estimated that about 20-50% of antibiotics usage in acute-care hospitals is either unnecessary or inappropriate [10]. This phenomenon unnecessarily exposes patients to potential side effects of antimicrobial therapy [11].

Italy is among the European countries with the highest levels of antibiotic resistance and with the highest use of antibiotics both in the community and in the hospital setting [6, 7, 12].

In the hospital setting, about 40-50% of all antibiotic prescriptions involves peri-operative antibiotic prophylaxis [13], which is one of the tools to reduce the incidence of surgical site infections (SSI) [14].

According to guidelines in use and to scientific evidence, surgical prophylaxis should be limited to perioperative period, be given immediately prior to the onset of surgery and not extended beyond 24 hours from the surgical procedure [13, 15]. However, in many cases antibiotic prophylaxis is prolonged in the post-operative period, in the attempt to reduce the incidence of SSI [14, 15]. This

misuse of antibiotics is not justified, as it is ineffective in further reducing the incidence of SSI, can cause an increase in antibiotic resistance, and can predispose to serious infections [13-15].
This phenomenon may be accompanied by an inappropriate or excessive prescription for antibiotics at hospital discharge, related to a "defensive medicine" behavior [16].
Several studies demonstrate that hospital-based programs dedicated to enhance antimicrobials' use, generally known as antimicrobial stewardship programs, can both reduce hospital acquired infections and multi-drug resistant microorganisms, limiting in addition adverse events resulting from antimicrobials use [17].
Several methods of antimicrobial stewardship can be implemented in order to counteract this attitude (e.g. audit and feedback, continuing education, recommendations, etc.) [18], even if there is no unanimous consensus on the impact of different interventions [19].
The purpose of this study has been to evaluate the effect of an antimicrobial stewardship intervention focused on the reduction of antimicrobial prescription at the time of hospital discharge in patients at risk of SSI involved in a surveillance programme at the Ferrara University Hospital.

## Methods

### Setting

Ferrara University Hospital is an Italian tertiary public acute care hospital with 637 ordinary and 84 day-hospital beds, 24,023 regular admissions (excluding healthy new-borns), 8,022 admissions in day-hospital and 10,055 surgical operations per year (data referring to 2016).

### Antimicrobial stewardship intervention

With reference to existing data, demonstrating the opportunity to optimize antimicrobial prescription at discharge, particularly in surgical patients, in 2015 Ferrara University Hospital implemented a multidisciplinary antimicrobial stewardship intervention including five main components: three update meetings for health professionals, focused meetings for critical wards, reviews of some surgical prophylaxis protocols, recommendations to reduce broad-spectrum antimicrobials use, and planning of an audit.
The three update meetings focused on the most emerging infections in our hospital (infections due to *Clostridium difficile*, pneumonia, sepsis) and on responsible antimicrobial use. These meetings involved medical and nursing personnel and were held by a team, called "Operative Group for the responsible use of antimicrobials", composed of an infectious disease specialist, a microbiologist, a specialist in hygiene and preventive medicine (responsible for hospital infection control), and a nurse specialized in infection control. During each meeting the epidemiological characteristics, risk factors and hospital guidelines for diagnosis and therapy were discussed, with particular attention to the appropriate use of antimicrobials during the whole hospital stay, discharge included. In particular it was asked for the reduction of fluoroquinolones use, that were found to be overused in the past years if compared to regional data (e.g. 23.9 vs 14.4 DDD/100 inpatient days in 2013) [20].
Furthermore, the team performed focused meetings with health workers of the surgical units that showed the highest prescription of antimicrobials on discharge in 2014, in order to find out specific solutions.
Then, a review of some perioperative chemoprophylaxis protocols was made.
Finally, was highlighted the indication to follow the institution's guidelines to reduce the prescription for some types of antimicrobials (in particular broad-spectrum ones) and to indicate the motivation for the antimicrobial prescription in the discharge letter.
During these interventions, the surgical units staff was informed that in the future would have been performed an audit in order to check the situation about antimicrobial prescription at discharge.

### Inclusion and exclusion criteria

In order to determine the impact of the antimicrobial stewardship intervention, a study including surgical inpatients involved in the Italian national surgical site infection surveillance programme (SNICh) [21] had been performed.
We chose this group of subjects as these patients have a short hospital stay and a higher risk of developing SSIs, being therefore potentially exposed to a prolonged antimicrobial prophylaxis or to an inappropriate prescription at discharge. The study involved all inpatients undergoing an operative procedure included in the SNICh surveillance program during the last quarter of 2014 (pre-intervention group) and the last quarter of 2015 (post-intervention group).
In this study, surgical inpatients in SNICh surveillance admitted in surgical units that did not use the digital discharge letter (otolaryngology, gynaecology, obstetrics, and ophthalmology wards) or patients died during the hospital stay were excluded.

### Data collection

The same method to collect data for both periods was used. Demographic, clinical and surgical characteristics of patients were extracted from computerized register of surgical operations. Information on the antimicrobials prescribed at discharge and the characteristics of the post-operative course were extracted from the digital discharge letters stored in institution's data warehouse.
Data were recorded in anonymous form on an electronic worksheet for processing. For each patient the information considered were the following: age, gender, and duration of hospital stay (days); American Society of Anesthesiologists (ASA) score [22]; type of surgery (elective or urgent-emergency surgery); operative procedures, surgical wound contamination class and pros-

thetic implant material classified or definite according to the SNICh protocol [21]; duration of operative procedure (minutes); characteristics of the post-operative clinical course described in the digital discharge letter (regular or complicated); characteristics of antimicrobials prescribed at hospital discharge (number and typology of active principle, classified according to the Anatomical Therapeutic Chemical classification - ATC [23]) and characteristics of SSI (according to the SNICh protocol [21]), when applicable.
Data collection related to the two groups was completed in December 2015 and 2016, respectively.

### Objectives

The primary purpose of this study was to assess if a statistically significant change in antimicrobial prescription behaviour at discharge occurred after the stewardship intervention. Secondarily, it was checked if a change in SSIs rate among the studied groups occurred.

### Statistical analysis

Pearson's chi-square test, Fisher's exact test, and t-test were used to perform comparisons between the periods, as appropriate. *P* value < 0.05 was considered statistically significant. All analyses were performed using MedCalc Version 17.6.

## Results

The study included 993 surgical patients: 461 before the intervention of antimicrobial stewardship (pre-intervention group) and 532 after the intervention (post-intervention group). There was no statistically significant difference between the two groups in baseline demographic characteristics (Tab. I). Concerning the surgical characteristics of patients (Tab. II), in the post-intervention group there was a statistically significant increase in patients undergoing breast surgery, probably due to the reorganization of general surgery ward, which took place in 2015, and led to the creation of a breast surgery dedicated ward.
Overall, the proportion of surgical patients with prescription of antimicrobials at discharge decreased significantly, from 33% in the pre-intervention group to 24.4% in the post-intervention group ($p = 0.002$).
A statistically significant decrease in the prescription of antimicrobials occurred in (Tab. I and Tab. II): female gender (42% pre-intervention vs 27.8% post-intervention; $p < 0.001$); patients with ASA score II (38.5% vs 22.2%; $p < 0.001$); urgent-emergency surgery (48.4% vs 24%; $p < 0.001$); breast surgery (94.1% vs 47.5%; $p < 0.001$), gallbladder surgery (44.2% vs 10.8%; $p < 0.001$), and kidney surgery (63.6% vs 18.2%; $p = 0.03$); clean-contaminated class of surgical wound (33.3% vs 19.5%; $p = 0.02$); patients operated without prosthetic material implant (30.5% vs 20.6%; $p = 0.002$); surgery patients with post-operative course described as regular (33.6% vs 24.4%; $p = 0.005$).
Regarding the characteristics of antimicrobials (Tab. III), the most prescribed Anatomical Therapeutic Chemical categories in both periods were the combinations of penicillins with beta-lactamase inhibitors, in large part amoxicillin and enzyme inhibitors, prescribed in 21.9% of subjects belonging to the pre-intervention group and in 18% of patients in the post-intervention group. Al-

**Tab. I.** Demographic and clinical characteristics of patients.

| Variable | Pre-intervention Group | | | Post-intervention Group | | | *P* value (Pts AM) |
|---|---|---|---|---|---|---|---|
| | No. Pts (n = 461) | No. Pts AM (n = 152) | Pts AM% | No. Pts (n = 532) | No. Pts AM (n = 130) | Pts AM% | |
| Age, mean *(SD)* | 60.1 *(20.8)* | 58.9 *(19.3)* | - | 60.0 *(19.6)* | 59.4 *(19.0)* | - | 0.83 |
| Female | 226 | 95 | 42.0 | 284 | 79 | 27.8 | < 0.001 |
| Male | 235 | 57 | 24.3 | 248 | 51 | 20.6 | 0.33 |
| Hospital length of stay, mean days *(SD)* | 8.9 *(11.2)* | 7.8 *(9.5)* | - | 7.8 *(9.5)* | 6.4 *(6.5)* | - | 0.15 |
| ASA score: | | | | | | | |
| I | 29 | 9 | 31.0 | 44 | 12 | 27.3 | 0.73 |
| II | 187 | 72 | 38.5 | 212 | 47 | 22.2 | < 0.001 |
| III | 184 | 54 | 29.3 | 221 | 60 | 27.1 | 0.62 |
| IV | 48 | 14 | 29.2 | 35 | 5 | 14.3 | 0.11 |
| Missing record | 13 | 3 | 23.1 | 20 | 6 | 30.0 | 1.0 |
| Post-operative clinical course: | | | | | | | |
| Regular | 363 | 122 | 33.6 | 401 | 98 | 24.4 | 0.005 |
| Complicated | 98 | 30 | 30.6 | 131 | 32 | 24.4 | 0.30 |
| Pts who developed a SSI | 16 | 9 | 56.3 | 17 | 4 | 23.5 | 0.08 |

Pts = patients; Pts AM = patients with at least one antimicrobial prescription at discharge; SD = standard deviation; ASA = American Society of Anesthesiologists; SSI = Surgical Site Infection.

**Tab. II.** Surgical characteristics of patients.

| Variable | Pre-intervention Group | | | Post-intervention Group | | | *P* value (Pts AM) |
|---|---|---|---|---|---|---|---|
| | No. Pts (n = 461) | No. Pts AM (n = 152) | Pts AM% | No. Pts (n = 532) | No. Pts AM (n = 130) | Pts AM% | |
| **Surgical procedures**: | | | | | | | |
| Elective surgery | 370 | 108 | 29.2 | 403 | 99 | 24.6 | 0.15 |
| Urgent or emergency surgery | 91 | 44 | 48.4 | 129 | 31 | 24.0 | < 0.001 |
| **Operative procedure**: | | | | | | | |
| Breast surgery | 51 | 48 | 94.1 | 101 | 48 | 47.5 | < 0.001 |
| Herniorrhaphy | 62 | 9 | 14.5 | 75 | 13 | 17.3 | 0.66 |
| Gallbladder surgery | 52 | 23 | 44.2 | 74 | 8 | 10.8 | < 0.001 |
| Colon surgery | 52 | 11 | 21.2 | 73 | 8 | 11.0 | 0.12 |
| Laminectomy | 54 | 0 | 0 | 41 | 2 | 4.9 | 0.18 |
| Hip prosthesis | 31 | 5 | 16.1 | 22 | 3 | 13.6 | 1.0 |
| Thoracic surgery | 23 | 5 | 21.7 | 25 | 10 | 40.0 | 0.18 |
| Craniotomy | 22 | 0 | 0 | 21 | 3 | 14.3 | 0.11 |
| Kidney surgery | 22 | 14 | 63.6 | 11 | 2 | 18.2 | 0.03 |
| Spinal fusion | 14 | 1 | 7.1 | 14 | 3 | 21.4 | 0.60 |
| Other | 78 | 36 | 46.2 | 75 | 30 | 40.0 | 0.44 |
| **Prosthetic material implant**: | | | | | | | |
| Yes | 120 | 48 | 40.0 | 133 | 48 | 36.1 | 0.52 |
| No | 341 | 104 | 30.5 | 399 | 82 | 20.6 | 0.002 |
| **Duration of operative procedure, mean minutes (*SD*)** | 244 *(193)* | 249 *(206)* | - | 235 *(141)* | 255 *(179)* | - | 0.79 |
| **Surgical Wound Classification**: | | | | | | | |
| Clean | 243 | 81 | 33.3 | 306 | 82 | 26.8 | 0.10 |
| Clean-Contaminated | 87 | 29 | 33.3 | 118 | 23 | 19.5 | 0.02 |
| Contaminated | 18 | 6 | 33.3 | 24 | 8 | 33.3 | 1.0 |
| Dirty-Infected | 16 | 7 | 43.8 | 19 | 4 | 21.1 | 0.27 |
| Missing record | 97 | 29 | 29.9 | 65 | 13 | 20.0 | 0.16 |

Pts = patients; Pts AM = patients with at least one antimicrobial prescription at discharge; SD = standard deviation.

**Tab. III.** Characteristics of antimicrobials prescribed at hospital discharge (absolute value and percentage of patients with prescription of antimicrobial).

| ATC category | Pre-intervention Group No. Pts (%) (n = 461) | | Post-intervention Group No. Pts (%) (n = 532) | | *P* value |
|---|---|---|---|---|---|
| Combinations of penicillins, incl. beta-lactamase inhibitors | 101 | (21.9) | 96 | (18.0) | 0.13 |
| Fluoroquinolones | 38 | (8.2) | 17 | (3.2) | < 0.001 |
| Imidazole derivatives | 9 | (2.0) | 6 | (1.1) | 0.29 |
| Third-generation cephalosporins | 2 | (0.4) | 11 | (2.1) | 0.03 |
| Macrolides | 2 | (0.4) | 5 | (0.9) | 0.46 |
| Other | 10 | (2.2) | 9 | (1.7) | 0.58 |

ATC = Anatomical Therapeutic Chemical; Pts = patients.

though, this reduction was not statistically significant ($p = 0.13$). Differently, a statistically significant difference was recorded in the prescription of fluoroquinolones (decreasing from 8.2% to 3.2% comparing pre- and post-intervention group, respectively; $p < 0.001$) and in the prescription of third-generation cephalosporin (increasing from 0.4% to 2.1%; $p = 0.03$).

The indication for antimicrobial prescription on discharge (e.g. ongoing therapy in discharge) was recorded in the digital discharge letters for 9.9% pre-intervention and 24.6% of patients post-intervention ($p < 0.001$). Finally (Tab. I), the proportion of patients who developed an SSI during the SNICh surveillance period (within 30 days after the operative procedure, for patients operated

without prosthetic material implant, and within 1 year for procedures with prosthetic material implant) [21] did not significantly change comparing the two groups (3.5% pre-intervention vs 3.2% post-intervention; $p = 0.08$).

## Discussion

The need of our antimicrobial stewardship intervention originated from the analysis of antimicrobial prescription data of the last quarter of 2014 (Tabs I, II and III), higher than the regional mean. It could be speculated that this over prescription originated from an unjustified attitude in prolonging the surgical prophylaxis over the limit suggested by national guidelines [13] or from a "defensive medicine" behavior for the aim of reducing the risk of SSI.

For this reason, Ferrara University Hospital's "Operative Group for the responsible use of antimicrobials" implemented a multidisciplinary intervention in order to reduce this excessive antimicrobial prescription at discharge, without affecting patients' safety.

The comparison between pre- and post-intervention groups showed a statistically significant decrease (-8.6%; $p = 0.002$) in antimicrobial prescription at discharge. However, we did not observe a change in SSIs rate among the studied groups (from 3.5% to 3.2%; $p = 0.08$).

The change in prescription was particularly significant in breast surgery (Tab. II), that was, indeed, one of the most critical wards in the first year of data collection, probably due to poor compliance to the local surgical chemoprophylaxis guidelines. Other statistically significant reductions in antimicrobial prescription at discharge occurred in urgent-emergency surgery, in patients without a prosthetic implant and in patients with postoperative course described as regular. Probably these reductions represent an attempt to limit unnecessary prescriptions, according to the recommendations about the appropriate use of antimicrobials.

Concerning the type of used antimicrobial, there was a statistically significant reduction in prescription of fluoroquinolones, as suggested during the update meetings. Conversely, prescription of combinations of penicillins with beta-lactamase inhibitors, in large part amoxicillin and enzyme inhibitors, continued to be critical. Moreover, an inexplicable increase in the prescription of third-generation cephalosporin was recorded, even if the absolute value remained limited.

In both groups, the indication for antimicrobial prescription on discharge was explicitly reported in the minority of digital discharge letters. However, the presence of explicit motivation significantly increased, comparing pre- and post-intervention groups, reflecting the indications given at the time of the intervention.

One of the main limitations of this study is represented by the short period of examination (last quarter of the years in study), because it could be not representative of the whole year and/or could not detect potential long-term changes due to the intervention. Another important limitation is that the number of some categories of operative procedures are not homogeneous in the two years in study (e.g. breast surgery).

## Conclusions

This study seems to demonstrate that multidisciplinary interventions of antimicrobial stewardship are effective in influencing excessive prescription of these drugs at discharge, without affecting patients' safety. These results confirm, as other studies have demonstrated [17, 24, 25], that antimicrobial stewardship programs are effective in reducing and improving antibiotic prescription. Therefore, these programs are an important part of good practices to be maintained for an efficient infection risk management.

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## Authors' contributions

All Authors have made a substantial contribution to the conception, design, analysis and interpretation of data, drafting the article and revising it critically for intellectual content; all Authors approve the final version submitted to the *Journal of Preventive Medicine and Hygiene*.

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ORIGINAL ARTICLE

# Healthcare-associated *Clostridium difficile* infection: role of correct hand hygiene in cross-infection control

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Keywords

*Clostridium difficile* infection • Prevention HAI • HA-CDI • Pediatric HAI • Hands hygiene

Summary

**Introduction.** *Clostridium difficile (CD) is the most common cause of health-care-associated infectious diarrhea with increasing incidence and severity in recent years. The main cause of hospital's acquired cross infections can be attributed to incorrect hand hygiene. We described the epidemiology of CD infection (CDI) in a teaching hospital in Southern Italy during a two years surveillance period and evaluated the health-care workers compliance to hand hygiene.*
**Methods**. *CDI Incidence rates were calculated as the number of patients with positive* C. difficile *toxin assay per 10,000 patient-days. Compliance with hand hygiene was the ratio of the number of performed actions to the number of opportunities observed. Approximately 400 Hand Hygiene (HH) opportunities/year /ward were observed. We finally checked out if any correlation could be found.*
**Results**. *From January 2015 to December 2016 a total number of* 854 *CD determinations were performed in patients with clinical symptoms of diarrhea. The search for toxins A and B was positive in* 175 *cases (21,2%), confirming the diagnosis of CDI. Compliance to hand hygiene was significantly inversely associated with the number of CDIs: the lower the compliance of health-care workers with hand hygiene the higher was the number of cases of CDIs (p = 0.003).*
**Conclusions**. *According to our results proper handwashing of health-care workers appears to be a key intervention in interrupting CD cross infections regardless of age and type of department in which the patient is admitted.*

## Introduction

*Clostridium difficile* (CD) is the most common cause of health-care associated infectious diarrhea.
It has been estimated that CD infection (CDI) is responsible for over 500,000 enteric infections per year in the United States, the majority of which are hospital acquired [1-3]. Both the incidence and severity of CDI have increased in recent years [4]. At least 7–17% of adult hospitalized patients are colonized by CD, with higher rates observed in elderly long-term patients [5]. Recurrence occurs in 25-33% of patients with primary CDI treated with metronidazole or oral vancomycin. CDI includes a spectrum of clinical features ranging from asymptomatic individuals to CD-associated diarrhea (CDAD) and pseudomembranous colitis, which can lead to fulminant, relapsing, and/or fatal colitis [6, 7]. Risk factors for CDI are 65+ years of age, female gender, previous or concomitant antibiotic exposure, prolonged stay in a health-care facility, immunodeficiency, renal impairment, previous antibiotic exposure and chemotherapy [8-12].
Hand hygiene has also shown to be the most important risk factor in hospital's acquired infections [13].
As reported by another study, natural history of cases may explain differences in epidemiology of CDIs among hospitals and should be considered to identify the most effective measures to reduce their incidence [14]. Therefore, our study had the following objectives: describe the epidemiology of CDI in a teaching hospital in Southern Italy during two-year-surveillance period and evaluate the percentage of adherence to official hand washing procedures, by hospital care personnel, to determine whether any correlation does exist.

## Methods

This study was conducted between January 1, 2015, and December 31, 2016, in Catania University Hospital "*G. Rodolico*", a reference teaching and research hospital in Sicily, Italy.

### Study endpoints

The primary endpoint was the overall incidence of CDI/10,000 patients days over two years period. Secondary endpoint were: (i) incidence of CDI/10,000 patient days stratified per specialty area, (ii) proportion of children's cases, (iii) percentage of adherence to handwashing procedure.

### CD infection

For the definition of CDI we have used the following criteria proposed by the European Centre for Disease Prevention and Control (ECDC): diarrheal stool or toxic megacolon and positive laboratory assay for CD toxin A and/or toxin B in stools [15]. We only considered diagnoses of CDI confirmed by laboratory tests performed in the Central Laboratory. We did not consider clinical criteria and pseudomembranous colitis revealed by endoscopy or on a specimen obtained during endoscopy. We have separated the CDI diagnoses observed in outpatient settings.

A case of hospital-acquired CDI (HA-CDI) was defined according to the criteria of the *Clostridium difficile* Study Group of the European Society of Clinical Microbiology and Infectious Diseases as follows: any patient who developed symptoms of diarrhea at least 48 hours after admission to the hospital (HA-CDI case with hospital onset); any patient who was admitted with symptoms of diarrhea at the hospital with an onset of symptoms in the community within 4 weeks following discharge from the hospital (HA-CDI case with community onset) and patients who had stool samples positive for CD toxin A or B or positive for toxin-producing CD [16].

All stools samples were tested with a two-step algorithm for detecting toxigenic CD: an enzyme immunoassay for glutamate dehydrogenase (GDH) antigen and subsequent enzyme immunoassay for CD toxins A and B. The assay principle combines a two-step enzyme immunoassay sandwich method with final fluorescent detection (ELFA). Laboratory data were collected from the Central Information System.

Epidemiological characteristics of patients (age and gender) and clinical history were collected from the hospital's digital archives of the patients and then verified in clinical charts. Clinical history was defined as diagnosis according to International Classification Disease (ICD) 9th version, comorbidities, previous hospitalization and length of hospital stay.

Positive cases per GDH were stratified by year and by ward, namely (i) general medicine, (ii) surgery (iii), paediatrics and (iv) intensive care. The incidence of CDI was expressed as the number of CDI cases /10,000 patient days for both overall incidence and stratified per specialty area. Admissions and length of hospital days were extrapolated from the hospital's admission archives.

### Hand washing procedure

We assessed compliance to the hand washing procedures described in World Health Organization (WHO) guidelines [17], while delivering routine care. The WHO guidelines indicate 5 moments of hand's hygiene in health-care: before touching a patient or before having contact with an object belonging to the healthcare area; before a clean/aseptic procedure; after body fluid exposure; after touching a patient and after touching patient surroundings.

We used WHO Observation Form to directly assess adherence to the protocol in any of the above mentioned five moments by direct visual observation of health-care workers attitude on at least 200 opportunities every six months. Where several indications coincided in a single opportunity, as WHO required, each indication was recorded and the action was then multiplied by the number of indications. The observation data were collected anonymously by the hospital infection control group every six months, in different wards.

According to the WHO manual, we considered appropriate hand washing with water and soap or hand hygiene with alcoholic gel with the exception of dirty or contaminated hands with patients affected by CDI.

Data were imputed in a local database purposely developed.

Compliance was calculated by adding the results of each session and dividing the total number of positive actions by the total number of opportunities.

Results of compliance with hand hygiene through two years period of observation (2015 and 2016) are reported.

### Statistical methods

To identify the risk (probability) of infection in the patients, we used incidence rate. Incidence rates were calculated as the number of patients with positive CD toxin assay per 10,000 patient-days and were stratified per specialty and per age.

We calculated the compliance rate as the adherence to the procedure in the wards over the total number of opportunities observed in each ward.

We also calculated the overall compliance rate of the different four medical areas. We compared the incidence rate of CDI cases per area with its compliance rate to hand washing procedure.

We performed a covariance analysis in order to see if any difference in mean compliance could explain relative differences in incidence rates.

The degree of linear correlation between the incidence of CDI cases observed and the compliance rates was measured by means Pearson's statistic.

The significance level was set to $p < 0.05$.

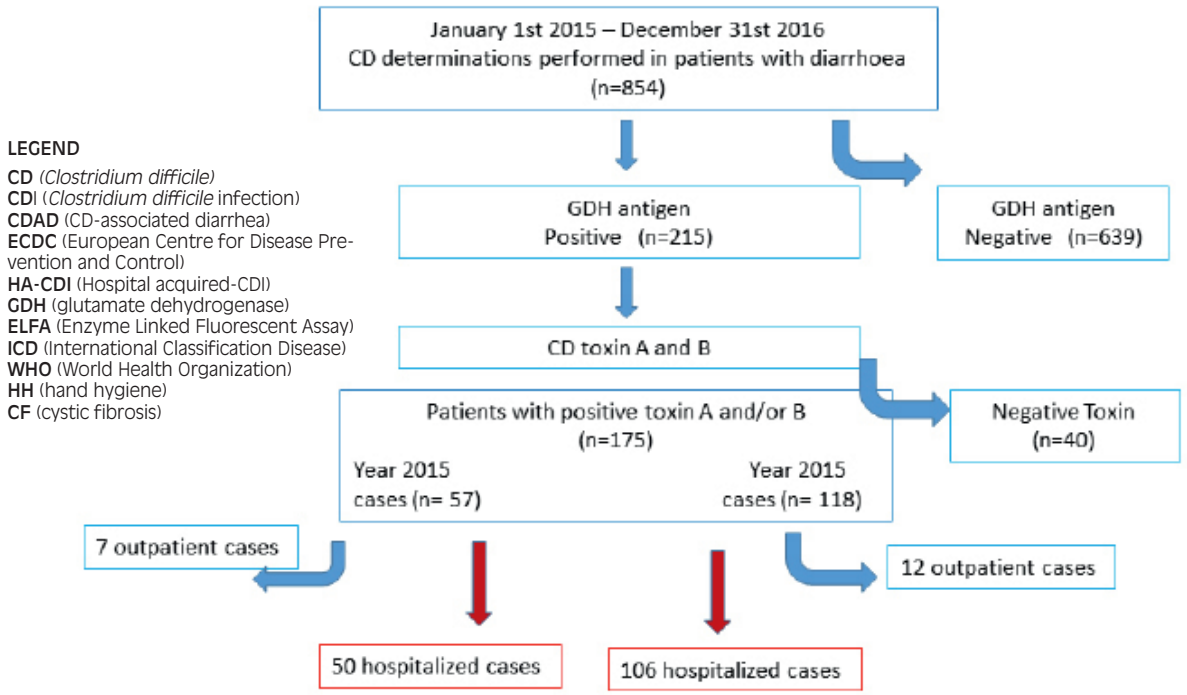
## Results

### CDI rates

From January 2015 to December 2016, a total of 854 CD determinations were performed in patients with clinical symptoms of diarrhea, who were either hospitalized or outpatients (Fig. 1). In 215 samples, glutamate dehydrogenase antigen (GDH) was positive. In these patients, the test for toxin A and B was positive in 175 cases (21.2%), confirming the diagnosis of CDI.

In Table I the number of stool sampled, the percentage of positive exams, the number of inpatient and outpatient cases observed, the incidence of CDI (cases/10,000 patients days) are described. In 2015, 57 positive exams were detected for CD. Fifty cases came from patients hospitalized in 10 wards and seven from outpatients.

**Fig. 1.** Study flow chart. Description of the path from the stool cultures to the definition of the number of *Clostridium difficile* infection cases in the different years.




**Tab. I.** Stool samples tested (numbers and incidence rates) and *Clostridium difficile* infection (CDI) cases (numbers and incidence rates) per 10000 patients-days per year.

| YEARS | ADMISSIONS | | | STOOL SAMPLES | | | CDI Cases | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Inpatients (*n*) | Outpatients (*n*) | Overall admissions (*n*) | Tested (*n*) | CD positive | % of positive sample | Inpatients (*n*) | *n*/10,000 Patients-days | Outpatients (*n*) | *n*/10,000 Patients-days |
| **2015** | 13056 | 6383 | 19439 | 770 | 57 | 7.4 | 50 | 0.1 | 7 | 0.03 |
| **2016** | 12640 | 5688 | 18328 | 825 | 118 | 14.3 | 106 | 0.23 | 12 | 0.05 |

During 2016, we had 118 positive CD tests 106 of which were diagnosed in 11 wards and twelve from outpatients. As can be seen in Table I, the number of CDI cases increased in 2016 despite fewer total admissions. In 2016, there was a 14% increase in the number of tests performed relative to the previous year. The overall incidence was 0.1/10000 patient-days in 2015, and this figure increased to 0.23/10000 patient-days in 2016.

The number of cases in different departments is given in Table II. CDI cases were most frequently diagnosed in general medicine wards. The number of hospital admissions refers only to units in which cases were detected.

In Table III we report the number of cases of total CDI divided by age groups. Approximately 28% of all cases involved children aged 0-17 years. Most of these patients exhibited surgical abnormalities of the gastrointestinal tract (25.6%). Only one paediatric patient was affected by cystic fibrosis. Approximately 35% of cases were confirmed in patients over 65 years of age. The other cases were distributed in the middle age group.

Age, sex, length of stays and outcome of cases are described in Table IV. Since we sampled approximately the same number of males and female we didn't find any difference between sex as others described [18]. It is particularly relevant the larger length of stay (LOS) in 2016, with an extreme case of 234 days, to which can be probably attributed a greater chance of CDI cases. The mean hospital length of stay of CDI was 27 days in 2015 and 27.6 days in 2016. Two patients relapsed in 2015 and four relapsed in 2016. The patients primarily treated with a cycle of metronidazole were subsequently treated with oral vancomycin. No fidaxomicin treatment was necessary.

**Tab. II.** Hospital admissions and incidence of *Clostridium difficile* infections (CDI) in the different wards per areas during the study period (2015-2016).

| | 2015 | | | | 2016 | | | |
|---|---|---|---|---|---|---|---|---|
| | Hospital admissions | No. Of CDI episodes | (% of positive cases) | Incidence/10.000 patient-days | Hospital admissions | No. Of CDI episodes | (% of positive cases) | Incidence/10.000 patient-days |
| General medicine area | **843** | 36 | 4.27 | 1.16 | **918** | 55 | 5.99 | 1.64 |
| Surgical area | **1705** | 4 | 0.23 | 0.06 | **1443** | 10 | 0.69 | 0.189 |
| Paediatric area | **1141** | 7 | 0.61 | 0.16 | **1866** | 38 | 0.53 | 0.55 |
| Intensive care | **207** | 3 | 1.44 | 0.39 | **219** | 3 | 1.36 | 0.37 |

**Tab. III.** *Clostridium difficile* Infections (CDI) stratified by area and by age groups.

| | | CDI *n* | 0-17 years | 18 - 65 years | > 65 years |
|---|---|---|---|---|---|
| **OVERALL** | | **156** | | | |
| General medicine area | 2015 | 35 | | 18 | 17 |
| | 2016 | 55 | | 26 | 29 |
| Surgical area | 2015 | 4 | | 3 | 1 |
| | 2016 | 10 | | 3 | 7 |
| Paediatric area | 2015 | 8 | 7 | 1 | |
| | 2016 | 38 | 34 | 4 | |
| Intensive care unit | 2015 | 3 | 2 | 1 | |
| | 2016 | 3 | 1 | 2 | |
| | | | **44 (28%)** | **58 (37%)** | **54 (35%)** |

**Tab. IV.** Age, sex, length of stays and outcomes of *Clostridium difficile* infections (CDI).

| | 2015 | 2016 |
|---|---|---|
| **Sex:** - Male | 29 *(50.5%)* | 55 *(47.4%)* |
| - Female | 28 *(49.5%)* | 61 *(52.6)* |
| **Age (years)** - Mean | 48.9 | 41.6 |
| - Median | 56 | 48 |
| - Range | 0-91 | 0-96 |
| **Length of stays (days)** - Mean | 27 | 27.6 |
| - Median | 22 | 16 |
| - Range | 3-144 | 2-234 |
| **Recurrence/relapse** | 2 *(3.6%)* | 4 *(3.4%)* |
| **Death** | 7 | 2 |
| - Age 0-17 | 0 | 1 |
| - Age 18-65 | 1 | 0 |
| - Age > 65 | 6 | 1 |
| - Ward | 1 ICU | 1 ICU |
| | 6 General Medicine area | 1 Paediatric Area |

**Tab. V.** Number of CDI, Incidence rates and mean Hand Hygiene Compliance rates stratified by area and by period.

| | Areas | CDI cases | Incidence/10000 patient-days | Number of opportunities | Hand hygiene compliance (%) |
|---|---|---|---|---|---|
| 2015 | General Medicine area 2015 | 35 | 1.13 | 848 | 47 |
| | Surgical area 2015 | 4 | 0.06 | 840 | 72 |
| | Paediatric area 2015 | 8 | 0.19 | 828 | 78 |
| | Intensive care unit 2015 | 3 | 0.39 | 492 | 58 |
| 2016 | General Medicine area 2016 | 55 | 1.64 | 823 | 44 |
| | Surgical area 2016 | 10 | 0.189 | 840 | 65 |
| | Paediatric area 2016 | 38 | 0.55 | 830 | 65 |
| | Intensive care unit 2016 | 3 | 0.37 | 457 | 60 |

The *C. difficile* International Classification of Diseases, ninth version, clinical modification (ICD-9-CM) code 008.45 was assigned as the principal discharge diagnosis only in 9 cases.
The most prevalent comorbidities in older patients were cardiovascular (32.4%) and gastrointestinal (20.6%) diseases.

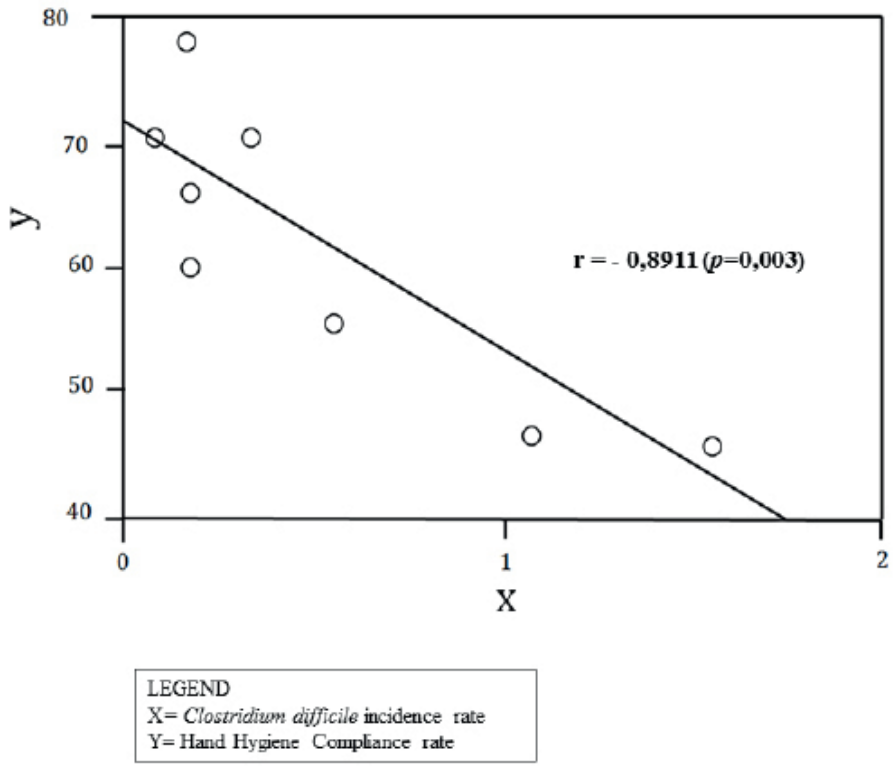
### Hand hygiene

Standardized documented activities requiring hand hygiene (HH), according to the WHO protocol, were verified. Approximately 400 HH opportunities/year/ward were observed. In total 5940 circumstances requiring hand hygiene were observed over two years. We calculated the mean compliance rate in each area; we directly observed two wards in the general medicine, surgical and paediatric areas and in the intensive care unit, twice per year. In Table V, we report the results of the percentage of adherence to the application of WHO guidelines on hand hygiene as observed during 2015 and 2016. The survey analysis showed high variability among the wards, ranging from the highest value reached in paediatric units in 2015 (78%) to the lowest value observed in general medicine wards in 2016 (44%).
Results from covariance analysis performed on data showed no significant difference in mean incidence rate between 2015 and 2016 ($p$ = 0,15) while common significant linear correlation was conversely found between adherence to hand washing procedure and incidence rates within medical areas. Negative linear correlation coefficient was -0.8911 ($p$ = 0.003) showing that the poorer adherence to the procedure the greater the incidence rate (Fig. 2).

## Discussion

CD is the most important cause of healthcare-associated diarrhea in both normal and immunocompromised hosts and is increasingly important as a community pathogen [19]. It has been found to be the major aetiologic agent of antibiotic-associated pseudomembranous colitis, a clinically defined syndrome associated with a recent history of antibiotic use in which pseudomembranous nodules or plaques can be found in the distal and sigmoid colon and rectum. If unrecognized or untreated, this disease can be fatal.
Our increase in CDI cases is consistent with that recently reported in the literature [20, 21]. We argue that since tests were performed only in patients with gastrointestinal symptoms of diarrhea, the greater number of tests performed in 2016 relates to an increased amount of positive cases founded.
As shown in Table III, patients hospitalized in internal medicine wards were at higher risk for CDI and CDI incidence increased with age over 65, similarly reported in other studies [14, 20, 21]. Older patients have more comorbidities and are hospitalized more frequently than

Fig. 2. Linear correlation between *Clostridium difficile* incidence rates and Hand Hygiene compliance rates.



younger patients [22]. In our study, the most prevalent comorbidities were cardiovascular (32.4%) and gastrointestinal (20.6%) conditions.
Interestingly we found a high incidence of positive cases (28%) in patients under 18 years old. Our 44 diagnoses referred to children that had diarrhea and diseases involving malformations of the digestive system. CD colonization of health individuals is associated with changes in distal gut microbial composition [23]. This phenomenon is much more frequent in paediatric patients, especially in infants. CDI is a relatively uncommon but costly complication after paediatric operative procedures [24]. Infants and paediatric patients with cystic fibrosis (CF) have shown to be asymptomatic carriers of toxigenic CD with reported CD colonization rates as high as 50% in infants and from 22 to 46% in the others [25-27]. However, despite this high rate of colonization, the occurrence of CDI in CF remains rare.
The large number of cases in paediatric subjects in our study is probably due to the high concentration of children with severe connatural surgical pathologies treated in our paediatric surgery or to children treated in our regional centers for diagnosis of cystic fibrosis and for the treatment of oncology disease in paediatric age.
The mean LOS is roughly the same in the two years with a large variability from one case to another. Hospital LOS has a double relationship with CDI because its increase is a well-known risk factor for cross-CDI and patients with CDI tend to stay in the hospital longer [28]. The permanence of a patient colonized by CD is a risk factor for nosocomial infection, which can be easily transmitted by the improperly washed hands of the assisting staff or relatives who are unidentified disseminators of the germ itself.
As can be seen in Table I the number of positive tests in 2016 were more than twice those positive in 2015, while incidence rates increased accordingly in inpatients, more than those occurred in outpatients. This confirm the role of proper hand-washing in CD cross-infections, as far as most health care-associated infections are preventable with good hand hygiene. It means cleaning hands at the right time and in the right way. Hand hygiene is a key intervention in interrupting transmission between patients, health care personnel and visitors [29, 30].
In our hospital, we have regular monitoring and evaluation quality protocol to control hand-washing hospital procedure. We perform hand washing following the five times for hand hygiene set by the WHO, as previously cited.
Our results gave us knowledge of how health-care workers perform hand hygiene. The data confirm the low compliance to hand hygiene practices of healthcare workers: no department reached 80% compliance, which is the limit recommended by the WHO. Not surprisingly we found a reverse correlation between the number of CDI cases recorded and the percentage of adherence to hand washing: the lower the compliance with HH, the higher the number of CDI.
Since this practice remains well below WHO recommendations, continual efforts are required to reach the optima targeted goal to prevent HA- CDI. A better knowledge of the importance of hand hygiene remains an effective health care-associated infection control intervention. Nevertheless, other measures for infection control must be reminded such as isolation of infected patients, use of gloves, gowns and chemical agents for environmental disinfection. Hydrogen peroxide vapours for terminal decontamination has been proven to be effective against CD, as has been recently reported [31-33].
Finally, our analysis suffers from some limitations. Firstly, we considered only diagnoses of CD infection carried out by laboratory tests. For diagnosis, we used EIAs that are easy and fast to perform but with a sensitivity ranging from 63% to 99%; thus, false-negative results could occur. Moreover, we did not consider pseudomembranous colitis revealed by endoscopy or on a specimen obtained during endoscopy. This decision may have resulted in missed cases.
Secondly, our study was a single centre study in a teaching hospital and results may not be reproducible in different contexts. HH observations were carried out by trained staff twice a year, a greater number of observations or video recordings of the actions might lead to different results.

## Conclusions

CD is a well-known cause of hospital-acquired infectious diarrhea with prolonged hospitalizations, increasing patient morbidity and healthcare costs [34, 35]. Clinicians should consider a diagnosis of CDI in patients with severe diarrhea. Early recognition of CD colonization may help to prevent the spread of HA-CDI and the risk of transmission to non-infected patients or healthcare workers.
To reduce the incidence of CDI, it is imperative to be aware of at-risk population, which might be different in general or specialized hospitals. The large number of cases in paediatric subjects in our study is probably due to the high concentration of children with severe connatural surgical pathologies treated in our paediatric surgery centre and children who were treated in our regional reference centres for cystic fibrosis or oncology pathology.
Given the results of our survey, we propose that screening is performed in all patients admitted to the Intensive Care Unit, in all immunosuppressed patients over 65 years of age with the described comorbidities and in paediatric patients with gastrointestinal abnormalities or tumours. Screening should be performed by detecting GDH in stool in order to select colonized patients and prevent outbreaks.
Because of the difficulties associated with the isolation of infected patients in a single room with personal bathrooms, proper hand-washing remains a key intervention in interrupting transmission between patients, health care personnel and visitors.
Continuous surveillance is required to determine trends and verify whether more toxigenic strains have an in-

creasing impact in the community and in a hospital setting [36].
Further studies are required to verify whether the proposed measures might restrict the spread of infections due to secondary outbreaks.

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## Author's contribution

RR conceived, designed the research, wrote the manuscript, GG performed the tables and data quality control, LL provided statistical data and the final correction of the manuscript, SA performed microbiological analysis,RS collected data, LVM collected data, MS performed the literature review, MM coordinated the research.
All Authors revised the manuscript and gave their contribution to improve the paper.
All Authors read and approved the final manuscript.

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ORIGINAL ARTICLE

# Counseling intervention to improve quality of life in patients with pre-existing acute myocardial infarction (AMI) or chronic obstructive pulmonary disease (COPD): a pilot study

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## Keywords

Counseling • Tertiary prevention • Chronic disease • Nutrition • Smoke • Quality of life • Chronic obstructive pulmonary disease • Acute myocardial infarction

## Summary

**Background.** *In the light of diagnostic and therapeutic advances, patients with a previous myocardial infarction or with a diagnosis of chronic obstructive pulmonary disease are vulnerable and need continuous monitoring over time. These pathological frameworks have a strong impact on the economy and on the status of the population and require effective and low-cost solutions.*

**Aims**. *The objective of this clinical trial is to evaluate the efficacy in the short term of a telephone counseling intervention to modify the lifestyles of these two patient populations.*

**Methods**. *In May 2015, all the patients included in the study underwent a questionnaire to evaluate their eating and smoking habits and their quality of life. After randomization in two groups, the intervention group received telephone counseling related to the correct lifestyles. The control group did not undergo any intervention. In September-October 2015, the same initial questionnaire was administered to evaluate changes in patients' behavior.*

**Results.** *64 patients were included in the study: 34 were assigned to the intervention group and 30 to the control group. The outcomes evaluated were: quality of life, assessment of eating habits and smoking status. After the telephone counseling, the intervention group (34 persons) showed a significant improvement in the score of adherence to the Mediterranean diet ($p = 0.01$) and a significant reduction in the percentage of smokers ($p = 0.01$) compared to the population that did not receive any intervention (30 persons). On the other hand, the changes related to the quality of life questionnaire were not significant.*

**Conclusions**. *A single telephone counseling intervention is effective in modifying the lifestyles of patients with a previous myocardial infarction or diagnosed with chronic obstructive pulmonary disease in the short term, reducing their risk profile.*

## Introduction

Cardiovascular diseases are the first cause of death in the western world. In 2014 cardiovascular diseases were responsible for 29.5% of all deaths in Italy [1]. These pathological frameworks have a strong impact on the resources of the health system since they are not only the cause of the subject's death, but often turn into chronic conditions that accompany the individual in the rest of his life and make him/her a vulnerable person. However, there is no effective cure for chronic obstructive pulmonary diseases (COPD) although several treatments are available to control the symptoms and avoid dangerous complications. In both these patient populations it is therefore essential to implement multidisciplinary secondary and tertiary prevention programs to reduce exposure to modifiable risk factors and in order to achieve maximum adherence to the therapeutic program.

In the literature, many epidemiological studies report high inhomogeneities in the incidence rate of cardiovascular diseases in relation to different geographical areas. Compared to the Northern Europe Countries and the United States, there is a lower incidence of coronary heart disease in the Countries of Southern Europe and in particular in those facing the Mediterranean basin such as France, Spain, Greece and Italy [2-4]. This geographical variability has been attributed to environmental factors, lifestyles and different eating habits, which in the Mediterranean Countries traditionally reflect the characteristics of the "Mediterranean Diet". According to the LYON study, the Mediterranean diet decreases the mortality rate for coronary heart disease by 50% [5]. Other data show that an increase in adherence to the Mediterranean diet may result in a reduction in the overall incidence of cancer or mortality from cancer between 6 and 12% [6]. In fact, it is widely considered a food model to be pursued, both in primary and in secondary prevention,

since it is substantially able to change the cardiovascular risk profile towards achieving and maintaining good health and longevity [7, 8]. The Guidelines for a Healthy and Correct Italian Food provide the "nutritional recommendations" that shape the characteristic Mediterranean diet: abundant consumption of fruit and vegetables, cereals, legumes, olive oil, fish, and, in less quantity, of meat, sausages, cheese and derivatives. An ideal dietetic pattern prefers poly and monounsaturated fats, in particular of the oleic acid contained in olive oil, limiting the intake of "trans" and saturated fats and cholesterol [7, 9].

At the same time, the tobacco epidemic is one of the most important public health challenges. The WHO estimates that in the world cigarette smoking kills about 6 million people every year, of which 5 million are smokers or former-smokers. About 50% of current smokers will die from cigarette-related illnesses [10]. Tobacco is a known or probable cause of at least 25 diseases, including chronic obstructive pulmonary disease (COPD) and other chronic lung diseases, oncological diseases, heart diseases and vasculopathies. Among the tumors, there is sufficient scientific evidence with respect to a direct causal relationship between cigarette smoking and tumor of lung, larynx, oral cavity, pharynx, esophagus, pancreas, bladder, cervix, stomach and acute myeloid leukemia [11]. The risk of premature death and the likelihood of developing smoking-related diseases depend on several factors, including the number of years spent smoking, the number of cigarettes daily smoked, the starting and terminating age of smoking, and if the person was already ill at the time of smoking cessation.

Considering the scientific evidences of literature on the important health consequences deriving from modifiable lifestyles, it is necessary to consider the need to actively intervene on these aspects. Particularly interesting for possible health outcomes are the most susceptible populations, i.e. those diagnosed with previous acute myocardial infarction (AMI) or COPD.

Preventive Medicine, by enhancing the factors useful to health and the removal or correction of causes and states of predisposition and/or risk to the disease, cooperates to achieve a state of complete physical, mental and social well-being of the individual and the community. At the same time, it contributes to decrease the costs of the health services, reducing disability and increasing work capacity. In order to achieve this goal, Health Promotion is an effective tool expressly aimed at promoting, modifying or eliminating behaviors capable of influencing the health conditions of individuals and of the population.

The objective of this research study is to estimate, through a pilot randomized clinical trial, the efficacy of a tertiary prevention counseling intervention on patients with AMI and COPD in reducing tobacco use and increasing food behavior and health-related quality of life.

## Materials and methods

The study population was made of patients previously involved as cases in a case-control study that investigated the factors associated with the etiopathogenesis of the considered clinical scenery [12]. Patients who accepted to participate in the study were 64: 33 patients included as cases with AMI and 31 patients included as cases with COPD. All patients included in the study received and signed the informed consent to participate. The study received approval from the Ethics Committee of the Policlinic Umberto I of Rome.

The subjects included in the study as cases with myocardial infarction were patients admitted to the Coronary Units after a first myocardial infarction event (ICD-9 code: 410-14), male and female, aged between 35 and 70, with intact state of consciousness and capacity for judgment.

Concerning the COPD patients, they were admitted to the Respiratory Diseases Unit with an established diagnosis of COPD according to the GOLD Guidelines and classified as COPD, COPD exacerbation, chronic respiratory failure, chronic bronchitis or pulmonary emphysema. The sample included male and female subjects, between the ages of 40 and 80, with intact state of conscience and capacity for judgment.

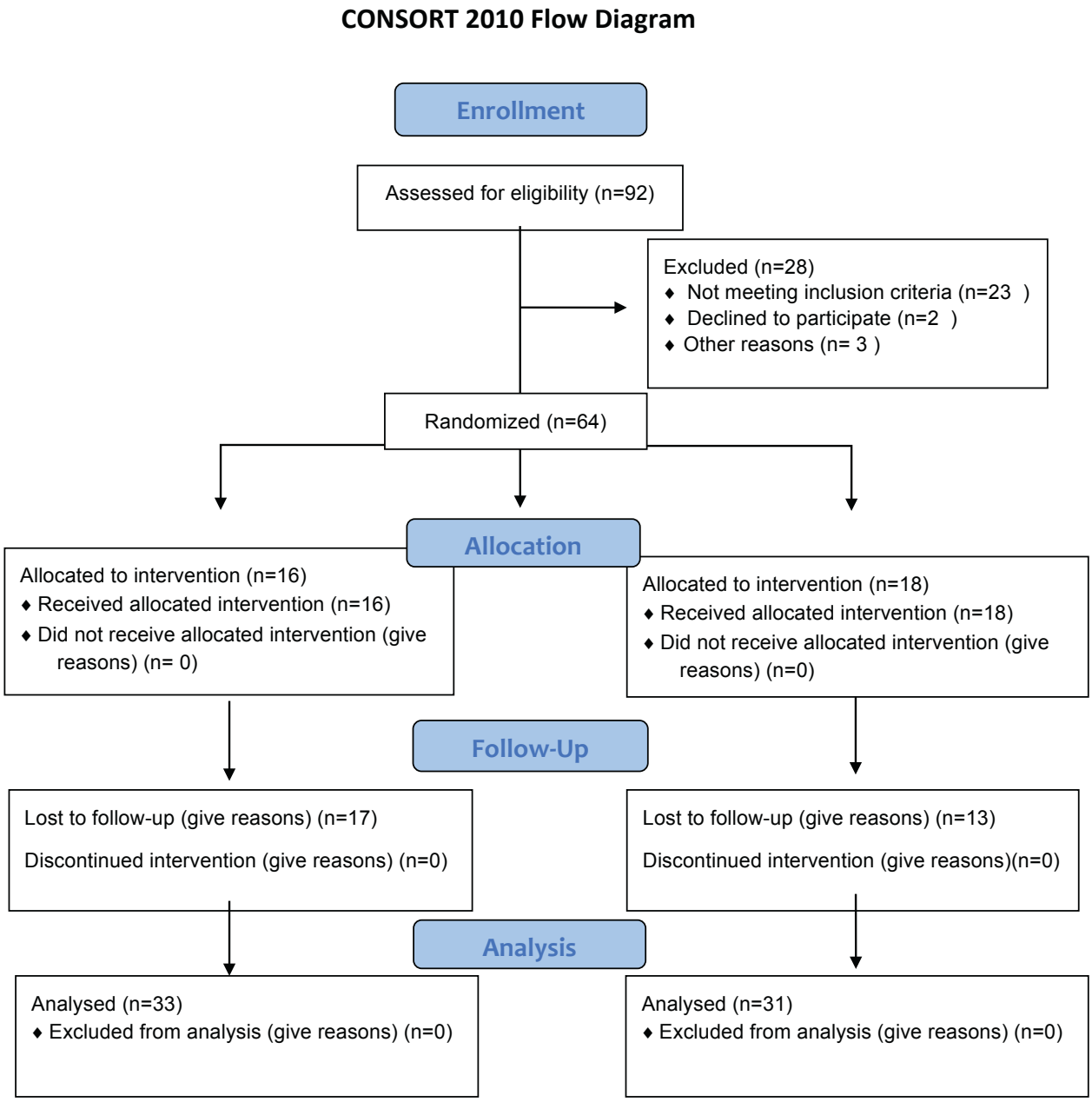
Patients of each of the two diagnostic categories considered, AMI and COPD, were divided into 4 groups based on exposure to "smoking" and "poor diet" risk factors. For each pathological category were therefore obtained: a group of exposure to both risk factors; a group of exposure to smoking and not to bad diet; a group of exposure to bad diet and not to smoking; a group of non-exposure to any of the two risk factors. Within each of these subsets, the patients were randomly referred to an intervention group or to a control group. The randomization of the subjects was performed using the random numbers tables. Following randomization, 34 patients were assigned to the intervention group and 30 to the control group.

All the study participants in May 2015 were given a questionnaire comprising a registry section gathering information on sex, marital status, number of children, number of family members, educational level and smoking status (current, former or never smoker).

To assess the differences between the two groups at the end of the study, before and after the intervention a questionnaire was administered to all the participants that investigated eating habits (SUN PROJECT questionnaire) and smoking habits (exposure to cigarette smoke), Fagerström's smoking addiction test and Mondor's smoking cessation test [13]. Quality of life was measured using the SF-12 questionnaire from which their MCS (Summary of mental components) and their PCS (Physical Component Summary) were calculated [14].

In May 2015, patients who were part of the intervention group were contacted by telephone with the aim of encouraging adherence to the Guidelines for a healthy and correct diet, giving further food advices, answering doubts, questions or clarifications, and promoting cessation of smoking habit.

Patients' nutrition education interventions took place through counseling activities and training interventions by experts in Food Science: after the assessment of eat-




ing habits and the assessment of the degree of adherence to the Mediterranean diet, the health professionals gave provisions regarding food in accordance to the Guidelines for a healthy and correct diet (INRAN) [9, 15].

The interventions on smokers who suffered of heart attack or who have been diagnosed with mild or moderate COPD had the aim to promote the motivation to quit, to inform smokers about the resources available for cessation and to direct the smoker to planned routes. These counseling interventions were structured in the light of the "Clinical Guidelines to encourage the cessation of smoking habits" drawn up by the National Institute of Health which provides a list of suggestions, called the 5 A's for a good structure:

1- ASK = ask the subject if he smokes;

2- ADVISE = information on the effects of smoking and recommend to quit;

3- ASSESS= define the characteristics of the subject;

4- ASSIST = verify and implement a therapeutic path to monitor and reinforce cessation;
5- ARRANGE = implement actions to prevent relapse [16].
In the period between September and October 2015, all the participants were contacted again in order to collect the same data on tobacco smoking, dietary behavior and health-related quality of life.

## Results

A descriptive analysis was performed considering the data obtained from the personal data section of the administered questionnaire. The patients who underwent the intervention were 26 males (76.5%) and 8 females (23.5%). Those who were assigned to the control group were 19 males (63.3%) and 11 females (36.7%). Regarding marital status, most patients in the intervention group were married (23 people, 67.6%), 18 patients (52.9%) claimed to have two children and 14 (41.2%) cohabited with two people. The general educational level was medium since 9 patients (26.5%) declared that they only attended elementary schools, 13 patients (38.2%) junior high schools, 7 patients (20.6%) high schools, and only 5 patients (14.7%) held a bachelor's degree. In the control group, on the other hand, most patients were married (19 people, 63.3%), 11 patients (36.7%) claimed to have three children and 14 (46.7%) lived with two people. In this case, the general educational level was medium-low since 9 patients (30.0%) attended elementary schools, 13 patients (43.3%) middle schools and 8 patients (26.7%) high schools.
In the period before the telephone intervention, the smoking patients who were assigned to the intervention group were 15 (44.1%) while the non-smokers were 19 (55.9%). In the control group, 11 patients (36.7%) were smokers, 19 (63.3%) were non-smokers. Therefore, at the initial randomization, the two groups taken into consideration for the study were very similar, except for the variable "number of children" which did not seem to be crucial for the purposes of the statistical analysis. The results of the descriptive analysis are shown in Table I.
After 4-5 months, in September-October 2015, all the patients included in the study were contacted by telephone to investigate the variations in the answers to the same questionnaires administered before the intervention. All the patients included in the study answered to the follow up questionnaire. The results emerged from the statistical analysis are shown in Table II.
Nonparametric tests were used, and median values were taken into account. After the telephone intervention, analyzing the median values of the MCS and PCS, there were no improvements in the quality of life of the patients. The p values of the PCS and MCS variables do not indicate a significance in terms of effectiveness of the telephone intervention (p = 0.941 and p = 0.213, respectively). Analyzing the subgroups of the AMIs and the COPD a significance is shown on the MCS mental score for COPD patients.

**Tab. I.** Baseline socio-demographic characteristics of the patients.

| Variable | Intervention group (%) | Control group (%) | p |
|---|---|---|---|
| SEX | | | |
| Male | 26 (76.5%) | 19 (63.3%) | 0.251 |
| Female | 8 (23.5%) | 11 (36.7%) | |
| CIVIL STATUS | | | |
| Single | 3 (8.8%) | 2 (6.7%) | |
| Married | 23 (67.6%) | 19 (63.3%) | 0.931 |
| Divorced | 4 (11.8%) | 4 (13.3%) | |
| Widower | 4 (11.8%) | 5 (16.7%) | |
| SONS | | | |
| 0 | 3 (8.8%) | 3 (10.0%) | |
| 1 | 4 (11.8%) | 6 (20.0%) | |
| 2 | 18 (52.9%) | 6 (20.0%) | 0.031 |
| 3 | 2 (5.9%) | 11 (36.7%) | |
| 4 | 4 (11.8%) | 3 (10.0%) | |
| 5 | 2 (5.9%) | 1 (3.3%) | |
| 6 | 1 (2.9%) | 0 (0.0%) | |
| COHABITANTS | | | |
| 1 | 7 (20.6%) | 6 (20.0%) | |
| 2 | 14 (41.2%) | 14 (46.7%) | |
| 3 | 7 (20.6%) | 5 (16.7%) | 0.673 |
| 4 | 6 (17.6%) | 3 (10.0%) | |
| 5 | 0 (0.0%) | 1 (3.3%) | |
| 6 | 0 (0.0%) | 1 (3.3%) | |
| EDUCATIONAL LEVEL | | | |
| Elementary school | 9 (26.5%) | 9 (30.0%) | |
| Junior high school | 13 (38.2%) | 13 (43.3%) | 0.184 |
| High school | 7 (20.6%) | 8 (26.7%) | |
| Degree | 5 (14.7%) | 0 (0.0%) | |
| SMOKING STATUS | | | |
| Yes | 15 (44.1%) | 11 (36.7%) | 0.545 |
| No | 19 (55.9%) | 19 (63.3%) | |

**Tab. II.** Results of the trial concerning HR-QoL scales, diet and tobacco use.

| Variable | Intervention group | Control group | P |
|---|---|---|---|
| PCS pre (all) | 34.3 (21 – 56.7) | 35.8 (20.8 – 59.6) | 0.476 |
| PCS post (all) | 33.3 (21-57.5) | 33.7 (19.5-54.7) | 0.941 |
| *p* | 0.877 | 0.514 | |
| AMI pre | 40.6 (23.6 – 56.7) | 49.8 (20.8 – 59.6) | 0.276 |
| AMI post | 39.8 (24.6 – 57.5) | 38.8 (19.5 – 54.7) | 0.606 |
| *p* | 0.861 | **0.022** | |
| COPD pre | 32.3 (21 – 41.7) | 32.1 (24.9 – 42.6) | 0.890 |
| COPD post | 31.6 (21 – 40.9) | 32.5 (23.9 – 37) | 0.831 |
| *p* | 1.00 | 1.00 | |
| MCS pre (all) | 40.4 (22.6-59.5) | 35.7 (25.8-66.9) | 0.861 |
| MCS post (all) | 42.4 (22.5 – 56.2) | 39.9 (25.8 – 52.5) | 0.213 |
| *p* | 0.427 | 0.293 | |
| AMI pre | 39.4 (27.9 – 58.6) | 48.2 (32.6 – 66.9) | **0.045** |
| AMI post | 42.9 (28.1 – 56.2) | 46.7 (27.8 – 52.5) | 0.901 |
| *p* | 0.134 | 0.831 | |
| COPD pre | 41.3 (22.6 – 59.5) | 35.9 (25.8 – 46.7) | **0.03** |
| COPD post | 42.1 (22.5 – 49.6) | 30.3 (25.8 - 47) | **< 0.01** |
| *p* | 1.00 | 1.00 | |
| DIET SCORE | 7 (3-9) | 5 (3-9) | **0,010** |
| SMOKING STATUS | | | |
| Before | 44,1% | 36,7% | |
| After | 20,6% | 26,7% | **< 0.01** |

Statistical analysis shows positive trends related to patient follow-up in terms of adherence to the Mediterranean diet and cessation of smoking habits. From the results of the collected data can be seen a greater adherence to the Mediterranean diet of the patients undergoing the intervention rather than the patients in the control group. Considering a range from 3 to 9, the medians of the Intervention group and the Control group were different. In fact, the Diet score is 7 in the intervention group and 5 in the control group. P = 0.01 indicates a high validity of the effectiveness of the telephone intervention.
As far as concerns smoking, in the control group the percentage of smokers at the time of admission was 36.7% and that at September follow-up was 26.7%, with a difference of 10.0 %. In the intervention group, the difference has doubled. At zero time, the percentage of patients who declared smoking was 44.1% while following the telephone intervention, the percentage of smokers fell to 20.6%, highlighting a difference between the pre- and post-intervention of 23.5%. Also in this case the p = 0.01 indicates a high significance and therefore the effectiveness of the telephone intervention performed on the patients. In addition to the parameters of the ARR of 26.1% and RRR of 1.96, the NNT equal to 3.8 highlights the effectiveness of the treatment: this value indicates the estimate of the number of patients to be submitted to treatment to obtain a unit of advantage over the comparison treatment.

## Discussion

This scientific project is based on the evidence that the chronic patient, and in particular the patient with AMI and with COPD, is called to be an active subject, who must become independent and protagonist of the management of his own condition, together with the healthcare professional. There is evidence that not only pharmaceutical treatment is needed for patients with chronic conditions, while more interest is needed to non-pharmacological lines of treatment [17].
The concept of care comes to detach from the usual imaginary of making a diagnosis, prescribing a therapy and assisting the person in acute. Health promotion interventions are permanent, integrated and patient-centered processes and there is scientific evidence that after an AMI event, being smoker negatively correlates with the individual's HLR-QoL [18]. The individual must be exposed to sensitization, information, learning and psychological support activities concerning his disease, the therapies and the behaviors to be implemented to prevent complications.
This study shows that, beneath the differences related to quality of life were not relevant, after the telephone counseling the intervention group showed a significant improvement in the score of adherence to the Mediterranean diet and a significant reduction in the percentage of smokers. However, other psychosocial smoking cessation interventions based on behavioral therapeutic approaches and telephone support, showed to be effective at 1 year follow up, in promoting abstinence in patients affected by coronary heart disease [19].
The strengths of this study are represented by the short-term effectiveness demonstrated in modifying the life habits of the patients involved and by the fact that this result was obtained in an economic way, after one single telephone counseling intervention.
Weaknesses are represented by the limited number of the sample population and by the evaluation of the outcomes which is limited to short-term and therefore does not give any information about the permanence of behavioral changes induced in patients. The improvement of lifestyle, although initially difficult to achieve because it aims to modify behavioral aspects deeply rooted in the population, is a process that produces significant changes in the health of the subject. The intervention helps the patient and his family to understand the pathology, to live healthier and improve their quality of life.

## Conclusions

The project aims to modify the lifestyles to reduce the incidence of the main chronic-degenerative diseases and decreasing the mortality rate for coronary heart disease. It has shown that even with a single telephone counseling intervention is effectively possible to intervene on the education of the patient in the post-acute period about his illness. It helps to implement the strengthening of the awareness and the ability to choose of the individual through the promotion of good eating habits and the benefits resulting from the cessation of cigarette smoking. This study is a good starting point for carrying out larger studies, with repeated counseling interventions over time and long-term efficacy evaluation. Further fields of investigation could be represented by the evaluation of the outcomes also in terms of health, assessing the differences in the percentages of complications, exacerbations and hospitalizations between a population of patients who received the intervention and a population that did not receive any intervention.

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## Authors' contributions

GLT, RAC, MC and ELS conducted the literature search, the selection of articles, data extraction and write-up of the manuscript. RS, AF, MM, LA, RS and AM, were involved in the design of the study and revision of the paper.

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ORIGINAL ARTICLE

# Predictors of colorectal cancer screening intention among Iranian adults: an application of the preventive health model

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## Keywords

Colorectal neoplasms • Preventive health model • Iran

## Summary

**Objective**. *Colorectal cancer (CRC) is the third most common cancer among adults in Iran. CRC screening is an effective way in reducing mortality rate from this cancer. However, the screening rate of CRC is very low among Iranian adults. This study investigated predictors of Iranian average-risk adults ' intention to take up CRC screening with fecal occult blood test using a mediator model.*

**Methods**. *Participants of this cross-sectional study comprised of 477 average-risk adults who were selected using a national sampling frame in Hamadan city, west of Iran. Data was collected through the questionnaire based on the preventive health model constructs. Structural Equation Modeling (SEM) was employed to test the relationship using Smart PLS 2.0 software*

**Results**. *All measures were robust in terms of the reliability and validity. Benefit ($b = 0.12$, $p < 0.01$), self- efficacy ($b = 0.36$, $p < 0.01$), social support ($b = 0.10$, $p < 0.05$) and barriers ($b = -0.14$, $p < 0.01$) predicted the intention to be screened for CRC. Self- efficacy partly mediated the effects of social support and perceived barriers on intention. The study model explained approximately 24% of the variance in CRC screening intention with fecal occult blood test*

**Conclusion**. *Our findings indicated that the preventive health model constructs such as self -efficacy, social support and barriers are useful in understanding CRC screening intentions and can help health planners to develop effective interventions to encourage Iranian adults to undergo CRC screening.*

## Introduction

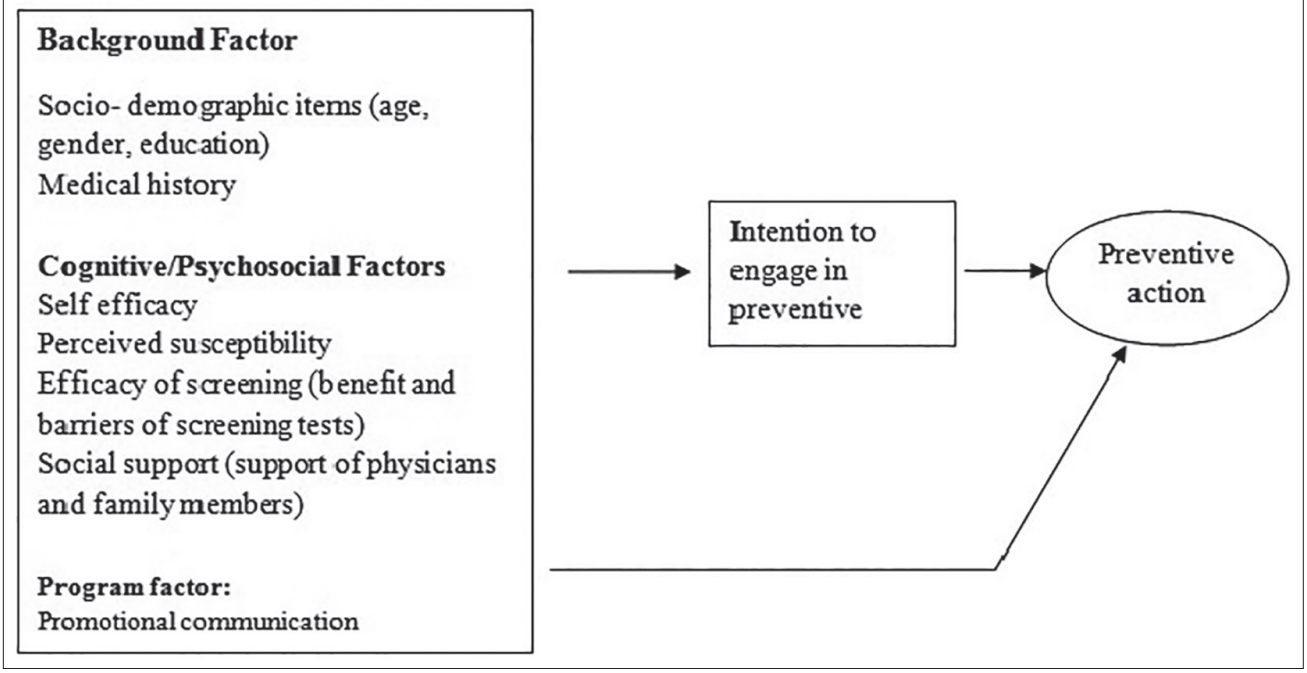
Colorectal cancer (CRC), with 1.36 million diagnoses and 694,000 deaths in 2012, is the third most common cancer in adults worldwide [1]. In the Islamic Republic of Iran, after stomach and breast cancers, CRC is the third most common cancer in both genders [2]. Because of the slow progression of the CRC, this disease is highly curable in its earlier stage and screening can reduce the incidence and mortality of CRC [3, 4]. However, due to lack of screening programs in many countries including Iran, only 39% of CRC are diagnosed at the early stage [5]. Routine screening for CRC is recommended starting at age 50 years for men and women at average risk [4, 6]. The trend of cancer occurrence is observed in younger than 40 years of age in Iran [7] Hence, for this setting, it seems that beginning regular screening at age less than 50 is a more conservative approach.

Several screening modalities are available, including fecal occult blood testing (FOBT), multitarget stool DNA, flexible sigmoidoscopy (FS), colonoscopy, barium enema and CT colonography [6]. FOBT is the first option for CRC screening in countries with restricted resources [8]. Economic evaluations have indicated that FOBT is a cost-effective method of screening compared to FS or colonoscopy in average-risk individuals [9, 10].

At the time of the study (2015), there were no national screening programs for CRC in Iran. Guidelines for the early detection and screening of CRC were approved by the CRC Task Force in 2016. In this program, people aged 50-69 years are called and evaluated by health care providers. Then, Fecal Immunochemical Test (FIT or iFOBT) should be done. Patients refer to the doctor with positive family history or abnormal FIT. Since 2016, this program has been implemented in pilot form in four cities of Iran, but it has not yet become a regular national screening program.

The low screening rates in some countries [11, 12], as well as in Iran [13], highlight the necessity to recognize the factors that predict screening behavior and intention, and eventually to design effective interventions to undergo screening [14]. Evidence suggests that the psychosocial and cognitional factors such as attitudes

Fig. 1. Conceptual framework of preventive health model.




and self-efficacy are important because they are more modifiable factors than others affecting the at-risk population's healthy behavior [13, 15]. Identifying the socio-cognitive models of health behavior offers significant perceptions into the types of factors that affect a person's decision to use screening tests [16].

In the health promotion and disease prevention literature, including cancer preventive behaviors, intention has been considered as the most powerful predictor of person's engagement in a given health behavior [17, 18]. Preventive Health model (PHM) (Fig. 1), which combines elements from the health belief model [19], the theory of reasoned action [20] and social learning theory [21], suggests that intention is affected by four series of factors including background factors, cognitive and psychosocial constructs (e.g., perceived susceptibility to disease and perceived barriers), social support and influence, and program factors (e.g., interventions by health providers) [22]. This model has been applied to predict intention and behavior for CRC screening [18, 23]. The framework has been also used to design interventions and strategies to improve screening uptake [24].

In health behavior literature, self-efficacy has been consistently mentioned as one of the strongest determinants of intention and/or behavior in a range of health behaviors [25]. Self-efficacy is a feeling an individual has so that he or she can successfully engage in a behavior in a particular situation with known outcomes. Given that self-efficacy has been frequently cited as one of the strongest predictors of intention/ health behavior, it is important to examine whether it mediates the effect of other psychosocial determinants of intention to undergo CRC screening. In this study we examined mediating effects of self-efficacy on the association between two constructs of PHM (i.e., social support and perceived barriers) and intention to adhere to CRC.

Social support having been conceptualized in a variety of ways, may facilitate intention/ behavior directly through providing a stress-buffering effect. On the other hand, some previous investigations suggested that self-efficacy at least acts as a partial mediator of this relationship [26, 27]. For example, Gage reported that self-efficacy was the partial mediator of the relationship between social support and health practices [26]. Similar to social support, in conceptual frameworks such as PHM, it is assumed that a perceived barrier has a direct effect on intention. However, some investigators have tested pathways between barriers and different constructs including self-efficacy [28, 29]. The literature, however, shows mixed findings on the mediating effects of self-efficacy. For example, results of Hill and Startup study did not support the mediational role of self-efficacy [30]. Studies on psychosocial factors -associated with CRC screening abound in the literature [13, 31]. The aim of the study was twofold: (1) to identify the determinants of Iranian average-risk adults ' intention to take up CRC screening (FOBT), and (2) to examine whether self-efficacy would mediate the effects of social support and barrier on intention to take up CRC screening (FOBT).

## Methods

### Setting and study design

This cross-sectional study was conducted on 480 average-risk adults in Hamadan city, the capital of Hamadan province, in 2015 with a population about 600000, placed in the west of Iran. The population over 40 years old is 171648 people [32].

Participants were recruited using cluster random sampling. A total of 20 clusters were randomly selected from Multiple Indicator Demographic and Health Survey (IrMIDHS-2010) [33]. Sample size of Hamadan province in IrMIDHS consisted of 74 clusters (urban cluster = 44, rural cluster =30). In current study, we selected 20 clusters among 24 urban clusters of Hamadan city (the capital of the province). Then, in each cluster, one house was selected as a starting point or 'Cluster Head' and moved to the right direction of each cluster head, 24 people above 40 years were entered into the study. Participants were eligible for the study if they were 40 years or older, had no history of CRC and polyp, and had mental ability to respond the questions. Data were collected by four trained senior public health students via face to face interviews. Two women and one man were excluded from the study due to imperfect or apathetic responses.

This study was approved by ethics committee of Hamadan University of Medical Sciences. The participants were given information about the purpose of the study and individual informed consent was obtained from interested individuals.

### Measures

The survey instrument was generated by the literature review [13, 34, 35] and qualitative data were collected through 10 focus group interviews (61 persons) and 20 individual interviews with adults 40 years and older (results of this part of the study are reported elsewhere). Briefly, the results of the individual and group interviews indicated that several factors were associated with CRC screening, including awareness and knowledge about CRC and its screening, financial problems, low priority of health concerns, fear of detection of cancer, mistrust in the health care system and problems related to the nature of CRC screening tests.

The interviews permitted the researcher to hear the participants talk about CRC screening in their own words. The participants' own words and statements from interviews helped to build survey questions.

At the beginning of the research, a pilot study was administered to 30 adults from the people of interest to acquire feedback about understandability, time of completion, reliability and face validity of the items. Also, content validity of questionnaire was confirmed by health education and promotion experts (n = 9) and gastroenterologist (n = 1).

The questionnaire contained two parts: The first part assessed demographic characteristics of the participants including age, sex, educational level, marital status, employment, medical insurance, and family history of CRC or polyps. The second part measured six constructs of the preventive health model as follows.

Perceived susceptibility: perceived susceptibility toward CRC was assessed using four items (e.g., "Compared with persons at my age, it is less likely that I will develop CRC"). The items were rated on a 5-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5. Three items were reverse coded during data analysis in order that higher scores on this items reflected more positive susceptibility participants (Cronbach's alpha = 0.73).

Perceived benefit: Perceived benefit to CRC screening was assessed using three items. A sample item is "If I have FOBT, I can prevent the disease progression". The items were rated on a 5-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5 (Cronbach's alpha = 0.70).

Perceived barriers: Perceived barriers toward CRC screening was measured by seven items (e.g., "Having the FOBT test will be unpleasant and hard to me"). The items were rated on a 5-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5 (Cronbach's alpha = 0.75).

Social support: Social support toward CRC screening was measured by three items (e.g., "My family encourages me to have the FOBT"). The items were rated on a 5-point Likert scale ranging from strongly disagree =1 to strongly agree = 5.

Self -efficacy: Self-efficacy toward CRC screening was assessed using seven items. For example ("I can have FOBT, although it is unpleasant"). A 5-point Likert scale was employed for the items (Cronbach's alpha = 0.81).

Intention: Intention to be screened for CRC was measured through three items (e.g., "I intend to have a FOBT (CRC screening) in the next year"). The items were rated on a 5-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5 (Cronbach's alpha = 0.74).

The third part assessed factor program using one item. The item was rated on a 5-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5.The interview lasted nearly 15 min to complete the questionnaire.

### Data analysis

Structural Equation Modeling (SEM) [36] was used to assess the adequacy of PHM to explain average-risk adult's intentions to undergo screening (FOBT) for CRC. SEM is a combination of two models: (1) a measurement model or outer model (relating observed variables to latent variables), (2) a structural model or inner model (relating latent variables to other latent variables). SmartPLS 2.0 software was employed for SEM analysis [37]. In the current study, our decision to select PLS was due to the existence of formative construct (Social support) [38].

Construct validity and reliability could be assessed through a number of indices such as factor loadings, cross-loadings, average variance extracted (AVE), composite reliability and Cronbach's alpha. In addition, two important criteria, the level of the path coefficient and the significance of the path coefficient were utilized to measure the power of the relationship between latent variables in structural models. The predictive power of the model was examined by calculating Q2 indexes of intention. Finally, a goodness of fit (GoF) index was calculated to display the model fit to the data. Furthermore, the results of the descriptive data were acquired with SPSS version 20.

## Results

The data were gathered from 477 adults (271 females and 206 males). Mean age (sd) of the adults was 53.63 (10.27) years (range 40-82). The majority of participants had high school or lower degrees and most were married (86.4%). Other demographic variables are demonstrated in Table I.

### Measurement model results

The initial assessment of the measurement model for reflective constructs (susceptibility, benefit, barrier, self-efficacy and intention) displayed that 5 indicators of the constructs were deleted from the data set because of outer loading value lower than 0.6, recommended by Chin [39].After deletion of the items, all the outer loadings exceed 0.6 for further analyses ($p < 0.05$).

For the five reflective constructs, the Cronbach's alpha ranged from 0.70 to 0.92, exceeding the recommended threshold value of 0.70 [40]. Composite reliability ranged from 0.81 to 0.95, exceeding the recommended threshold value of 0.70 [38]. And communality ranged from 0.51 to 0.86, exceeding the recommended threshold value of 0.50. Additionally, average variance extracted (AVE) for each reflective construct was 0.50 and higher, meaning that latent variable explains more than 50% of its indicator variance, indicating acceptable convergent validity [38].

**Tab. I.** Demographics characteristics of survey participants (N = 477).

| Characteristics | N (%) |
|---|---|
| **Gender** | |
| Female | 271 (56.8) |
| Men | 206 (43.2) |
| **Occupation** | |
| Housekeeper | 235 (49.3) |
| Employee | 156 (32.7) |
| Retired | 72 (15.1) |
| Unemployed | 14 (2.9) |
| **Marital status** | |
| Single | 12 (2.5) |
| Married | 402 (86.4) |
| Divorced/widow | 52 (10.9) |
| non-response | 1 (0.2) |
| **Education** | |
| illiterate | 79 (16.6) |
| Lower High school | 228 (47.8) |
| High school | 95 (19.9) |
| Higher education | 73 (15.3) |
| non-response | 2 (0.4) |
| **Health insurance** | |
| Yes | 376 (78.8) |
| No | 101 (21.2) |
| **Family history of colorectal cancer/polyps** | |
| Yes | 34 (7.1) |
| No | 442 (92.7) |
| Non-response | 1 (0.2) |
| **Prior screening** | |
| Yes | 19 (4) |
| No | 458 (96) |

The loading factors for the items on each construct were higher than loadings with all the remaining constructs (the cross-loadings), and the AVE squared root of any construct was higher than its correlation values with other constructs (Fornell and Larcker test) [38]. These results support discriminant validity at the latent variables level (Tab. II).

The formative construct (social support) was tested by each item weight, t-value and multicollinearity [38]. The t-value indicates whether the path from the indicator to the construct is significant. Critical t-values for a two-tailed test are 1.65 ($p < 0.1$), 1.96 ($p < 0.05$), and 2.58 ($p < 0.01$) [38]. All the items were found to have statistically significant outer weights except one item that was deleted from the construct.

Multicollinearity test performed using SPSS indicated that each indicator variance inflation factor (VIF) was less than cut-off value of 5 and each indicator tolerance value was less than cut-off value of 2 [38].

### Structural model results

Figure 1 shows the structural model results. Benefit ($\beta = 0.12$, $p < 0.01$), self-efficacy ($\beta = 0.36$, $p < 0.01$) and social support ($\beta = 0.10$, $p < 0.05$) revealed positive direct relationship with CRC screening intention and barriers ($\beta = -0.14$, $p < 0.01$) and education years ($\beta = 0.16$, $p < 0.01$) revealed negative direct relationship with CRC screening intention. Additionally, susceptibility ($\beta = 0.03$, $p > 0.05$), factor program ($\beta = 0.03$, $p > 0.05$) and age ($\beta = 0.07$, $p > 0.05$) did not associate with CRC screening intention. The model explained 24% of the variability in intention to undergo CRC screening ($R^2 = 0.24$).

The results revealed a significant indirect relationship between barriers and CRC screening intention ($\beta = -0.14$, $p < 0.01$) through the mediating role of self-efficacy and also a significant indirect relationship between social support and CRC screening intention ($\beta = 0.08$, $p < 0.01$) through the mediating role of self-efficacy. Thus, self-efficacy was a partial but not complete mediator. The $R^2$ value for self-efficacy is 0.206 that suggesting 21% of the variance of self-efficacy can be explained by barriers and social support.

The model's predictive power was tested by calculating Q2 indexes of intention (Q2 = 0.21) and self-efficacy (Q2 = 0.12), exceeding the recommended threshold value (Q2 > 0) [41], indicating an adequate predictive value of the model. Finally, GoF = 0.36, indicating the model good fit [42].

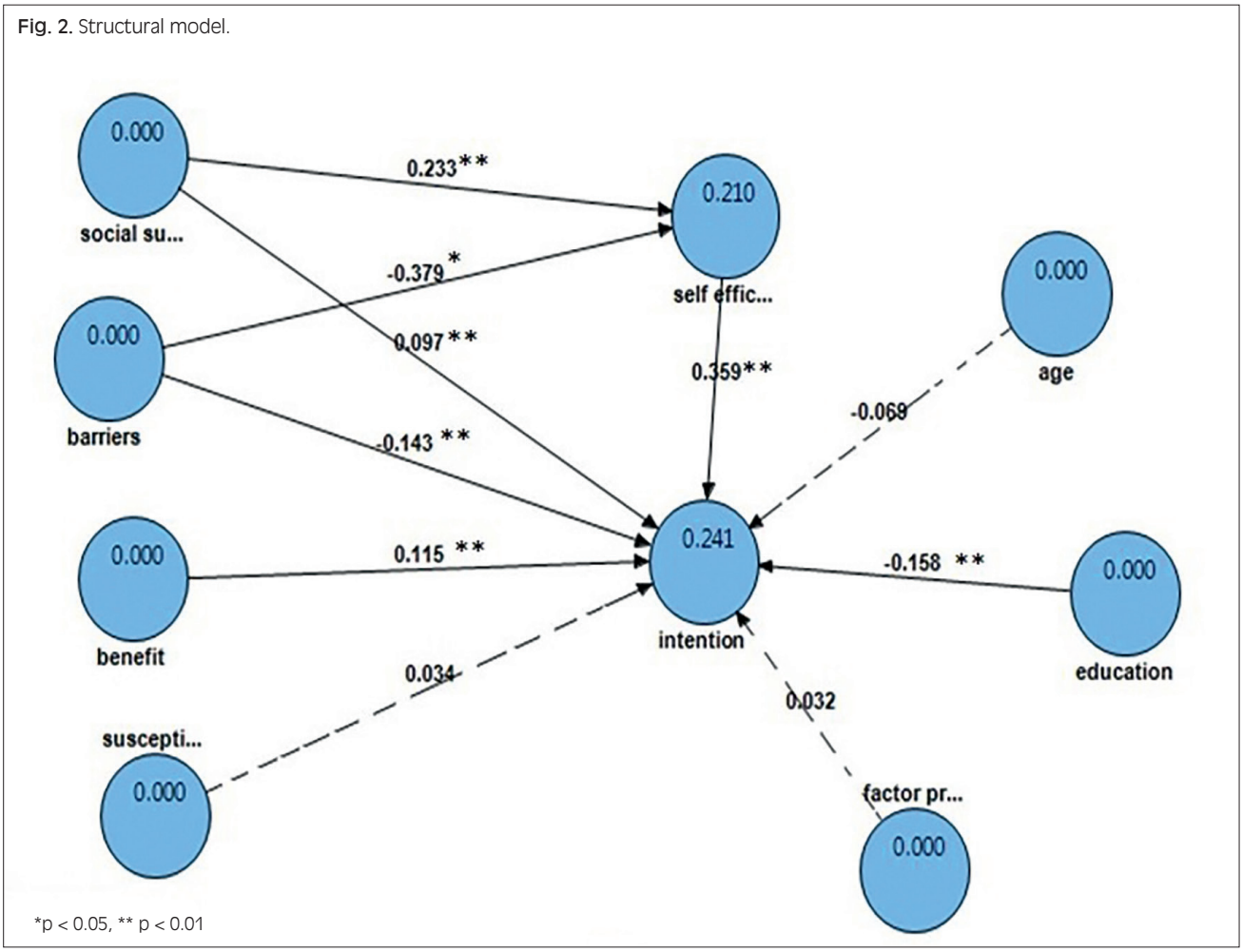
## Discussion

Considering very low level of uptake of CRC screening in Iran, identifying the determinants influencing this health behavior is critical to design an evidence-informed intervention. To our knowledge, this is the first study about the predictors of intention CRC screening (FOBT) using a mediator model among Iranian population. We found that lower perceived barriers and higher perceived

**Tab. II.** Discriminate validity of Constructs-Fornell-Larcker criterion.

| Variable | Barriers | Benefit | Intention | Self efficacy | Susceptibility |
|---|---|---|---|---|---|
| Barriers | **0.4210** | | | | |
| Benefit | -0.135864 | **0.8557** | | | |
| Intention | -0.266733 | 0.182054 | **0.929** | | |
| Self efficacy | -0.388773 | 0.160378 | 0.431935 | **0.7662** | |
| Susceptibility | 0.081112 | -0.180311 | -0.037354 | -0.138540 | **0.9008** |

**Fig. 2.** Structural model.




benefits, stronger social support, higher self-efficacy and lower education were associated with stronger intention to undergo screening with FOBT. However, perceived susceptibility, factor program and age were not associated with intention. Also, self-efficacy mediates effects of social support and perceived barriers on intention.

The findings demonstrated that perceived benefits and perceived barriers were identified as the significant predictors of screening intention. Perceived barriers were negatively associated with intention to undergo screening with FOBT whereas perceived benefits were positively associated with intention to undergo screening with FOBT. This indicates that participants with high-perception of benefits and low-perception of barriers were more likely to express that they intention to undergo screening than participants having low perception of benefits and high perception of barriers. Therefore, researchers and educators in interventions program can use educating the people about the benefits of CRC screening and trying to relieve their worry about the barriers to undergo screening for CRC. This finding is similar to results reported in Zheng et al. [43] and Gregory et all studies [14] who found lower levels of perceived barriers, higher levers of perceived benefits were significantly associated with high intention respectively.

Contrary to findings from at least two other studies [14, 34], social support was one of the predictors of screening intention. Our finding suggests that family member may be a main source of adults' social support that could help average-risk adults overcome barriers of CRC screening and could reinforce the adult's intention through increased perceived ability to undergo CRC

screening. Boonyasiriwat et al. [44] found that support from family and friends was associated with stronger intention to undergo CRC screening among relatives of CRC cases. Other studies have also indicated social support has a direct effect on intention or behavior [45, 46]. The current study findings showed self-efficacy which includes the confidence to perform a special behavior was a strong predictor of screening intention so that adults with higher self -efficacy expressed greater intention to be screened for CRC. Prior studies on the association between self-efficacy and intentions indicate consistent results [22, 47]. Also Watts et al. found that self-efficacy can be important in initiating screening intention [18]. Also, self-efficacy partially mediated the relationship between social support and intention, and relationship between perceived barriers and intention in current study. Thus, social support and barriers not only indicated direct impact on intention to screening with FOBT but also had indirect impact via self-efficacy. Our appraisal of the mediating role of self-efficacy, in predicting CRC screening intention among adults could inform health researchers concerning the utility of this construct in designing future interventions. These results guide us to believe that social support, barrier and self-efficacy are important to successfully increase adults' intention to undergo FOBT screening. Some previous studies suggested that perceived susceptibility predicted screening intention [14, 48]. The current study indicates this construct do not have significantly effects on screening intention. Our data indicated that enhancing the perceived susceptibility of CRC might be less important for screening intention than increasing other construct of PHM. The Extended Parallel Process Model might be helpful to perceive the results regarding perceived susceptibility. According to this model, if adults believe that the early detection of CRC will not decline the risk of CRC, the perception of this risk will not increase the intention to undergo screening [49].

Physician`s recommendations can play an important role, in that eligible persons need to be able to talk about their doubts and their perceived barriers [50]. Physician`s recommendation in health care system to undergo screening for the CRC has been considered in the current study as a program factor. Lack of significant relationship between program factor and intention was inconsistent with results of study done by Boonyasiriwat et al. [44] who reported a positive and direct relationship between health-care provider recommendation and intention. Further, our results regarding education years were surprising. Lower years of education were associated with higher screening intentions. This finding was inconsistent with those of previous studies that reported individuals who intended to screen were more likely to have higher education [51]. Hence, further investigations are essential due to a negative relationship between screening intention and education years among adults in Hamadan city.

In this study, we used a national sampling frame to select the participants and collected data on a broad range of socio-demographic characteristics which makes the findings generalizable to the population. Study limitations include the inability to measure screening behavior (undergo FOBT). Although screening intention has the strongest association with screening behavior, measuring actual behavior (undergo screening) would fortify the overall study. Secondly, cross sectional nature of the study limits causal inferences. Third, the use of self-report measures may raise response bias.

## Conclusions

The findings of this study indicated the effectiveness of PHM in predicting the intentions of Iranians to undergo a screening with FOBT for CRC. Self-efficacy, benefits, barriers, and social support were all directly associated with intention to undergo a screening. A partial mediating role of self-efficacy in the association between social support and barriers with intention was revealed. Given that CRC is curable in its earlier stage and screening could reduce the burden of this disease, we must develop theory-based educational programs that encourage Iranian adults to undergo screening.

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## Authors' contributions

FB was involved in conceptualizing, generating of the project, data collection, data analyses and also drafting the manuscript. AKS was involved in conceptualizing, generating of the project, and also drafted the manuscript. JF assisted with the data analyses. SMMH and SB assisted with the conceptualization of the project. All authors read drafts of the manuscript and provided comments.

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ORIGINAL ARTICLE

# Alcohol use and abuse: a cross-sectional study among Italian adolescents

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Keywords

Alcohol laws • Parents alcohol consumption • Alcohol initiation

Summary

**Introduction**. *Alcohol is recognized as one of four major risk factors for non-communicable diseases. Exposure to alcoholic beverages during the adolescence has been linked to increased heavier drinking habits: obviously, the age of alcohol initiation resulted an important determinant of alcohol dependence. The aim of this study is to analyze knowledge, attitudes and practices in alcohol habit of adolescent population.*

**Methods**. *943 students from 13 schools (middle and upper secondary schools) of the Bari district were enrolled in the study: in each school one class for each age was randomly selected. The research was carried out by an anonymous, self-administered questionnaire which investigated alcohol consumption, knowledge of alcohol consumption of parents and knowledge of the law regulating alcohol consumption.*

**Results**. *34.8% (328) have never consumed alcoholic drinks while 65.2% (615) declare the use of alcohol; the average age of alcohol initiation was 12.2 years. 35.7% (329/921) of mothers and 36.6% (335/915) of fathers drink alcohol only on special occasions. 17.9% (168/939) considered that alcohol could be free sale at all while 16.4% (154/939) reported that sale is forbidden for children under 14.*

**Conclusions**. *The higher prevalence of alcohol habits and the poor knowledge on alcohol law seemed to indicated the need of improving public health efforts in the prevention of alcohol consumption among Italian adolescents.*

## Introduction

According to World Health Organization (WHO) estimate, approximately 2 billion people worldwide consume alcohol and almost 80 million showed an Alcohol-Use Disorder.

Globally, alcohol consumption has increased in recent decades, with a most important trend in Low and Middle-Income Countries. Alcohol actually causes 2.5 million deaths annually, representing 3.8% of the total worldwide mortality. 5.9% of all deaths worldwide are attributable to alcohol consumption; this percentage is greater than the proportion of deaths from HIV/AIDS (2.8%), violence (0.9%) or tuberculosis (1.7%). Also, 5.1% of the global burden of disease and injury is attributable to alcohol, as measured in disability adjusted life years (DALYs) [1, 2].

In the setting of a rising prevalence of Non-Communicable Diseases (NCDs), alcohol is recognized as one of four major NCDs risk factors by WHO: pre-deceasing for non-communicable diseases is strong related to preventable heart disease, strokes, diabetes, cancers and asthma as a result of increased levels of exposure to tobacco use, unhealthy diets, physical inactivity and the harmful use of alcohol [3, 4]. Although alcohol is not known to be carcinogenic in animal experimentation, there is strong epidemiological evidence that consumption of alcoholic beverages increases the risk of oral pharynx, esophagus, and larynx cancers. The risks are essentially thought to be related to ethanol content and appear to be linked to the most commonly used alcoholic beverages in each population. These risks show an increase linear with the amount of ethanol drunk, but it is still unclear whether there is any defined threshold below which no effect is evident.

Corrao G. et al published an important meta-analysis to evaluate the relationship between alcohol consumption and the risk of 15 diseases. Strong trends in risk were observed for cancers of the oral cavity, esophagus and larynx, hypertension, liver cirrhosis, chronic pancreatitis, and injuries and violence. Less strong direct relations were observed for cancers of the colon, rectum, liver, and breast. For all these conditions, significant increased risks were also found for ethanol intake of 25 g per day. Threshold values were observed for ischemic and hemorrhagic strokes. For coronary heart disease, a J-shaped relation was observed with a minimum relative risk of 0.80 at 20 g/day, a significant protective effect up to 72 g/day, and a significant increased risk at 89 g/day. No clear relation was observed for gastroduodenal ulcer [5].

We can describe several determinants of at risk use of alcohol: the volume of alcohol consumed over time; the pattern of drinking (occasional or regular drinking; the drink context; the quality and the safety of alcoholic

beverages). Alcohol is able to damage nearly every organ and system in the body. Its use contributes to more than 60 diseases and conditions: it is the fifth leading contributor to the global disease burden.
Alcohol abuse problem is associated with numerous social consequences, such as crimes, violence, unemployment and absenteeism. It generates health-care and societal costs and it contributes to disparities in health between and within countries.
Europe is the Region where alcohol consumption per capita is the highest in the world. Indeed, 75% of EU citizens reported to have drunk alcoholic beverages during the past 12 months. A quarter of the population (25%), however, appears not to have consumed alcohol at all at least during this period. Data about prevalence of alcohol consumption in Europe are based on respondents' own declarations. For cultural reasons, in some countries respondents tend to under-report their consumption, therefore we have to consider this concern when reading this analysis. In particular, differences between public opinion survey results and results of epidemiological studies are possible [1-4, 6].
Although country prevalence of alcohol consumers ranged between 60% in Italy to 93% in Denmark, the majority of EU Member States and acceding/candidate Countries seem to indulge in drinking some kind of alcoholic beverage. Most probably due to religious motives 53% of residents in the Turkish Cypriot Community declared they had not drunk any alcohol in the past 12 months. Conversely, the 14.7% of the world's population aged 15+ years lives in the WHO European Region, and in this Region more than a quarter (25.7%) of the total alcohol consumed worldwide is annually drunk [1].
In particular the alcohol abuse represents a big problem for European young people. 1 in 4 deaths among young men (aged 15-29) and 1 in 10 deaths among young women is due to alcohol abuse (often caused by road traffic accidents, homicide, violence and even liver disease). According to the WHO estimates, weekly drinking across the EU is reported by 5% of 11-year olds, 12% of 13-year olds and 29% of 15-year olds. Over 90% of 15-16 year-old Europeans have drunk alcohol at some point in their life with the average age for getting drunk for the first time being 14 years. In 2003, around 23% of 15-16 year-old boys in the EU reported binge drinking at least 3 times in the previous 30 days, according to European School Survey project on Alcohol and other Drugs (ESPAD) [5-9].
Although the age considered appropriate or acceptable for alcohol drink varies across nations, there is consistent agreement concerning the effect of alcohol on adolescents, both on the health both on the behaviors.
Exposure to alcoholic beverages before or during the early teenage years has been linked to increased heavier drinking habits: obviously, the age of alcohol initiation resulted an important element to predict the risk of alcohol dependence and it has been frequently investigated. The early-adolescent onset of alcohol use could be considered a marker of risk or a causal element of later dependence. Evidences suggested that alcohol initiation at ages 11-14 greatly heightens the risk of progression to the development of alcohol disorders; adolescents therefore are a reasonable target for intervention strategies that seek to delay first use as a means of averting problems later in life. Therefore Boyd et al. supposed the "genetic predisposition" of development of alcohol dependence [10-12].
The relationship between age at first alcohol consumptions and development of various psychiatric comorbidities has been confirmed. A lot of local experience and studies concluded that young age at drinking onset is significantly related to alcohol dependence and to experience AUDs, psychotic symptoms, intermittent explosive disorder and panic disorder [13, 14].
It resulted that alcohol use in adolescents could reduce volume of hippocampus, prefrontal cortex as well as white matter, resulting in deleterious alterations of various cognitive abilities including memory, planning and spatial tasks [15].
The role of parents could be an important determinant of alcohol attitude. Parental control is negatively associated with alcohol and other substances use and abuse, whereas attending friends who consumed alcohol increases the risk of alcohol use and abuse. Specifically, poorly monitored adolescents are more likely to use drugs, and drug-using adolescents seek out like-minded friends [16].
The majority of reviews agreed with the conclusion that parental alcoholism increases the probability of problem drinking and even chemical dependency in children; frequently, in this context, young people are introduced to alcohol by their parents. The mistreatment of children, including sexual abuse, physical abuse and neglect, may also lead to childhood psychopathology and later to problem drinking. Instead, good family relations and good parental knowledge of the law regulating alcohol consumption can impact favorably upon adolescent outcomes, including alcohol use [17-19].
Due to the central role of alcohol prevention among adolescents, authors designed this study that seeks to analyze knowledge, attitudes and practices in alcohol habit of adolescent population.

## Methods

This is a cross-sectional study. The study was carried out in 2013.
943 students from 13 schools (middle and upper secondary schools) of the Bari district were enrolled in the study: schools were enrolled by a convenience sample and in each school one class for each age was randomly selected. The research was carried out by an anonymous, self-administered questionnaire, developed by the authors on the basis of most important evidences in the literature. The questionnaire has been validated in a pilot school class before the start of the survey.
The aim of the questionnaire was to develop a cognitive research on drink consumption, mainly by investigating the following end-points:

- alcohol consumption;
- knowledge of alcohol consumption of parents;

- knowledge of the law regulating alcohol consumption.

The questions required more than one options of answer.

### Statistical analysis

Compiled questionnaires were exported to a Microsoft Office Excel spreadsheet and analyzed with STATA MP12 software.

All questionnaires were included in the statistical analysis even in case of missing. Therefore the number of data are different in the different questions.

Continuous variables are expressed as mean ± standard deviation, range, median and IQR; categorical variables were expressed as proportions. For continuous variables the normality analysis was performed and, for those not normally distributed, a normalization model was set. For some variables, it was not possible the normalization, then non-parametric tests have been used.

T-student test for independent groups has been used to compare independent groups and chi-square test has been used to compare proportion between independent groups.

Spearman's ranks were used to investigate the relation between:

- age of respondents and knowledge of the law regulating alcohol consumption;
- age of respondents and age of alcohol initiation;
- age of respondents and mother's alcohol consumption;
- age of respondents and father's alcohol consumption;
- knowledge of the law and age of alcohol initiation;
- mother's alcohol consumption and father's alcohol consumption;
- age of alcohol initiation and mother's alcohol consumption;
- age of alcohol initiation and father's alcohol consumption;
- age of alcohol initiation and gender.

Significance was assumed for $p < 0.05$.

## Results

943 subjects were enrolled in the study, of which 521 were males (55.25%) and 422 females (44.75%), with an average age of 14.4 ± 2.2 years (range 10-20).

Subjects included in this study attended 13 secondary school in the Bari district; the number of subjects per school ranged from 61 to 104.

Among subjects interviewed, 34.8% (328) have never consumed alcoholic drinks while 65.2% (615) declare the use of alcohol.

Among boys, 70.1% (365/521) consumed alcoholic drinks almost one time during the life: while among girls 59.2% (250/422) (Tab. I; chi-square = 12.0; p = 0.0005).

Among girls, the average age of alcohol initiation was 12.7 ± 3.9, while it was 11.9 ± 4.2 years among males (Tab. II; t = 3,0; p = 0,002).

According to the opinion of our students, the frequency of alcohol consumption is more frequent among fathers than among mothers (Tab. III).

35.7% (329/921) of mothers and 36.6% (335/915) of fathers, drink alcohol only on special occasions (parties, recurrences, evenings in company, etc.). 34.96% (322/921) of mothers never consumes alcoholic drinks while among fathers, 12.9% (118/915) never drink alcoholics ($p < 0.0001$). 17.7% (162/915) of fathers drink alcohol every day only during meals and 3.6% (33/915) also out of meals, while 8,25% of mothers (76/921) drink alcohol every day only during meals ($p < 0.0001$). 13.9% of interviewed subjects declared that they had not notice about the alcohol consumption of their parents (Tab. III).

939 students answered the question about knowledge of the Italian law on alcohol consumption in Italy. 17.9% (168/939) considered that alcohol could be free sale at all while 16.4% (154/939) reported that sale is forbidden

**Tab. I.** Prevalence of alcohol consumption, per gender.

| Alcohol consumption | Male (%) | Female (%) | Total (%) |
|---|---|---|---|
| Nevers | 156 (29.9%) | 172 (40.8%) | 328 (34.8%) |
| Almost one time during the life | 365 (70.1%) | 250 (59.2%) | 615 (65.2%) |
| Total | 521 (100%) | 422 (100%) | 943 (100%) |

chi-square = 12.0; p = 0.0005

**Tab. II.** Mean, standard deviation (DS), range, of age of alcohol habit beginning, per gender.

| Age of alcohol habit beginning | Mean | DS | Range |
|---|---|---|---|
| Male | 11.9 | 4.2 | 1-17 |
| Female | 12.7 | 3.9 | 1-19 |
| Total | 12.3 | 4.1 | 1-19 |

t = 3.0; p = 0.002

**Tab. III.** Knowledge of enrolled subjects about parental alcohol consumption and differences between mothers and fathers.

| Frequency | Parents (Total) (n = 1836) | Mothers (n = 921) | Fathers (n = 915) | Chi-square | p |
|---|---|---|---|---|---|
| Nevers | 440 (24.0%) | 322 (34.96%) | 118 (12.9%) | 122.6 | < 0.0001 |
| Every days during and also out of meals | 45 (2.4%) | 12 (1.3%) | 33 (3.6%) | 10.2 | 0.0014 |
| Every days only during meals | 238 (13.0%) | 76 (8.25%) | 162 (17.7%) | 36.3 | < 0.0001 |
| 4-5 times per week out of meals | 15 (0.8%) | 2 (0.2%) | 13 (1.4%) | 8.2 | 0.0042 |
| 4-5 times per week during meals | 159(8,7%) | 52 (5.6%) | 107 (11.7%) | 21.2 | < 0.0001 |
| Only during special parties | 664 (36.2%) | 329 (35.7%) | 335 (36.6%) | 0.16 | 0.69 |
| Before drunk but now do not drink any more | 19 (1%) | 10 (1.1%) | 9 (1%) | 0.05 | 0.83 |
| I don't know | 256 (13.9%) | 118 (12.8%) | 138 (15.1%) | 1.97 | 0.16 |

Tab. IV. Knowledge of enrolled subjects about Italian law on alcoholic sale, per gender

| Law about selling of alcoholic beverage in Italy | Total (939) | Male (518) | Female (421) | Chi-square | p |
|---|---|---|---|---|---|
| Free to everyone | 168 (17.9%) | 86 (16.6%) | 82 (19.5%) | 1.3 | 0.25 |
| Forbidden for children under 14 years of age | 154 (16.4%) | 78 (15.1%) | 76 (18.0%) | 1.5 | 0.22 |
| Forbidden for children under 16 years of age | 319 (34.0%) | 181 (34.9%) | 138 (32.8%) | 0.5 | 0.5 |
| Forbidden for children under 18 years of age | 295 (31.4%) | 171 (33.0%) | 124 (29.4%) | 1.4 | 0.2 |
| I don't know | 3 (0.3%) | 2 (0.4%) | 1 (0.2%) | 0.2 | 0.7 |

for children under 14. 34.0% (319/939) of respondents think the sale forbidden for subjects aged less than 16 and 31.4% (295/939) for subjects aged less that 18 years. 0.3% (3/939) stated having no idea about this topic. There were no statistically significant differences in the distribution of these opinion between the two genders (Tab. IV).

Spearman's rank showed significant associations for:

- age of respondents and age of alcohol initiation (rho = 0,7; p = 0,000);
- age of respondents and father's alcohol consumption (rho = -0,1; p = 0,030);
- mother's alcohol consumption and father's alcohol consumption (rho = 0,4; p = 0,000);
- age of alcohol initiation and gender (rho = -0,1; p = 0,001).

## Discussion and conclusions

This survey, carried out among a large sample of adolescents of Bari's district, shows an higher prevalence of subjects who reported alcohol initiation at young age. Only 35% of enrolled people had never drunk alcohol in their life: in female (40.8%) proportion resulted higher than male people (29.9%).

The majority of interviewed adolescents have had an alcoholic drink before the age of 15 years. The average age of first alcohol use resulted 12 years; in addition resulted a correlation between age of alcohol initiation and gender (rho = -0,1; p = 0,001): boys experienced their first drink at younger age than girls. This elements is consistent with literature data: according the WHO "Global status report on alcohol and health 2014", an early initiation of alcohol use (before 14 years of age) is a predictor of impaired health status because it is associated with increased risk for alcohol dependence and abuse at later ages [1, 20]. Initiating alcohol use earlier in adolescence is associated with an increased risk of binge drinking and higher quantity of consumption in late secondary school; public health efforts must be oriented in supporting policy for delaying alcohol initiation for as long as possible to reduce the risk for problematic use in later adolescence and the alcohol-related harms that may accompany this use.

Alcohol habit seems to be very common among father: only 12.9% never consumed alcohol drinks, while more than 20% drink alcohol every day; on the contrary, 35% (322/921) of mothers never consumes alcoholic drinks. Several reviews confirmed that parents affected by alcohol use disorders display particular patterns of alcohol consumption and thereby increase the likelihood that their children will develop drinking patterns associated with high risk of alcohol use disorders when they are introduced to alcohol [1, 21, 22].

Actually in Italy the sale of alcohol is forbidden for children under 18 years of age (Law No. 189, November 8, 2012); until this law prohibition already concerned people under 16 years. Although law provisions, young people resulted not well informed about sale restrictions of alcoholic drinks: 18% considered that alcohol's sale is free and 16% considered that alcohol's sale is forbidden only for children under 16 years of age [23].

This is a pilot study who investigate only some elements of young people attitude and practice about alcohol consume. Major weakness regarded the design (convenience sample) and the use of a questionnaire, because a part of respondents could not report their alcohol habits for fear of parents.

For the future, it would be necessary to add information about quantity of alcohol consumed: data from literature suggested that there is a dose–response relationship between alcohol and acute and chronic diseases and injuries causally impacted by alcohol. In addition it would be investigate the frequency of alcoholic drink consume and the presence of heavy episodic drinking (HED), that was justified as a temporary behaviour associated with the freedom of young students [24].

In this regard HBSC probably represents the pioneer cross-national study gaining insight into young people's well-being, health behaviours and their social context. This research, carried out in collaboration with the WHO Regional Office for Europe, is conducted every four years in 48 countries and regions across Europe and North America. With adolescents making about one sixth of the world's population, HBSC uses its findings to inform policy and practice to improve the lives of millions of young people. HBSC data of Italian adolescents reveal regional difference of alcohol consumption and frequency of heavy episodic drinking (HED). Our results seem in line with HBSC data [25].

However the study is consistent with literature data about alcohol habit in young people. Children, adolescents and elderly people are typically more vulnerable to alcohol-related harm from a given volume of alcohol than other age groups and frequently a greater proportion of the total alcohol consumed by young people is consumed during heavy drinking episodes [26].

Alcohol policies based on age-related vulnerability include partial or total advertising bans, restrictions on access to alcohol through minimum ages at which it is legal to purchase alcohol, and laws aimed to prevent any alcohol consumption by young people when driving vehicles. In considering the increasing burden of alcohol

disease in the last years WHO tried to define a global strategy to reduce the harmful use of alcohol: it contains a set of guiding principles for the development and implementation of alcohol policies, sets priority areas for global action, recommends ten target areas for national action, and gives a strong mandate to WHO to strengthen action at all levels [1, 27].

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The authors declare that there is no conflict of interest.

## Authors' contributions

SP analysed data; SP, GA and BA drafted the manuscript; GA and RD conceived the study; GA, FC, DMA and CMF collected data and reviewed the manuscript. GA, DDV and TS supervised the project and reviewed the manuscript. All authors discussed the results and contributed to the final manuscript.

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Overview

# Tuberculosis in Genoa: the contribution of Edoardo Maragliano (1849-1940) and the Medical School of the University of Genoa

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Keywords

Edoardo Maragliano • History of tuberculosis, Public health

Summary

*Between nineteenth and twentieth centuries, medicine knew the beginning of an incessant development: the birth of new medical specialties (radiology, for instance), the introduction of new devices in medical and surgical wards, and the discovery of bacteria represented important milestones in that first historical period. The Medical School of the University of Genoa, head by Edoardo Maragliano, full professor of internal medicine, took on a relevant role in the battle against tuberculosis, through the experimental demonstration of the existence of an immune response against M. tuberculosis and the production of an inactivated vaccine. During his career, Maragliano surrounded himself with graduate assistants and students, who would later become full professors of internal medicine in prestigious universities and excellent physicians. In order to allow the correct diagnosis and educate his young colleagues, Maragliano endowed his clinic laboratories of haematology, biochemistry, microbiology and radiology. Under his supervision, the assistants of the Genoa University Medical Clinic issued over two thousand scientific publications.*

In the second half of the Nineteenth century, medicine knew a new era: the development of physiology, biochemistry, microbiology and cellular pathology defined diseases through the clinical observation and the scientific experimentations performed in the academic laboratories. The character of the scientist firstly appeared in the Central Europe. Another phenomenon characterized the development of a modern medicine: the integration of new medical devices was due to the intensification of scientific research in diagnosis and therapy. All things considered permitted the upgrade of specialization thanks also to other factors, such as demographic increase of population, mainly in industrial cities where the request of health enhanced enormously [1, 2].

Indeed, infectious diseases were the principal cause of morbidity and mortality within and among population. At the end of the Nineteenth century, around the world, twenty-five per cent of bodies showed signs of tuberculosis at the autoptic table, and in urban populations (in particular, industrial settlements) fourteen per cent of death were caused by *M. tuberculosis*. The mortality trend was bimodal, with peaks between the ages of one to twentyfive. The mortality percentage was higher in women than in men. Contributing factors were also cold seasons and poor hygienic conditions [3]. In this ardous scenario, the announcement of the discovery of *M. tuberculosis* on 25$^{th}$ March 1882 by Robert Koch (1843-1910), drove the scientific community to work on the therapies. Koch himself elaborated a combination of proteins obtained from tubercular bacteria as a therapy for the disease [4]. Other methods of immunization were developed until 1890; nevertheless because of the inefficacy of tuberculin and the observation that not all people were affected by tubercular disease, a negativistic attitude arose towards the possibility of understanding tuberculosis pathogenesis and establishing any method of immunity activation [3, 5].

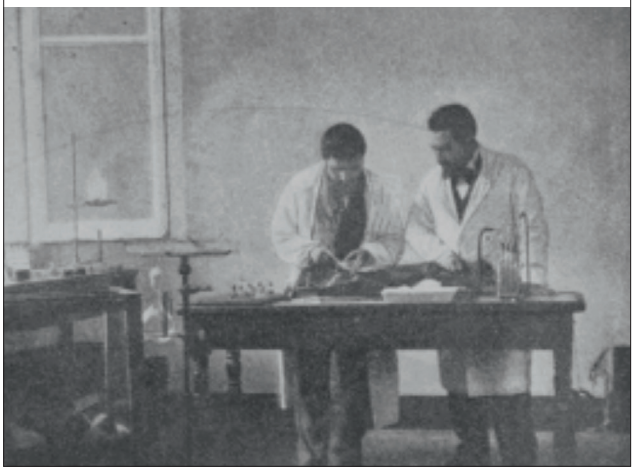
In Genoa, the Medical School of the University of Genoa, driven by Edoardo Maragliano (1849-1940; Fig. 1), played a central role in the definition of the pathophysiology and prevention of tuberculosis. Maragliano was full professor of internal medicine at the University of Genoa from 1881 until his retirement, in 1924 [6]. During this period, Maragliano and his collaborators were able to demonstrate, for the first time, the existence of innate and specific immunity against M. tuberculosis [7]. In 1895, Maragliano found a "tubercular antitoxin" in serum from infected animals: this discovery led Maragliano and his collaborators to use animal serum for serotherapy in humans. Then, they successfully used bacterial derivatives to induce components of innate immune response in animals and humans. Moreover, they observed that better were nutritional and environmental conditions of patients, better was the response of patients to serotherapy. Maragliano, indeed, was the first clinician who understood the importance of the influence of environmental conditions, not only from a clinical point of view, but also from a social one, in order to give a medical and a social support to patients and their families. Even if scientific community was skeptical, in particular because of the use of inacti-

Fig. 1. Edoardo Maragliano.

vated vaccine, Maragliano defended the need to prevent tuberculosis with any type of vaccine, even inactivated or attenuated one [5, 6].

Maragliano believed that: "The first duty of a physician is to lead young colleagues to a correct diagnosis, a firm prognosis and a useful therapy, applying all sciences achievements at the patient bedside" [8]. For these reasons, though he always subordinated laboratory examination to clinical observation, he provided his laboratories of equipment for serology, microbiology and, above all, radiology, in connection with the clinic in order to deal the different problems connected with medicine. Vincenzo Sciolla (Fig. 2), an associate

Fig. 2. Vincenzo Sciolla (on the left).



of Maragliano's, looked after the first use of radioscopy in the Medical Clinic for one year, because of his premature death. In 1897, Marco Sciallero, another associate of Maragliano's, became the chief of the radiologic lab, until his retirement for radiation injuries. Maragliano charged his son, Vittorio (1878-1944), with the radiologic lab: in 1913, Vittorio became full professor of radiology [3, 8, 9]. Also, his brother, Dario, began to practice medicine in the Medical Clinic directed by his father, who entrusted him a surgery service within the Clinic; he became full professor of surgery at the University of Genoa [10]. In every phase of his studies, Maragliano relied on his collaborators, who became full professors of medicine and directors of medical clinics: about them, Giovan Battista Queirolo (1856–1930) in Pisa; Livierato Panagino (1860-1936) e Spiro Livierato (1881-1962) in Genoa and Athens, respectively; Pietro Castellino (1864–1933) in Naples; Rocco Jemma (1866-1949; figure 3), pediatrician, in Naples; Luigi Devoto (1864-1936) in Milan; Luigi Lucatello (1863-1926; figure 4) in Padua; Amerigo Barlocco (1880-1926) in Modena [3, 11, 12].

Among his collaborators who became professors in medicine, Luigi Devoto had a relevant role: under the influence of Maragliano's clinical precepts and social ideas, he began to study the tuberculosis diffusion among nurses and led undergraduates in the poorest neighbourhoods of Genoa. Devoto himself recognized the role of

Fig. 3. Rocco Jemma.

his master in his interest about workers' pathology. After a brilliant academic career, with Maragliano's aid, Devoto founded in Milan the first medical clinic in the world, the so–called "Clinica del Lavoro", whose purposes were the diagnosis, the therapy and the prevention of occupational diseases [13]. Maragliano often remembered his collaborators who prematurely dead. Besides Vincenzo Sciolla, Dr. Gaetano Salvioli (1852-1888) also represented a great bereavement for Maragliano. In 1883, Gaetano Salvioli discovered *S. pneumoniae*, one year before Albert Fraenkel. Gaetano Salvioli died five years later because of typhus contracted at the dissection room [14]. According to Maragliano, "affections born in school, always refreshed by working together, create relationships which are not lower than ones of blood and give to a father the tears and anguishes when he sees his children abducted by death, without the hope they were gathered around the bedside of their father" [11]. All his collaborators considered him a severe, but right and equanimous master, demonstrating himself a strong dedication to work, with renunciations and sacrifices. In public competitions, Maragliano aided his collaborators to achieve prestigious academic positions or direction of important medical clinics in Italy, such as Luigi Lucatello, who became Dean of the University of Padua [6, 7, 15].
Although Maragliano's contribution to the fight against tuberculosis was criticized and forgotten by his contemporaries, all his collaborators contributed to spread in the universities and in the hospitals the knowledge he created, based on clinical observation and research in laboratory. His zeal and fervour in the fight against tuberculosis also had relevant social consequences, like the institution of the first *Sanatorium* in Italy at the end of the nineteen century [11].

**Fig. 3.** Rocco Jemma.

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The Authors declare that there is no conflict of interest.

## Authors' contributions

The Authors conceived the study, drafted and revised the manuscript, read and approved the last version.

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