

supplemento 1
numero **4** anno 39
luglio
agosto
2015

EPIDEMIOLOGIA & PREVENZIONE

Rivista dell'Associazione italiana di epidemiologia

e&p

Editors/A cura di:

Luigi Bisanti, Eugenio Paci, Rossella Coppola,
Carlo Signorelli

Proceedings of the 48th National Congress of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI)



SELECTION OF CONTRIBUTIONS, REVIEWS, AND ORIGINAL PAPERS



Atti del 48° Congresso Nazionale
della Società Italiana di Igiene, Medicina
Preventiva e Sanità Pubblica (SItI)

SELEZIONE DI INTERVENTI, REVIEW
E ARTICOLI ORIGINALI

EDIZIONI
inferenze



Rivista fondata da **Giulio A. Maccacaro**

Anno 39 (4) 2015

Epidemiologia & Prevenzione
è indicizzata in **Medline**,
Science Citation Index Expanded,
Journal Citation Reports/Science Edition

Pubblicazione bimestrale Registrazione
del Tribunale di Milano

n. 239/1977 Spedizione in AP - 45% - art. 2 comma 20b legge
662/96 - Milano.

Iscrizione al Registro degli Operatori
di Comunicazione (ROC) n. 11747.

Una copia: 13,50 euro.

Abbonamento annuo: informazioni e condizioni sul sito
www.epiprev.it

Gestione abbonamenti: ufficio abbonamenti
tel. 02 48702283, fax 02 48706089.

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Testata associata

A.N.E.S.
ASSOCIAZIONE NAZIONALE
EDITORIA PERIODICA SPECIALIZZATA

Stampa

Arti grafiche Ancora srl - Milano

EPIDEMIOLOGIA & PREVENZIONE



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Versamento su conto corrente postale n. 55195440 intestato a Inferenze scarl, via Ricciarelli n. 29, 20148 Milano (segnalare la causale del versamento).
Accredito tramite c/c bancario presso: UNIPOL BANCA P.za Wagner n. 8, 20145 Milano, IBAN: IT53P 03127 01600 00000003681 intestato all'impresa editoriale Inferenze scarl, via Ricciarelli n. 29, 20148 Milano.

Si ringrazia la Fondazione IRCCS Istituto nazionale dei tumori di Milano che ospita l'Impresa sociale.

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Proceedings of the 48th National Congress of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI) Selection of contributions, reviews, and original papers

Atti del 48° Congresso Nazionale
della Società Italiana di Igiene, Medicina Preventiva
e Sanità Pubblica (SItI)
Selezione di interventi, review e articoli originali

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Luigi Bisanti (E&P), Eugenio Paci (E&P), Rossella Coppola (SItI)
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Milan 2015: creating a safer, healthier, and sustainable world

Milano 2015; creare un mondo più sicuro, più sano e più sostenibile

There are always many reasons why one should visit Milan. Some may come for its art, such as Leonardo da Vinci's Last Supper. Some may come for the opera at the world-famous La Scala. Others may come for the shopping, in via Montenapoleone, or to enjoy the beauty of the nearby Italian lakes and mountains.

In 2015 there are even more reasons to come to Milan. It is the setting for EXPO 2015, a vast complex in which the countries of the world demonstrate their commitment to "Feeding the Planet, Energy for Life". This provides an appropriate backdrop for two other major events concerned with the health and well-being of our societies, at national and European level. Two major conferences will be held in parallel at the Milan Conference Centre (MiCo). These are the 48th National Congress of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI) and the 8th European Public Health (EPH) Conference, which showcases the work of the 14,000 members of the much younger European Public Health Association.

All three of these events recognize the enormous challenges that face our societies, in Italy, Europe, and the world. Indeed, it would be impossible to ignore them. Every day images appear on television screens and in newspapers of the horrors of war, in Ukraine, North Africa, and the Middle East, or its consequences, with thousands already having drowned in the Mediterranean. There are also challenges nearer to home, as the imposition of austerity policies leaves a generation of young people without the opportunities that their parents and grandparents had to gain a step on the ladder to employment and security.

Yet these three events also offer hope for the future. At EXPO 2015 one can enter row after row of imaginatively designed national pavilions displaying ideas and innovations that can contribute to food security for a growing world population, such as the celebration of beauty and biodiversity in the Italian pavilion, or the opportunity, in the United Kingdom's pavilion, to imagine oneself as one of the bees, whose pollination is essential for a third of everything we eat.

The two public health conferences will bring together researchers, teachers, and practitioners, with the shared goal of giving Italy, and Europe, a better, healthier, and more secure future. Speakers will describe new ways of making the invisible visible. They will draw attention to the needs of vulnerable pop-

ulations. They will explore ever more imaginative approaches to exploiting the wealth of data about how we live our lives. They will offer many lessons on what works to improve health and, as importantly, what does not. And they will discuss new ways to translate this evidence into policy and practice.

In these ways, both SItI and EUPHA will demonstrate their commitment to making our societies better places in which to live, creating a world in which threats to health are anticipated and confronted and where policies are informed by evidence. They will demonstrate their determination to strengthen public health capacity, both among the workforce of today and among future generations. But above all, they will provide an opportunity for shared learning, exploiting the remarkable natural laboratories provided by the 20 Italian regions and the 53 countries of the European region.

This supplement of *Epidemiologia & Prevenzione* contributes to this process. It showcases some of the best studies presented at the 48th National Congress of SItI, with 26 papers summarizing presentations in the main conference sessions (plenary and workshops), 9 reviews written by SItI working groups, and over 12 original papers selected from the best abstracts presented. Papers have been published in English, the international language of science, to place work of the highest quality by Italian researchers, working at all levels and in all parts of the country, on the European stage.

For centuries, scholars, writers, musicians, and scientists have come to Italy for inspiration. Copernicus, Goethe, Ibsen, Keats, Wagner – the list is almost endless and the legacy is apparent in the most unexpected places, such as the Padua children's ward in the English hospital named after William Harvey, who studied in that city and discovered the circulation of the blood. Now it is the turn of Europe's public health community to draw inspiration from all that this remarkable country has to offer.

Carlo Signorelli
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and Public Health (SItI)

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REVIEWS
REVISIONI

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Seminar
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Thursday 15 October
h. 14.00-14.30
Amber Room 1

Green areas and public health: improving wellbeing and physical activity in the urban context

Spazi verdi e salute pubblica: migliorare il benessere e l'attività fisica nei contesti urbani

Daniela D'Alessandro,¹ Maddalena Buffoli,² Lorenzo Capasso,³ Gaetano Maria Fara,⁴ Andrea Rebecchi,² Stefano Capolongo,^{2,5} and the Hygiene on Built Environment Working Group on Healthy Buildings of the Italian Society of Hygiene, Preventive Medicine and Public Health (SIItI)

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Abstract

Introduction. The green areas play an important role in improving the environmental quality and climate of the city. However, despite the undoubted importance of these areas, the benefits to public health are still under investigation.

Results. The Authors perform a review of studies on the relationship between health and green areas and describe the main areas for which evidence on this relationship is currently available. They include: effects on air quality, on social cohesion, on mental health, with particular reference to the stress, and on physical activity.

Conclusions. Most of the evidence comes from cross-sectional and descriptive studies and the approaches used to measure the association show themselves to be often unsatisfactory. The Authors conclude the review stressing the need for greater integration between the different professionals involved in urban planning and in health care analysis in order to identify research approaches more appropriate to understand such complex issues, striving toward a planning design of green areas that will satisfy both environmental sustainability and health requirements.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 8-13)

Key words: green space, urban context, health, physical activity, design

Riassunto

Introduzione. Le aree verdi assumono un ruolo molto importante nel migliorare la qualità ambientale e il clima delle città. Tuttavia, nonostante l'indiscussa importanza di tali aree, i benefici per la salute pubblica sono ancora oggetto di studio.

Risultati. E' stata svolta una revisione degli studi sul rapporto tra aree verdi e salute. Sono descritti i principali ambiti sui quali sono oggi disponibili evidenze circa la relazione tra spazi verdi e salute. Essi includono: gli effetti sulla qualità dell'aria, sulla coesione sociale, sulla salute mentale, con particolare riferimento allo stress e sull'attività fisica.

Conclusioni. La maggior parte delle evidenze derivano da studi descrittivi e di prevalenza e gli approcci utilizzati per la misura dell'associazione sono spesso non soddisfacenti. Gli autori concludono la revisione sottolineando la necessità di una maggiore integrazione tra le diverse professionalità coinvolte nella progettazione urbana e nella tutela della salute per individuare approcci di ricerca più adeguati per comprendere problematiche così complesse, in modo da giungere a una progettazione delle aree verdi che soddisfi le esigenze di sostenibilità ambientale e di salute.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 8-13)

Parole chiave: spazi verdi, contesti urbani, salute, attività fisica, progettazione

INTRODUCTION

About 3.4 billion people (half of the world's population) live in urban areas today: it has been estimated that the proportion will rise to 60% by 2030, and the absolute number will be 6.3 billion by 2050.¹ The understanding of how urban environment affects health outcomes and how it could produce health benefits is therefore an urgent priority, as recognized by WHO in the declaration of 2010 as the Year of Urban Health.

Unfortunately, due to increasing urbanization, combined with the spatial planning policies of densification, nowadays homes have become more and more separated from green environments, although, as argued by van de Berg et al.,² a restricted access to green spaces may increase vulnerability to the impact of stressful life events on mental and physical health.

At present, several studies provide evidence, albeit still rather weak, of some association between green spaces, wellbeing, and health.³⁻⁶ In the most recent years, this topic has gained an increasing interest.

RESULTS

A «web of knowledge» search with just two terms, «green space and health», yielded 2 hits for 1990-1999, 34 for 2000-2009, and 45 from 2010 to June 2013.⁷ The reasons for this rise in interest are many. Some papers reflect concerns that urbanization, environment degradation, and lifestyle changes are qualitatively diminishing occasions for human contact with nature; others consider nature as just one aspect of the physical environment that may be potentially beneficial for health. In general, research aimed to propose practical measures that could directly or indirectly provide access to nature, including interventions about housing, transportation, and recreation.

In the same paper,⁷ the Authors performed a «review of reviews» on the topic until April 2013, involving 56 relevant reviews. Of the peer-reviewed articles, the majority appeared in journals focused on public health or environmental planning.

The reviews varied considerably in methodology, guiding aims, and environmental aspects discussed.

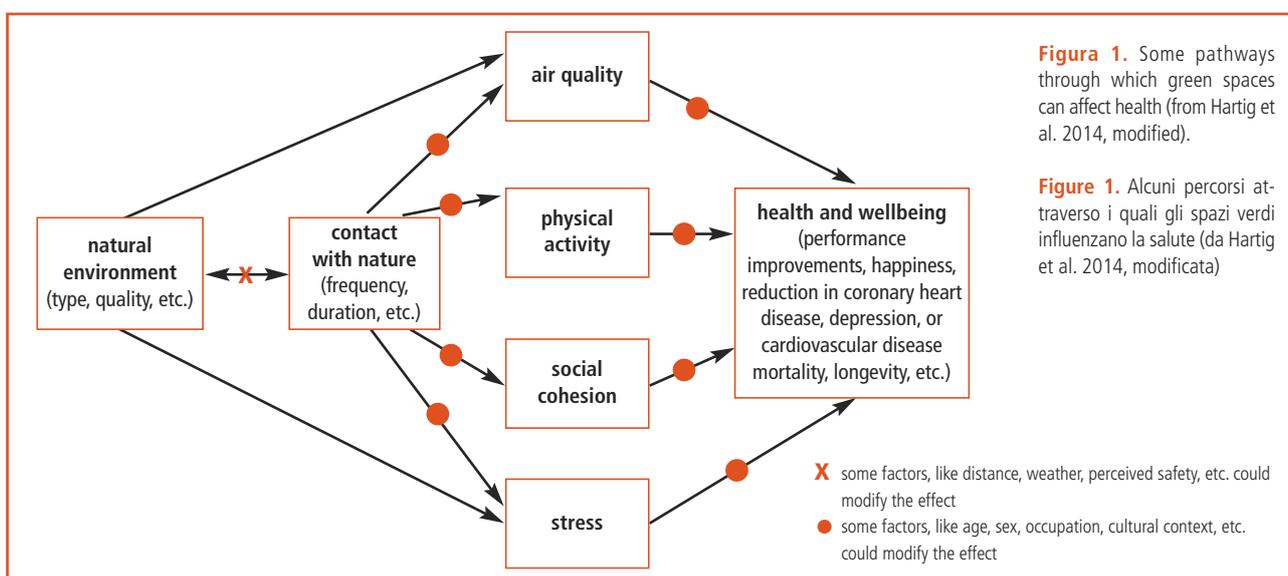
Despite this variety in methods, aims, and focus, there was a strong agreement about the methodological state of the art. The reviews agreed about the following conclusions:

- most of the studies are observational;
- few primary studies have investigated in a consistent and rigorous way the relationships between contact with nature and health;
- few primary studies have explored how the effects may vary by population subgroup, type of natural environment, or type of contact with nature;
- consistent and objective measurements of both exposure to nature and health-related outcomes remain elusive.

Reviews showed three common weaknesses:

- search strategies did not always address the variety of environments or settings that count as “natural”;
- reviews from individual-based disciplines tended to ignore evidence from others (e.g., psychology *vs.* epidemiology);
- the variety of health outcomes used in primary studies was not well addressed.

Nevertheless, the reviews generally agreed that beneficial effects from contact with nature do occur. Contact with nature may affect health via multiple pathways, that have received relatively large amounts of research attention: air quality, social cohesion, stress reduction, and physical activity (figure 1). Pathways mostly proceed from the natural environment to health effects via contact with nature, but two of them also proceed directly from the natural environment to stress and air quality, respectively, implying that the natural environment may affect air quality and health without engaging first with nature as such. The two-headed arrow between “natural environment” and “contact with nature as such” acknowledges that these are connected in a two-way relationship. The two-headed arrows between the boxes describing air quality, physical activity, social contacts, and stress also imply their recip-



rocal relatedness; however, each may be related with all the others and not only with the ones closeby.

Air pollution

Interactions between green spaces and health may lead to positive and negative effects, involving both social and physical health effects.⁸ Impermeable surfaces such as roofs, facades, and roads impair the microclimate by disturbing the radiation and energy balance of areas. *Vice versa*, green areas in one's living environment may ameliorate air pollution, and the urban heat island effect.^{9,10} Trees, shrubs, and other kind of vegetation may affect air quality and, through it, human wellbeing and health. Trees and other vegetation may reduce levels of some pollutants, including gases and particulate matter (PM), but they may also contribute to air pollution by releasing hydrocarbons, including isoprene and terpenes, with considerable variation by species.¹⁰⁻¹² Some trees and plants release pollens, aggravating asthma and allergies. In fact urban and sub-urban ecological changes can affect the geographical range of diseases related to pollens, insects, and parasites.^{13,14} Finally, trees improve air quality indirectly when they cool urban environments and reduce building energy demand.⁷ Hence, the positive benefits of green space cannot be generalized.

Social cohesion

Natural features and open spaces in a residential area can play an important role in residents' feelings of attachment towards the community, and their interactions with other residents. Social cohesion refers to shared norms and values, the existence of positive and friendly relationships, and feelings of being accepted and of enjoying membership. It is more a characteristic of neighbourhoods than of individuals¹⁵ and therefore more likely to be influenced by physical characteristics of the neighborhood, such as the availability and quality of green spaces and natural elements. At the same time, green spaces that are perceived to have become overgrown or to be unmanaged, may have a negative effect on peoples' wellbeing by increasing anxiety caused by fear of crime.⁷ Kneeshaw-Price et al.¹⁶ evaluated five neighbourhood crime-related safety measures to determine how they were interrelated. They found that neighbourhood-active children living in the lowest crime-quartile neighborhoods had 40 minutes more of total MVPA (moderate to vigorous physical activity) in comparison to neighborhood-active children living in the highest crime-quartile neighbourhoods.

Generally, the few available studies suggest a positive relationship between social cohesion and natural environments.^{7,17} As argued by Hartig et al.,⁷ social cohesion within a neighborhood does not lend itself to experimental research, which makes it difficult to determine whether relations with environmental features are causal. Some researchers¹⁸ found a positive association between the presence of trees and grass in common spaces and informal social contact with neighbours. Moreover, the relationship between greenery and social contacts appeared to be mediated by the use of the common spaces. The research also showed that social contact was positively related to one's sense

of safety. Subsequent studies showed that residents with more trees and grass around their buildings displayed less aggressive behaviour, and their buildings were associated with fewer crimes.^{19,20} More recent research suggests similar positive effects of greening vacant lots, especially a reduction in gun assaults and disorderly conduct.²¹

Stressful life

In general, individuals living in areas that lack green spaces may be more vulnerable to the negative impacts of stressful life events because they have less opportunities for nature-based coping strategies than individuals living in areas with abundant green spaces.² Thus, the availability of green space in the surroundings may be an important environmental factor that moderates the relationship between stressful life events and health. According to the WHO, mental health promotion should include actions that create living conditions and environments that support mental health and allow people to adopt and maintain healthy lifestyles.²² Green spaces are thought to influence mental health through an increase in physical activity, by providing places for neighbourhood residents to meet, encouraging social ties, and alleviating stress and mental fatigue.²³ Van de Berg et al.² observed that respondents with a higher amount of green space in a 3 km radius were less affected by experiencing a stressful life and had a better perceived mental health. The moderating effects of green space were found only for those within 3 km, presumably because the 3 km indicator is more affected by the presence of larger areas of green space.

Nevertheless, findings from the studies on green spaces and mental health relationship are not homogeneous. Most studies were cross-sectional, and are thus subject to reverse causality. Gascon et al.,²⁴ in a recent systematic review, found limited evidence of a causal relationship between surrounding greenness and mental health in adults, whereas the evidence was inadequate in children. However, at least two longitudinal studies in the UK provided evidence that individuals living in greener areas had better mental health outcomes over time,^{25,26} while a study in Sweden found an additive protective effect of green space and physical activity on mental health among women.²⁷ Astell-Burt et al.²⁸ reported a protective effect of green space on minor psychiatric morbidity across the lifecourse in early adulthood for men. In contrast, the benefit of green space for women emerged later in adulthood.

Despite the advantages of longitudinal designs, concerns about unmeasured confounds remain, most notably the inability to control for non-random selection of residents into neighborhoods. For this reason Cohen-Cline et al.²³ examined the association between access to green space and mental health among adult twin pairs, a way to address this self-selection problem because they provide a method of controlling genetic and environmental confounds. Authors have hypothesized that greater access to green space is associated with less depression, but provide less evidence for effects on stress or anxiety. Access to green spaces showed psychological health benefits for socioeconomically deprived populations, in at least three stud-

ies;²⁹⁻³¹ green space may therefore narrow health inequalities. A recent large, cross-sectional international study,³² although not proving causality, concludes that socioeconomic inequalities in mental wellbeing were smaller among urban dwellers reporting good access to recreational/green areas and there was no such difference for the other tested neighborhood services. There are reasons that support the plausibility of a causal effect: for example, green spaces between residences and heavily trafficked roads can reduce occupant noise annoyance, vegetation can conceal displeasing structures, and landscaping around housing can help residents maintain privacy and avoid feelings of crowding.^{33,34}

Hordyk et al.,³⁵ investigating everyday practices of immigrant children and families in the context of urban green spaces such as parks, fields, backyards, streetscapes, gardens, forests and rivers, observed that activities in natural environment serve as a protective factor in the health and wellbeing of this population, providing emotional and physical nourishment in the face of adversity. Participants accessed urban nature to minimize the effects of inadequate housing, strengthen social cohesion and reduce emotional stress.

Physical activity

A growing body of evidence suggests that a major determinant of physical activity is access to green spaces. In 2004, the *Guide for Community Preventive Services* of the CDC recommended «creation of or enhanced access to places for physical activity based on strong evidence of their effectiveness in increasing physical activity and improving physical fitness».^{36,37} As the *Guide* noted, most of the evidence for this recommendation derived from cross-sectional studies. Low rates of physical activity are an important contributing factor to rising levels of obesity, as well as risk of cardiovascular disease, hypertension, type 2 diabetes, stroke, colon cancer, and premature death. Physical activity also promotes mental health across the life span.^{38,39} Recent evidence suggests that the health benefits of increased physical activity are largest among those who were initially physically inactive⁴⁰ and in youth.⁴¹⁻⁴³ The outdoor environment may influence how much physically active an individual is by offering suitable spaces for certain types of performances. It may also attract people outdoors because of the experiences it offers. Such outings ordinarily entail some form of physical activity, at least walking. An important precondition for the use of natural environments for physical activity is individuals' (perceived) safety.^{7,16} Although there are possible negative effects associated with physical activity (e.g., sports injuries) as well as with being in a natural environment (e.g., Lyme disease from tick bites), most of these effects are not specific to physical activity in a natural environment.

The built environment is an important factor of influence, as it can facilitate or inhibit participation in physical activity. The literature has examined how different aspects of public open space, such as access to, size, and design features, are associated with participation in physical activity. Proximity to parks and recreational settings are generally associated with greater physical activity.⁴⁴ Qualitative evidence further shows that safety,

aesthetics, amenities, maintenance, and proximity of public open spaces are important attributes for supporting physical activity.⁴⁴

Despite the increasing number of studies in this field, there are some inconsistencies that confuse urban designers and policy makers and prevent the development of evidence-based guidelines. Koohsari et al.⁴⁴ in a recent review identified conceptual and methodological gaps that need to be addressed to progress research on public open space and physical activity, which include:

- **uneven definition of open space**, which introduces difficulties in comparing and collating evidence across different studies. While there is a lack of research into the influence different types of public open space have on physical activity, there is some evidence that non-park public open spaces might be important for physical activity (e.g., walking trails). As such, there might be specific requirements for designing a walking trail to accommodate a wide range of physical activities within a small linear place compared with a park.

- **use of longitudinal and experimental study design when possible**: in particular research on public open spaces and physical activity would benefit from experimental studies that measure behaviours before and after the introduction of new public open space or renovation of existing public open space. This point could take advantage from the increase in urban regeneration interventions that several countries, including Italy, are promoting. A recent study of people who relocated from one neighbourhood to another, found that gaining access to three different types of public open space (parks, sport fields, beach) increased daily walking by 18-20 minutes for each type of public open space gained.⁴⁵

- **exploring public open space exposure in multiple contexts**: previous studies have primarily focused on public open space in a residential context, while the effect of public open space in other settings (e.g., around workplaces and schools) has been ignored. Karusisi et al.⁴⁶ found that the number of supermarkets around workplaces was associated with walking for transport among workers. Dalton et al.⁴⁷ observed that active travel to work was negatively associated with the availability of free car parking at workplaces.⁴⁸

- **moving specific measures of physical activity into public open space**: public open space can influence activity in at least three ways:

- a. it can be a setting where people engage in physical activity;
- b. it can be a destination to which people actively travel either to be active or simply to socialize;
- c. it can be used as part of a route to pass through to reach another destination. Hence public open space can contribute to different types of physical activity behaviours. Few studies have attempted to understand the variety of ways public open spaces influence physical activity.

Koohsari et al.⁴⁴ also considered the importance of the quality of public open space, in terms of features and characteristics related to physical activity or walking, but also on the char-

acteristics of surrounding built environment and on the association between public open space type and user profiles (age group, socio-demographic group, sex). Furthermore they stress the need to identify threshold values needed to attract people to public open space.

CONCLUSIONS

Providing adequate public green spaces means offering people both physical and psychological health benefits. As argued by Wolch et al.,¹⁰ most studies reveal that the distribution of such space often disproportionately benefits the most affluent communities. Giving everybody access to green spaces is therefore increasingly recognized as an issue of environmental justice. Many cities in other countries (e.g., both the US and China) have implemented strategies to increase the supply of urban green space, especially in deprived neighborhoods. Strategies include greening of marginal urban land and reuse of obsolete or underutilized infrastructures.

The definition of appropriate and innovative solutions could benefit from collaboration between different professions.^{49,50} Therefore it is necessary to encourage the integration of information between various professional figures, such as urban na-

ture conservationists, urban planners, environmental psychologists, and public health specialists.^{49,51} Hartig et al.⁷ underline that a lot more remains to be done to help environmental policy makers and designers to establish realistic assessments of what nature can and cannot do in their domain of activity. Part of this task involves explaining how health benefits might overlap (or conflict) with other benefits, such as better storm water management, species preservation, and carbon sequestration. At the same time, a comprehensive methodology for analysis of the associations between aspects of the urban environment and residents' health needs to be identified and implemented.⁵² As argued by Rydin et al.,¹ the absence of such a methodology is largely attributable to the complex nature of urban systems, in which many factors affect social and health outcomes, compounded by the scarcity of consistent data available at the urban scale. In this field, Koohsari et al.⁴⁴ suggest several indications to improve research approaches. Building a body of evidence in this way could contribute to provide much-needed data to urban designers to plan a public open space system able to promote public health.

Conflicts of interest: none declared

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WORKSHOP 5
Thursday 15 October
h. 8.30-10.00
Brown Room 3

Incidence of infection-associated cancers in Italy and prevention strategies

Incidenza dei tumori di origine infettiva in Italia e linee di prevenzione

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Abstract

Chronic infections and infestations represent major causes of cancer. Overall, *Helicobacter pylori*, HPV, HBV, and HCV are estimated to account for 15% of all human cancers. We have estimated that cancers associated with 6 pathogens in Italy account for 31,000 yearly cases, 42.0% of which is attributable to *H. pylori*, 34.7% to HBV and HCV, 19.8% to HPV, 2.9% to KSHV, and 0.2% to EBV. These figures represent 8.5% of all incident cases of cancer in Italy.

The implementation of anti-HBV vaccination programs in countries with high endemicity resulted in a significant impact on the incidence of hepatocellular carcinoma, and the availability of antiviral drugs is a real opportunity to drastically reduce the cases attributable to HCV.

Primary prevention of cervical cancer mainly involves HPV vaccination; two vaccines (bivalent and quadrivalent) are available and a new vaccine (9-valent) has recently been approved by the FDA. Secondary prevention is based on screening programs that include Pap smear cytology and/or HPV test.

To reduce the burden of HIV-associated cancers, prevention programs include primary prevention of HIV infection, early diagnosis and treatment, restoration of immune function, reduction in the prevalence of associated infections and risk factors, and secondary prevention.

To date, anti-HBV and anti-HPV vaccinations, eradication of *H. pylori* infection, treatment of HCV and HIV carriers with antivirals, and HPV-related cancer screening prove to be the most effective strategies for the prevention of infection-associated cancers.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 14-20)

Key words: infection-associated cancers, incidence data in Italy, hepatitis B and C viruses, human papillomaviruses, human immunodeficiency virus

Riassunto

Le infezioni e infestazioni croniche sono associate con una proporzione rilevante dei tumori umani. *Helicobacter pylori*, HPV, HBV e HCV sono complessivamente responsabili del 15% dei tumori nel mondo. In Italia, abbiamo stimato che i tumori associati con 6 agenti patogeni incidano per 31.000 casi all'anno, il 42,0% dei quali è attribuibile a *H. pylori*, il 34,7% a HBV e HCV, il 19,8% a HPV, il 2,9% a KSHV e lo 0,2% a EBV. Nel complesso, questi valori rappresentano l'8,5% di tutti i casi incidenti di tumore in Italia. L'applicazione della vaccinazione anti-HBV in Paesi a elevata endemia ha determinato un notevole impatto anche sul carcinoma epatocellulare primitivo e la disponibilità di farmaci antivirali rappresenta una concreta possibilità di ridurre l'incidenza di questo tumore, specie quello attribuibile ad HCV.

La prevenzione primaria del carcinoma cervicale si basa principalmente sulla vaccinazione anti-HPV mediante due vaccini (bivalente e quadrivalente); recentemente, l'FDA ha approvato un nuovo vaccino (nove-valente). La prevenzione secondaria si basa su programmi di screening che utilizzano Pap-test e HPV-test.

Per ridurre l'incidenza dei tumori HIV-correlati sono stati promossi programmi di prevenzione incentrati sulla prevenzione primaria dell'infezione da HIV, diagnosi precoce di sieropositività, riduzione della prevalenza di infezioni e fattori di rischio concomitanti e sulla prevenzione secondaria.

Nel complesso, le vaccinazioni contro HBV e HPV, l'eradicazione dell'infezione da *H. pylori*, il trattamento con antivirali dei portatori di HCV e HIV e gli screening oncologici per HPV rappresentano oggi le armi più efficaci per la prevenzione dei tumori di origine infettiva.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 14-20)

Parole chiave: tumori di origine infettiva, incidenza in Italia, virus dell'epatite B e C, papillomavirus umani, virus dell'immunodeficienza umana

GLOBAL BURDEN OF INFECTION-ASSOCIATED CANCERS

Chronic infections and infestations represent major causes of cancer. In the population of individual countries, the incidence of cancers attributable to infectious agents, as evaluated in studies published between 1981 and 2005, varied between 3.6% and 29.4%.¹ In the world population, taking into account the infections categorized in Group 1 by the International Agency for Research on Cancer (IARC), the attributable fraction was estimated to be 15.6% in 1990,² 17.8% in 2002,³ and 16.1% in 2008.⁴

There are large geographical differences in the incidence of infection-associated cancers, with 26.3% of cases occurring in developing countries and 7.7% in developed countries.³ These regional disparities depend on the different endemic burden of infections and infestations associated with cancer, on the different age composition of the populations of the various countries, as well as on the uneven application of both primary and secondary prevention strategies.

OVERVIEW OF CHRONIC INFECTIONS AND INFESTATIONS ASSOCIATED WITH HUMAN CANCERS

Table 1 provides a list of the pathogenic agents, including DNA viruses, RNA viruses, bacteria, protozoa, and trematodes, that are known or suspected to play a role in the epidemiology of human cancers, along with the main associated cancers. Eleven of these pathogens are classified in IARC Group 1, three in Group 2A, and four in Group 2B. Three viral or bacterial infections share a particularly heavy burden. *Helicobacter pylori* was estimated to be responsible for 90% of non-cardia gastric cancer cases and 5.2%⁴ or 5.5%³ of all human cancers. Persistent infection with HPV is associated with virtually 100% of cervical cancer cases and with a variety of other cancers in both men and women, thereby accounting for an estimated 4.8%⁴ or 5.2%³ of all human cancers. Worldwide, chronic infections with HBV and HCV were estimated to be associated with 54.4% and 31.1% of hepatocellular carcinoma cases, respectively.³ These hepatotropic viruses are responsible for 4.9%³ or 4.7%⁴ of all human cancers. Thus, collectively, the above chronic infections (*H. pylori*, HPV, HBV, and HCV) are associated with approximately 15% of all human cancers. Other epidemiologically relevant cancers are those associated with the herpesviruses EBV (0.9%⁴ or 1.0%³) and KSHV (0.3%⁴).

INCIDENCE OF INFECTION-ASSOCIATED CANCERS IN ITALY

We estimated the incidence of cancers associated with 6 infectious agents, all of them classified as IARC Group 1, in the general Italian population. We did not estimate HIV-related cancers in order to avoid the risk of counting the cancers caused by immunodeficiency together with the cases directly related to this infection.

The incidence data for malignant neoplasms of the liver, cervix uteri, and Kaposi's sarcoma refer to the year 2014.⁵ For can-

cers of the oral cavity, oropharynx, nasopharynx, and larynx we used estimates from Globocan 2012.⁶ For anal and non-cardia gastric cancers we applied each cancer's sex-specific proportion according to Italian cancer registries⁷ to the estimates for Italy in 2014.⁵ For vulvar and vaginal cancers we considered their relative ratio to cervix uteri according to Italian cancer registries.⁵ To estimate penile carcinoma we applied its ratio to all cancer sites but skin according to Italian cancer registries⁷ to the estimate of all sites but skin for Italy in 2014.⁵ To estimate Burkitt's and MALT lymphomas we applied the age- and sex-specific incident rates (2000-2012) from SEER to the Italian population.⁸

Population attributable fractions (PAFs) for head and neck squamous cell carcinomas, including oral cavity, oropharyngeal, nasopharyngeal, and laryngeal carcinomas,⁹ for HPV-related cancers, including vaginal, vulvar, and anal carcinomas¹⁰ and penile carcinoma,¹¹ as well as for non-cardia gastric cancer, MALT, cervical cancer, and Kaposi's sarcoma⁴ were estimated in the world population. The PAF for Burkitt's lymphoma was estimated in the US and European populations.⁴ The PAF for nasopharyngeal carcinoma was estimated in low-incidence Regions.⁴ PAFs for malignant neoplasms of the liver were estimated in the Italian population.¹²

The results of our estimates are shown in **table 2**. Overall, the cancers associated with the considered infectious agents account for more than 31,000 incident cases (almost 18,000 in males and more than 13,000 in females), 42.0% of which is attributable to *H. pylori*, 34.7% to HBV and HCV, 19.8% to HPV, 2.9% to KSHV, and 0.2% to EBV. These figures represent 8.5% of all incident cases of cancers in Italy (excluding skin carcinomas) during the same period, which have been estimated to be 365,000.⁵ Clearly, these estimates are just tentative, due to the uncertainties in assessing both the incidence of cancer and the PAFs.

GENERAL STRATEGIES AIMED AT PREVENTING INFECTION-ASSOCIATED CANCERS

In principle, the primary prevention of infection-related cancers is more easily affordable than prevention of other types of cancer: not only will the prevention of an infectious disease result in the primary prevention of the associated cancer, but even its therapy, such as eradication of *H. pylori* infection or use of anti-HIV, anti-HBV, or anti-HCV drugs, will avoid evolution towards malignancy.¹³

As reported below, certain infection-associated cancers provide paradigmatic examples of primary prevention and oncological screening.¹³ Subsequently, after the onset of cancer and its therapy, it is still possible to apply tertiary prevention, for instance by means of antiangiogenic agents.¹⁴

PREVENTION OF HEPATOCELLULAR CARCINOMA ASSOCIATED WITH HBV AND HCV INFECTIONS Mechanistic considerations

There are multiple, diversified mechanisms leading to primary hepatocellular carcinoma (HCC) in chronic HBV carriers. Liver fibrosis followed by cirrhosis occurs in 20-30% of chronic HBsAg carriers within 20-30 years, and this is a pre-

[IARC Group*] Pathogens	Main associated human cancers
DNA viruses <i>papillomaviridae</i> [1] human papillomaviruses (HPV), alpha types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [2A] HPV, alpha type 68 [2B] HPV, alpha types 26, 30, 34, 53, 66, 67, 69, 70, 73,82, 85, 97, and beta types 5 and 8 [3] HPV, alpha types 6 and 11, other beta and gamma types	<ul style="list-style-type: none"> ■ cervical cancer, cancers of the anogenital region, head and neck cancers, colorectal cancer
<i>herpesviridae</i> [1] Epstein-Barr virus (EBV, HHV4) [1] Kaposi's sarcoma virus (KSHV, HHV8)	<ul style="list-style-type: none"> ■ Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma ■ Kaposi's sarcoma, primary effusion lymphoma
<i>polyomaviridae</i> [3] simian virus 40 (SV40) [2A] Merkel cell virus (MCV) [2B] BK virus (BKV) [2B] JC virus (JCV)	<ul style="list-style-type: none"> ■ malignant mesothelioma? ■ Merkel cell carcinoma ■ no specific target detected ■ no specific target detected
<i>hepadnaviridae</i> [1] hepatitis B virus (HBV)	<ul style="list-style-type: none"> ■ hepatocellular carcinoma
RNA viruses <i>flaviviridae</i> [1] hepatitis C virus (HCV)	<ul style="list-style-type: none"> ■ hepatocellular carcinoma, B-cell non-Hodgkin's lymphoma
<i>defective virus</i> [3] hepatitis D virus (HDV)	
<i>retroviridae</i> [1] human T-cell leukemia virus-I (HTLV-I) [3] human T-cell leukemia virus-II (HTLV-II) [1] human immunodeficiency virus-1 (HIV-1) [2B] human immunodeficiency virus-2 (HIV-2) [NA] human endogenous retrovirus (HERV-K) [NA] xenotropic murine leukemia virus-related virus (XMRV)	<ul style="list-style-type: none"> ■ adult T-cell leukemia-lymphoma ■ Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anal cancer, conjunctival cancer ■ breast cancer? ■ prostate cancer?
Bacteria [1] <i>Helicobacter pylori</i> [NA] <i>Salmonella typhi</i> [NA] <i>Streptococcus bovis</i> [NA] <i>Chlamydia pneumoniae</i> [NA] <i>Mycobacterium tuberculosis</i> [NA] Bartonella species	<ul style="list-style-type: none"> ■ non-cardia gastric cancer, MALT lymphoma ■ gallbladder carcinoma? ■ colorectal cancer? ■ lung cancer? ■ lung cancer? ■ vascular tumors?
Protozoa [2A] <i>Plasmodium falciparum</i> [NA] <i>Trichomonas vaginalis</i>	<ul style="list-style-type: none"> ■ Burkitt's lymphoma (+EBV) ■ prostate cancer?
Trematodes [1] <i>Schistosoma haematobium</i> [2B] <i>Schistosoma japonicum</i> [3] <i>Schistosoma mansoni</i> [1] <i>Opistorchis viverrini</i> [3] <i>Opistorchis felinus</i> [1] <i>Chlonorchis sinensis</i>	<ul style="list-style-type: none"> ■ urinary bladder cancer ■ colorectal and liver cancer ■ cholangiocarcinoma ■ cholangiocarcinoma

* Group 1: sufficient evidence of carcinogenicity to humans; Group 2A: probably carcinogenic; Group 2 B: possibly carcinogenic; Group 3: inadequate evidence of carcinogenicity to humans; NA: not available.

Table 1. Pathogenic agents and main associated human cancers. / **Tabella 1.** Agenti patogeni e principali tumori umani associati.

cursor condition for development of 80%-90% of HCC cases.¹⁵ HBV-DNA is also able to integrate into the hepatocyte DNA, and several alterations can occur in the host genome, such as HBx gene expression, chromosomal deletions, fusion transcripts, translocations, DNA amplification, and genomic instability, which independently contribute to HCC development.¹³ Interactions between HBV infection and chemical hepatocarcinogens are also of crucial importance in the pathogenesis of HCC.¹⁶ On the other hand, HCV lacks reverse

transcriptase activity, and is thus unable to integrate its genome into the host cell DNA, while viral protein expression has a critical role in hepatocarcinogenesis by altering signal transduction pathways;¹⁵ this has two important implications:

- HCV-induced cirrhosis is the necessary mechanism for its carcinogenesis;
- due to the lack of DNA integration into the host genome, antiviral drugs have the potential to achieve a “sterilizing” effect in chronically infected subjects.¹⁷

Prevention programs

Avoiding viral infection through **primary prevention** measures is crucial in order to obtain a dramatic decrease in HCC incidence. Regarding HBV, universal vaccination programs of newborns/infants have been introduced in 183 world countries, with 81% coverage overall with 3 doses.¹⁸ There is clear evidence on the impact of immunization on HCC in countries where such programs have been implemented for a long time, as was first demonstrated in cohorts of Taiwanese children aged 6-14 years¹⁹ and, later, in adolescents aged 16-19 years.²⁰ Similar results are reported from Thailand, China, Singapore, Korea, Japan, and Alaska, and are expected to be available from Gambia in the coming years.²¹

No vaccine is presently available for HCV due to the high variability of envelope proteins. Primary prevention of HCV infection is based upon identification of infectious blood donors through anti-HCV detection and NAT (nucleic acid testing), careful application of universal precautions for blood-borne infections, and adequate sterilization of non-disposable medical equipment. Of course, the same measures represent an important complement to hepatitis B vaccination for the prevention of HBV-related HCC.

With regard to HCC **secondary prevention**, data on the impact of IFN (interferon) therapy for HBV-related cancers are conflicting, due to the lack of pre-treatment patient stratification for relevant cancer predictors and exclusion of patients at higher risk of developing HCC, such as those unfit to receive IFN owing to advanced hepatitis. The advent of user-friendly oral NUC (nucleoside/nucleotide analogs) allowed for a broader and safe access of patients to effective anti-HBV therapy. HCC was prevented in patients with chronic hepatitis but not in those with cirrhosis, and in general in patients that could not achieve complete virological suppression. The re-analysis of outcomes following patient stratification for risk factors of HCC helped shed light on an association between NUC therapy and a reduced HCC risk only in non-cirrhotic patients.²²

As regards to HCV antiviral therapy, a meta-analysis of 30 observational studies of patients treated with interferon demonstrated a more than 70% reduction of HCC risk occurring independently of severity of the underlying liver fibrosis. The residual risk for HCC in SVR (sustained virologic response) patients might reflect persistence of cirrhosis following virus sterilization. The same factors predicting HCC in viremic patients, such as advanced age, portal hypertension, advanced fibrosis, and elevated alpha-fetoprotein levels, act as independent predictors of HCC in SVR patients, too. This further emphasizes the clinical advantages of treating patients early during infection.²² IFN-free, DAA (direct acting antiviral)-based regimens, such as sofosbuvir + ribavirin with a 24-week course, can also eliminate HCV infection in two-thirds of patients awaiting liver transplantation or already transplanted, with obvious positive consequences on their short- and long-term prognoses (**tertiary prevention**).²³

PREVENTION OF HPV-ASSOCIATED CANCERS

Foreword

Worldwide epidemiological studies indicate that 12 different

high-risk HPVs, namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, are associated with cervical cancer; they are therefore classified in IARC Group 1 (**table 1**).

A subset of anal, penile, vulvar, vaginal, and oropharyngeal cancers have been attributed to infection with high-risk HPVs, mainly to HPV 16.²⁴ Prevention of cervical cancer includes both primary prevention, through HPV vaccination and education about safe sexual practices, and secondary prevention through cervical cancer screening.

Primary prevention

Two vaccines (bivalent and quadrivalent) are available to protect against HPV types 16 and 18, which are responsible for approximately 50% and 20% of cervical cancers, respectively. In addition, the quadrivalent vaccine offers protection against HPV 6 and 11, which cause over 90% of genital warts. Vaccination programs are being widely implemented, primarily targeting adolescent girls, and efficacy has been widely demonstrated for both vaccines by showing a 93%-100% of vaccine efficacy in preventing cervical pre-cancers due to HPV 16 or 18. Millions of doses have been distributed worldwide so far, and all randomized controlled clinical trials of both vaccines provide evidence for an excellent safety profile.^{25,26} In some Italian Regions, vaccination programs have recently been extended to 12-year old boys, as recommended by the *2014 lifetime immunization schedule approved by the Italian scientific societies*.²⁷ Although this strategy is still debated, recent evidence shows a trend toward better results in cost-effectiveness of universal vaccination versus girls-only vaccination.^{28,29}

The convenience of extending the anti-HPV vaccination to males is also supported by the estimates reported in the present study. As inferred from the data available in **table 2**, HPV-related cancers in males appear to account for 38% of all the cases estimated in the Italian population. With regard to the issue of extending the HPV vaccination recommendation to older women, an economic modeling study regarding 330,000 25-year old women in Italy showed that immunization with the HPV vaccine is fully economically justified, with an ICER (incremental cost-effectiveness ratio) = € 33,918/QALY (quality adjusted life years) using the vaccine prices of 2011 (prices have gone down since then). The same analysis showed that a public health program of HPV vaccination would be justified (ICER < € 50,000/QALY) until 30 years without cross-protective effects of the vaccine, and up to 35 years considering cross-protection.³⁰ Moreover, a new vaccine (9-valent) has recently been approved by the FDA. It is indicated in girls and women 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.³¹

Secondary prevention

Secondary prevention involves screening asymptomatic patients or carrying out definitive tests in symptomatic or screen-positive patients to pick up precancerous lesions before they turn into cancer. Observational studies have shown that introduction of any regular cervical cancer screening program results in a drop

Cancer site or morphology	ICD 10	Infectious agent	PAF (%)	Sex	Estimated annual incident cases	Estimated incidence attributable to infectious agents
oral cavity	C00-C08	HPV	23.5	M	2,283	537
				W	1,524	358
				P	3,807	895
oropharyngeal (including hypo pharynx and pharynx)	C09-C10, C12-C14	HPV	35.6	M	1,214	432
				W	348	124
				P	1,589	566
nasopharyngeal	C11	EBV	80.0	M	315	252
				W	124	99
				P	439	351
laryngeal	C32	HPV	24.0	M	3,714	891
				W	335	80
				P	4,049	972
Burkitt's lymphoma	C83.7	EBV + <i>Plasmodium falciparum</i>	20.0	M	200	40
				W	100	20
				P	300	60
non-cardia gastric cancer	C16.1-C16.9	<i>Helicobacter pylori</i>	90.0	M	7,500	6,750
				W	5,500	4,950
				P	13,000	11,700
MALT (stomach)	C88.4	<i>Helicobacter pylori</i>	86.0	M	700	602
				W	850	731
				P	1,550	1,333
malignant neoplasms of liver	C22	HBV, HCV	86.8	M	8,600	7,465
				W	3,800	3,298
				P	12,400	10,763
anal carcinoma	C21.0	HPV	84.3	M	450	379
				W	650	548
				P	1,100	927
penile carcinoma	C60	HPV	46.9	M	182	85
uterine cervix cancer	C53	HPV	100	W	2,200	2,200
vulvar cancer	C51	HPV	40.4	W	900	364
vaginal cancer	C52	HPV	60.9	W	200	122
Kaposi's sarcoma	C46	HHV8	100	M	600	600
				W	300	300
				P	900	900
all the above tumors				M	25,758	18,034
				W	16,831	13,194
				P	42,589	31,238

Table 2. Estimated number of cancers attributable to 6 infectious agents in Italy. Cancer site, International classification for diseases-10 (ICD-10) codes, infectious agent, population-attributable fraction (PAF), estimated annual number of incident cases and estimated number of cases attributable to infectious diseases, by sex (M: men, W: women, P: people).

Tabella 2. Stima del numero di tumori attribuibili a 6 agenti infettanti in Italia. Sede del cancro, codici dell'International classification for diseases-10 (ICD-10), agenti infettanti, frazione attribuibile alla popolazione (PAF), numero annuale stimato di casi incidenti attribuibile a malattie infettive, distinto per sesso (M: uomini, W: donne, P: uomini + donne).

in the incidence of invasive cervical cancer and cancer deaths. Different methods are available for cervical cancer screening: cervical cytology (Pap test) is the globally preferred screening method and has been shown to reduce the incidence of invasive cervical cancer by up to 80%.

Two types of tests for HPV DNA are currently in use; one is a nucleic acid hybridization assay with signal amplification for the qualitative detection of high risk HPV types in cervical specimens, whereas the other is a polymerase chain reaction based assay. Testing for HR (high risk)-HPV has been investigated as a primary screening test in several randomized clinical trials. Cross-sectional as well as longitudinal studies have consistently demonstrated the superiority of HPV testing, compared with Pap testing, to prevent invasive cervical cancer

by detecting high-grade precancerous lesions. However, HPV testing is also associated with a lower specificity, especially in younger women.³²

By 2018, screening programs in Italy will rely more on HPV testing than cytology, with the following schedule: at 25-30/35 years Pap smear as a primary test and triage ASCUS (squamous cells of undetermined significance) with HPV test every 3 years; at >30/35 years HPV test as a primary test and triage with Pap smear every 5 years. Moreover, HPV testing will be the approach to follow up women treated for CIN-2 (cervical intraepithelial neoplasia-2) and with cytological abnormalities and negative colposcopy. The 5-year interval will lead to cost savings, and using the HPV test as the primary test will be key to improving uptake of cervical screening programs.³³

PREVENTION OF CANCERS ASSOCIATED WITH HIV INFECTION

Foreword

The association between HIV/AIDS and cancer is still unclear, although HIV is classified as a Group 1 IARC carcinogen³⁴ and several authors have associated an increased cancer risk with HIV-related immunodeficiency, chronic immune activation/inflammation, and immune dysfunction/senescence.³⁵ Epidemiological evidence suggests that the increased cancer risk observed among HIV-infected patients could be, at least in part, attributed to co-infection with other cancer-related viruses, such as KSHV, EBV, HPV, HBV, and HCV, and to a higher exposure to lifestyle risk factors for cancer, including smoking and alcohol use.^{35,36} Furthermore, the use of highly active antiretroviral therapy (HAART) has dramatically improved survival, and most HIV-infected patients live several decades after their diagnosis.

In most developed countries, effective treatment of HIV has contributed to increase the prevalence of HIV infection, thereby leading to a higher clinical impact of long-term morbidities, including cancers.³⁷ For instance, in Italy people living with HIV increased from 78,000 in 1990 to 120,000 in 2013 (<http://www.who.int/gho/hiv/en/>).

Prevention programs

Research programs aimed at understanding, preventing, and treating HIV-related cancers have been promoted.³⁸ These programs are based on the following five pillars:

- **Primary prevention of HIV infection.** Preventing HIV infection or, at least, limiting the number of HIV-infected cells and viral load would greatly contribute to the reduction of associated cancers.³⁹ For this reason, the development of effective vaccines against HIV may be one of the biggest challenges for medical science. Unfortunately, to date, no fully effective HIV vaccine is available and prevention strategies should therefore be based on the promotion of counselling for HIV testing in high-risk populations and implementation of behavioural measures aimed at controlling HIV transmission via sexual intercourse, blood and other body fluids, and perinatal exposure of fetuses and children.¹³
- **Early diagnosis and treatment of HIV infection, and restoration of immune function.** Early diagnosis of HIV infection, linkage to and retention in care, and adherence to antiretroviral therapy are crucial in reducing the cancer burden in HIV-infected subjects.⁴⁰ In addition, evidence from in vitro and in vivo model systems indicates that antiretroviral agents may have antitumor activity independent of their antiviral effect.⁴¹
- **Reduction in the prevalence of non-communicable risk factors.** A number of cancers observed among HIV subjects are

attributable to exposure to tobacco smoking (e.g., cancers of the lung, head and neck, bladder), alcohol consumption (e.g., cancers of liver and head and neck) and ultraviolet radiation (non-melanoma skin cancer).⁴² Accordingly, programs to encourage HIV-infected individuals to quit tobacco smoking and alcohol consumption and minimize unnecessary sun exposure should be a priority for public health authorities.

- **Primary prevention of concomitant cancer-related viral infections.** As previously discussed, prevention of chronic infections with other cancer-related viruses, such as HBV and HPV infections, should be optimized. Cancers caused by EBV and KSHV may be in principle preventable with vaccines, with early candidate vaccines for EBV showing promise.⁴³ Finally, encouraging HIV-infected people to limit the number of their sexual partners may reduce their risk of acquiring new HBV and HPV infections.
- **Secondary prevention.** Limited data exist regarding harms and benefits of cancer screening interventions specifically targeted to HIV-infected persons. For some cancers, performance of screening programs may be sufficiently different in HIV-infected individuals to warrant modified approaches. Thus, cancer screening interventions that have no evidence of benefit in the general population (e.g., anal, skin, and liver cancer screening⁴²) may be of value in HIV-infected individuals because of their different cancer risk profiles. However, the decision to screen HIV-infected persons for cancer is complex and should include considerations about the risk of the particular cancer, the life expectancy of the patient, and the specific benefits and harms that may stem from the screening interventions.⁴⁴

CONCLUSIONS

A high proportion of cancers are associated, with a variety of mechanisms, with chronic infections and infestations. In Italy, cancers associated with the 6 main pathogens appear to be responsible for almost 1 out of 10 cancers, with a total of 31,000 yearly cases, the large majority of which are attributable to either *H. pylori* (42.0%), HBV and HCV (34.7%), or HPV (19.8%).

The major strategies for the prevention of these cancers involve a variety of measures, including large-scale vaccinations against HBV and HPV, eradication of *H. pylori* infection, treatment of HCV-positive and HIV-positive subjects in order to avoid chronic infections, control of both concomitant infections and exposure to synergistically-acting lifestyle and environmental risk factors, and secondary prevention of the associated cancers, with special emphasis on cancer screening for HPV.

Conflicts of interest: none declared

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NOVITÀ EDITORIALI
Thursday 15 October
h. 10.00-11.30
Amber Room 1

Molecular epidemiology tools in the management of healthcare-associated infections: towards the definition of recommendations

L'epidemiologia molecolare nella gestione delle infezioni correlate all'assistenza: verso la definizione di raccomandazioni condivise

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Abstract

Introduction. Healthcare-Associated Infections (HAIs) are an important cause of morbidity and mortality worldwide and have a significant economic impact for health systems. Molecular epidemiology tools have a central role in HAI prevention programs. In order to give an overview of their specific advantages and disadvantages we reported current and new molecular typing methods for HAI outbreak detection and epidemiological surveillance.

Methods. The current review was drafted as a short version of a longer document written by the Public Health Genomics (GSP) working group, and the Italian Study Group of Hospital Hygiene (GISIO), entitled *Molecular epidemiology of Healthcare Associated Infections: recommendations from the Italian Society of Hygiene, Preventive Medicine and Public Health (SIIt)*. This text considers various aspects related to HAIs: the role of genotyping and bioinformatics, the organizational levels of laboratories, as well as ethical and economic aspects.

Conclusions. The use of molecular epidemiology represents a key tool in the management of HAIs, to be used as a complement to conventional control measures. The present contribution aims to increase knowledge on the proper use of such methods, given the major challenge HAI represents for National Health systems.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 21-26)

Key words: molecular epidemiology, healthcare-associated infections, genotyping methods

Riassunto

Introduzione. Le infezioni correlate all'assistenza (ICA) costituiscono un'importante causa di malattia e morte in tutto il mondo e hanno un notevole impatto sui costi sanitari. L'epidemiologia molecolare riveste un ruolo primario nei programmi di prevenzione e lotta alle ICA.

Metodi. Il presente contributo è ispirato dal lavoro di ricerca svolto per la stesura del documento *L'epidemiologia molecolare nelle Infezioni Correlate all'Assistenza: documento di indirizzo della Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica (SIIt)*, a cura dei due gruppi di lavoro SIIt Genomica in sanità pubblica (GSP) e Gruppo italiano studio igiene ospedaliera (GISIO); nel presente lavoro vengono considerati diversi aspetti legati alle ICA, dalla caratterizzazione molecolare al ruolo degli archivi bioinformatici, ai livelli organizzativi dei laboratori, agli aspetti socioeconomici.

Conclusioni. Il presente lavoro, focalizzato in particolar modo sulla realtà italiana, vuole contribuire alla sempre maggiore appropriatezza nell'utilizzo degli strumenti di prevenzione e controllo delle ICA, che costituiscono un'importante sfida per tutti i sistemi sanitari nazionali.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 21-26)

Parole chiave: epidemiologia molecolare, infezioni correlate all'assistenza, metodi di genotipizzazione

OVERVIEW OF HEALTHCARE-ASSOCIATED INFECTIONS

Epidemiology of HAIs and antimicrobial resistance

Healthcare-Associated Infections (HAIs) represent a major issue of patient safety, associated with significant morbidity, mortality, and costs.¹ Epidemiological surveillance of HAIs is the cornerstone of effective infection prevention and control programs.² Currently, the coordination of the European surveillance of HAIs is carried out at the ECDC (European Centre for Disease Prevention and Control), where surveillance relies on the activities of three working groups: HAI-Net (Healthcare-Associated Infections Surveillance Network), EARS-Net (European Antimicrobial Resistance Surveillance Network), and ESAC-Net (European Surveillance of Antimicrobial Consumption Network).³ In particular, the main priorities of HAI-Net are coordination of the surveillance of Surgical Site Infections (SSIs), the HAI surveillance in Intensive Care Units (ICUs), point prevalence survey of HAIs and antimicrobial use in acute care hospitals, and prevalence surveys of HAIs and antimicrobial use in European long-term care facilities.

Data from the ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals carried out in 2011-2012, which included 29 countries (231,459 patients), reported a HAI prevalence of 6%, ranging from 2.3% to 10.8%.³ The most frequently reported were respiratory tract infections (pneumonia 19.4% and lower respiratory tract 4.1%), SSIs (19.6%), and urinary tract infections (19.0%). The microorganisms most frequently isolated from HAIs were *Escherichia coli* (15.9%), *Staphylococcus aureus* (12.3%), *Enterococcus spp.* (9.6%), *Pseudomonas aeruginosa* (8.9%), and *Klebsiella spp.* (8.7%). HAI prevalence was highest in patients admitted to ICUs (19.5%), with at least one HAI versus 5.2% of all other wards). Italy participated in the study with 14,784 surveyed patients; 6.3% of them had a HAI.³ Pneumonia (21.6%) and other lower respiratory tract infections (2.4%) represented the most common type of HAI, followed by urinary tract infections (20.8%) and SSIs (16.2%), bloodstream infections (15.8%), and gastro-intestinal infections (6.6%). The most frequently isolated microorganisms were *E. coli* (13%), *K. pneumoniae* (11%), *P. aeruginosa* (11%), and *S. aureus* (8%).

As for incidence, two surveillance networks are active in Italy: SITIN (Sorveglianza italiana delle infezioni in terapia intensiva, Italian surveillance of infections in ICUs) which collects data from three surveillance Italian systems (GiViTI, Gruppo italiano per la valutazione degli interventi in terapia intensiva; SPIN-UTI, Sorveglianza prospettica delle infezioni nosocomiali nelle unità di terapia intensiva; and SITIER, Sorveglianza delle infezioni in terapia intensiva dell'Emilia-Romagna) and SNICH (Sistema nazionale di sorveglianza delle infezioni del sito chirurgico). Data from the last SITIN report showed an incidence of bloodstream infections of 4.2/1,000 patient-days in 2011, and 4.6 in 2012; incidence of urinary tract infections in 2011 and 2012 was respectively, 1.9 and 2.7/1,000 patient-days, while incidence of pneumonia was, respectively, 5.8 e 5.4/1,000 patient-days.⁴

In 2011, SNICH registered an SSI incidence of 1.3% for or-

thopaedic procedures, and 1.7% for non orthopaedic procedures.⁵

Recent years have seen a dramatic increase in HAIs caused by antibiotic-resistant bacteria, leading to extra healthcare costs, treatment failure, and deaths.⁶ In general, lower percentages for resistance are reported by countries in the north and higher percentages are reported by countries in the south and east of Europe. In the period 2010-2013, in Italy, as in the rest of Europe, there was an increase in combined *K. pneumoniae* resistance (fluoroquinolones, aminoglycosides and 3rd generation cephalosporins) from 26.3% to 41.8%; in particular, carbapenem-resistant *K. pneumoniae* showed an alarming increase in 2013, reaching 34.3% compared to 15.2% in 2010. Unlike the decreasing European trend, the percentage of methicillin-resistant *S. aureus* remained constant over this four-year period, with a value exceeding 30%. Generally speaking, antimicrobial resistance in Italy reached percentages that are from two (3rd-generation cephalosporin resistant and fluoroquinolone-resistant *E. coli*, piperacillin-tazobactam resistant *P. aeruginosa*) to four times (carbapenem-resistant *K. pneumoniae*) higher than the European average.

Socioeconomic impact of HAIs

The relevant HAI-related resource consumption has the potential to inflict significant economic consequences on national healthcare systems.⁷ Analysis of the socio-economic impact of HAIs includes several cost categories, such as direct costs (e.g., costs of instruments, equipment, therapy, days of hospitalization), indirect costs (morbidity, mortality, loss of productivity and profit) and intangible ones (e.g., psychological damage, pain, loss of social role).

Direct costs are usually paid by the healthcare system, while indirect and intangible ones are often borne by patients. The CDC (Centers for Disease Control and Prevention) of Atlanta calculate that, given the range of effectiveness of possible infection control interventions, the benefits of HAI prevention range from a low of \$5.7 to \$6.8 billion to a high of \$25.0 to \$31.5 billion per year.⁷ Comparing these costs with those for other important diseases such as stroke (about \$6.7 billion/year), or chronic obstructive pulmonary disease (\$4.2 billion), it is worth considering an investment in HAI prevention, given its cost effectiveness.^{7,8} An overview on literature reporting on the economic impact of HAI can be found in **table S1** (see supplementary material online). Two main categories of studies are represented: the first includes studies that estimate the cost of HAIs at different levels, e.g., for the National Health System, the insurance system, and a single hospital, while the second is about retrospective analyses of the cost of a single HAI, or the costs of a HAI outbreak.

MOLECULAR EPIDEMIOLOGY TOOLS

Molecular typing methods

Molecular typing methods are used in different fields to study the genomic organization and evolution of microorganisms, to discern and track individual strains and to identify patterns of infection and sources of transmission. Particularly, such tools are

Molecular typing methods	Advantages	Limits	Applications and notes
Pulsed-Field Gel Electrophoresis (PFGE)	<ul style="list-style-type: none"> ■ excellent discriminatory power ■ intra- and inter-laboratory reproducibility ■ high epidemiological concordance ■ moderate cost 	<ul style="list-style-type: none"> ■ lacking in ease of use and speed ■ low resolution for similar fragment size 	<ul style="list-style-type: none"> ■ useful for outbreak investigation and epidemiological surveillance, at local or large-scale level ■ international databases are widely available
Amplified Fragment Length Polymorphism (AFLP)	<ul style="list-style-type: none"> ■ excellent discriminatory power 	<ul style="list-style-type: none"> ■ lacking in ease of use ■ high cost 	<ul style="list-style-type: none"> ■ as PFGE
Random Amplification of Polymorphic DNA (RAPD) and Arbitrarily Primed Polymerase Chain Reaction (AP-PCR)	<ul style="list-style-type: none"> ■ rapidity and ease of use ■ low cost 	<ul style="list-style-type: none"> ■ low discriminatory power ■ low intra-laboratory reproducibility 	<ul style="list-style-type: none"> ■ extensively adopted for outbreak investigation
Repetitive-element Polymerase Chain Reaction (rep-PCR)	<ul style="list-style-type: none"> ■ high rapidity and discriminatory power for some microbial species ■ low cost 	<ul style="list-style-type: none"> ■ poor reproducibility 	<ul style="list-style-type: none"> ■ semi-automatic methods adopted for outbreak investigation and epidemiological surveillance at local level ■ not recommended for large-scale studies
Variable-Number Tandem Repeat (VNTR) typing	<ul style="list-style-type: none"> ■ excellent reproducibility ■ ease of use ■ accessibility ■ rapidity ■ moderate cost 	<ul style="list-style-type: none"> ■ moderate inter-laboratory reproducibility 	<ul style="list-style-type: none"> ■ multilocus VNTR analysis (MLVA) is adopted for outbreak investigation, but is not validated in epidemiological surveillance networks
Single Locus Sequence Typing (SLST)	<ul style="list-style-type: none"> ■ high discriminatory power for some species (e.g. <i>spa</i>-typing for <i>S. aureus</i>), ■ ease of use ■ rapidity ■ moderate cost 	<ul style="list-style-type: none"> ■ potential misclassification of particular types, due to recombination and/or homoplasmy 	<ul style="list-style-type: none"> ■ used to determine the relationships among bacterial isolates for outbreak investigation and epidemiological surveillance at local and international level
Multilocus Sequence Typing (MLST)	<ul style="list-style-type: none"> ■ excellent reproducibility 	<ul style="list-style-type: none"> ■ lacking in ease of use and not speed ■ limited accessibility ■ high cost ■ poor discriminatory power for some species 	<ul style="list-style-type: none"> ■ used for large-scale epidemiological studies and for performing bacterial population genetics studies ■ not suitable for local outbreak investigation and surveillance studies
Comparative Genomic Hybridisation (CGH): microarrays	<ul style="list-style-type: none"> ■ high throughput technique 	<ul style="list-style-type: none"> ■ the intra- and inter-laboratory reproducibility of microarray data needs to be established prior to the application ■ high cost ■ poor accessibility ■ do not allow the identification of sequences which are not included in the array ■ not yet suited for day-to-day clinical application 	<ul style="list-style-type: none"> ■ used in real-time outbreak investigations ■ rapid and microarray assays for diagnostic testing and epidemiological investigations have been developed ■ adopted for simultaneous genotyping and profiling to determine antimicrobial resistance and virulence potential
Optical mapping	<ul style="list-style-type: none"> ■ high accuracy ■ high discriminatory power 	<ul style="list-style-type: none"> ■ high cost ■ poor accessibility 	<ul style="list-style-type: none"> ■ successfully used in retrospective outbreak investigations to examine the genetic relationships among bacterial isolates (e.g., <i>E. coli</i> O104:H4)
Whole Genome Sequencing (WGS)	<ul style="list-style-type: none"> ■ high throughput technique 	<ul style="list-style-type: none"> ■ lacking in ease of use ■ limited accessibility 	<ul style="list-style-type: none"> ■ accurate identification and characterization of bacterial isolates ■ in the near future WGS will become a highly powerful tool for outbreak investigations and surveillance schemes in routine clinical practice

Table 1. Characteristics of the main molecular typing methods (ref. 9-11). / **Tabella 1.** Caratteristiche dei principali metodi di genotipizzazione (ref. 9-11).

used in the epidemiological surveillance of infectious diseases, including HAIs, and for outbreak investigation.^{9,10}

Over the last years different molecular typing methods have been implemented worldwide and guidelines and general criteria have been proposed to interpret the obtained results.^{10,11} However, typing methods need to be evaluated and validated with respect to a number of performance and convenience criteria.^{9,10} The performance criteria, based on intrinsic features

of a method, mainly refer to the stability and reproducibility of the marker assessed, providing universal typeability of all isolates. In addition, feasibility, time, cost, and portability, representing the convenience criteria, need to be considered.¹⁰ The latter criterion is of great importance, especially in large-scale surveillance, as the use of electronic databases allows microbiologists and public health institutions to monitor the spread of strains beyond the hospital/local level.

Finally, since analyses may depend on different interpretations and have different requirements, there is no universally applicable typing method. Nevertheless, the increasing need to communicate among laboratories and to exchange outbreak investigation or surveillance data requires a high degree of agreement on common methods. Such standardization is gradually being undertaken for the most popular and reliable typing methods. An important thematic issue published by *Eurosurveillance* in January 2013 provided a series of reviews and original research articles that evaluated the latest progress in molecular epidemiology strategies and tools, and illustrated their applications in public health. Following this document, the Public Health Genomics (GSP) working group and the Italian Study Group of Hospital Hygiene (GISIO), of the Italian Society of Hygiene, Preventive Medicine and Public Health (SIItI), wrote a collaborative document, entitled *Molecular epidemiology of healthcare associated infections: recommendations from the Italian Society of Hygiene, Preventive Medicine and Public Health (SIItI)*.^{12,13} This text has been drafted as a short version.

The previously mentioned *Eurosurveillance* issue included a review,¹¹ published on behalf of the ESCMID Study Group of Epidemiological Markers (ESGEM), conducted using the PubMed database with a combination of specific keywords to retrieve the relevant articles. **Table 1** reports the characteristics, advantages, and limits of the main molecular typing methods for the management of HAIs based on that review.

Bioinformatics and surveillance networks in bacterial molecular epidemiology

The development of DNA sequencing methods and other molecular methodologies has led to substantial improvement in microorganism identification, which is accompanied by generation of large amounts of data. Bioinformatics answered to the need to develop tools to store and analyze such a plethora of information, through dedicated algorithms for data sharing and integration, image analysis, and mining. Online databases for microbial typing data, analytic software for gel-based molecular typing techniques, and models for phylogenetic inference analysis have been developed, and this has made it possible for bacterial typing to extend beyond outbreak investigation at the local level.¹⁴ The ability to share information using the Internet has led to the evolution of specialized software in which nationwide or worldwide comparisons can be performed. PulseNet represents the forerunner of molecular subtyping networks, based on standardized PFGE protocols for the identification of pathogenic food-borne bacteria. Gradually, online database and networks for the other typing methods have grown and are continuously updated. Thanks to the portability of sequence data, Multilocus Sequence Typing (MLST) websites and databases are extensively and successfully adopted for nomenclature purposes, allowing disambiguation when analyzing and comparing results and to infer patterns of phylogenetic descent through comparison of allelic profiles.¹⁵ Sequence-based typing methods have led to the development of new analysis methodologies, such as eBURST or goeBURST, which have made it possible to determine the genetic

population structure of many bacterial species, bacterial evolution and spread.¹⁶ More sophisticated software has been developed to handle the ever larger amount of data generated by Next Generation Sequencing (NGS), and is slowly but successfully being applied to a variety of public health problems, ranging from outbreak investigations to long-term epidemiologic studies.

Finally, integration of genomic and epidemiological databases with NGS data will be the next frontier in bacterial epidemiology, in order to empower stakeholders in everyday public health decisions. As the spatial component in epidemiological studies is of great importance, the ability to monitor the geographic spread of clones at different levels can provide a comprehensive perspective of the dissemination of successful clones. Through the combined analysis of this information, the broader use of geographic information in phylo-geographical approaches will allow a better understanding of the spread of particular clones. Once NGS becomes widely adopted, the public health community challenges will be to define standards for analysis and reporting, in order to produce the desired reproducibility, and a common language for typing based on NGS to be useful in clinical settings.¹⁴

MOLECULAR EPIDEMIOLOGY IN THE MANAGEMENT OF HAIs **Role of molecular epidemiology in infection prevention and control programs**

Molecular epidemiology for the characterization of microorganisms represents an essential component in the surveillance of infectious diseases and outbreak investigations, especially for the prevention and control of HAIs.¹⁰ Furthermore, molecular typing methods have been successfully used to study markers associated with pathogenicity and antibiotic resistance. This approach has proven particularly useful over the last decade, as multidrug-resistant microorganisms have been implicated in severe HAIs and their occurrence has increased gradually, which has also made it difficult to control outbreaks.¹⁷⁻¹⁹

Generally, typing methods can be described as comparative or library typing. In comparative typing, which is mainly used for outbreak investigation, outbreak-related and unrelated isolates are tested to address infection control strategies. In the long term, comparison between outbreak related isolates with isolates from the past or future is not relevant. On the contrary, library typing methods are useful to compare strains from a current outbreak with previous circulating strains and can be used in different laboratories at various time intervals, in order to generate data to be aggregated in a single database for comparative assessment in great detail at any time.^{9,10,20}

Molecular characterization can be used to study the genetic relationships between isolates and identify their mode of transmission (person to person, with environmental surfaces or invasive devices). Besides, it allows to identify episodes of intra- or inter-hospital transmission, or in other healthcare settings, to design appropriate control measures to contain the epidemic spreads of isolates associated with colonization and/or HAI episodes.¹⁷⁻¹⁹ A molecular typing approach for HAI control

provides an insight into the population dynamics of microorganism circulation in order to allow the design of evidence-based strategies to decrease infection rates to the irreducible minimum.¹⁷

In order to improve collaboration between expert and reference laboratories to support prevention and control strategies, the ECDC facilitates, at the European level, interdisciplinary collaboration and the assessment of public health needs for the integration of molecular typing data into surveillance and epidemic investigations.²¹

In view of this premise, the central role that molecular epidemiology might gain in the management of HAIs is evident, both in dissecting the clonality among strains, thus confirming or denying the presence of pseudo-outbreaks, and showing the effectiveness and cost-effectiveness of HAI prevention and control programs.²² Understanding the clonality between microorganisms can allow to quickly establish the degree of relationship between them, thus resulting in a more accurate and rapid implementation of preventive measures or, in the case of absence of clonality, helps to avoid expensive measures of caution that are necessary when awaiting traditional investigations.²²

Ethical, legal and social aspects (ELSI)

The outstanding diagnostic potential of genotyping techniques in detecting the origin and routes of transmission of an outbreak raises many questions from an ethical point of view. These issues concern different aspects such as the right to privacy, respect for individual autonomy, informed consent, and moral obligation on the part of every individual to avoid the spread of a contagious disease.^{23,24}

Given the unique features of molecular techniques it would be necessary to implement a regulatory framework under which their use may be applied in public health practice. Molecular epidemiology for bacterial genotyping, as well as human DNA genotyping, is, in fact, gaining an increasing important role in court cases and legal affairs in order to help the process of attribution of responsibility. Nevertheless, it is crucial for every professional figure involved in the use of microbial forensics to

be well aware that molecular epidemiology can in no-way be considered as a substitute for a thorough epidemiological investigation that can integrate molecular methods with the other traditional epidemiological tools.²³ It must be clear that the use of molecular epidemiology without the contribution of other tools and professional figures such as hygienists or epidemiologists, could be insufficient to handle a case of causal attribution of responsibilities, thus resulting in negative consequences for the community and risks – such as stigmatization, penalties, economic risks – for the individuals involved.

CONCLUSIONS

Patient safety and quality of care have now gained the top of the political agenda of the European Union. Council Recommendation 2009/C 151/01 proposes an overarching EU-level strategy to promote patient safety and underlining the importance of correct management of HAIs as a cornerstone to achieve safety and a high quality healthcare delivery.²⁵ Proper education and training of health professionals on these topics is considered of crucial importance to achieve these goals.

This narrative review is based on the research made for the drafting of *L'epidemiologia molecolare nelle infezioni correlate all'assistenza: documento di indirizzo della Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica (SIItI)*,¹² a product of the joint effort of two different working groups of the Italian Society of Hygiene, Preventive Medicine and Public Health. These two documents may be considered a step toward the implementation of knowledge and education on HAI prevention and management in Italy, in line with the European recommendations.¹³

Acknowledgements

The authors would like to thank the following colleagues for their very insightful and constructive comments, which helped improve this manuscript: Beatrice Casini, Daniela D'Alessandro, Osvalda De Giglio, Carolina Ianuale, Maria Teresa Montagna, Andrea Piana, Luisa Sodano, Licia Veronesi, Raffaele Zarrilli

Conflicts of interest: none declared

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WORKING GROUP
SItI GISIO
Wednesday 14 October
h. 10.00-11.30
Amber Room 2

Appropriate perioperative antibiotic prophylaxis: challenges, strategies, and quality indicators

Appropriatezza della profilassi antibiotica perioperatoria: sfide, strategie e indicatori di qualità

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Abstract

Introduction. Surgical site infections (SSIs) are common surgical complications and perioperative antibiotic prophylaxis (PAP) contributes to the reduction of the associated risk. The aim of the present review article is to summarize the most recently published studies with a special focus on challenges, strategies and quality indicators of PAP.

Methods. Literature searches in the Medline database, using PubMed, were carried out for studies published from January 2011 to April 2015. Inclusion criteria were all types of epidemiological studies investigating: **i.** compliance with PAP recommendations at different levels by using process indicators, and **ii.** the effect of different interventions conducted in order to improve PAP compliance.

Results. A total of 28 studies were retrieved. Overall compliance with all included PAP indicators ranged from 9.4% to 80%. Generally, compliance with the PAP process indicators significantly improved after interventions.

Conclusions. The present review summarizes the recent published studies and indicates an overall inadequate compliance with PAP recommendations, underlining the need to develop and to implement successful strategies to improve adherence to guidelines. Different interventions were found efficacious in order to increase compliance with appropriate PAP administration.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 27-32)

Key words: perioperative antibiotic prophylaxis, surgical site infections, surveillance, compliance, guidelines

Riassunto

Introduzione. Le infezioni del sito chirurgico sono frequenti complicanze in chirurgia e la profilassi antibiotica perioperatoria (PAP) contribuisce alla riduzione del rischio. Obiettivo di questa revisione è riassumere gli studi più recenti concentrandosi sulle sfide, sulle strategie e sugli indicatori di qualità della PAP.

Metodi. Una ricerca bibliografica degli articoli, pubblicati dal gennaio 2011 all'aprile 2015, è stata condotta sul database Medline, utilizzando PubMed. Gli studi epidemiologici inclusi riportavano: **i.** l'adesione alle raccomandazioni sulla PAP a differenti livelli, utilizzando indicatori di processo; **ii.** l'effetto di differenti interventi condotti per migliorare l'adesione alla PAP.

Risultati. In totale, sono stati inclusi nella revisione 28 studi. L'adesione complessiva, considerando tutti gli indicatori di PAP, variava dal 9,4% all'80%. Generalmente, l'adesione alla linee guida sulla PAP migliora significativamente dopo gli interventi.

Conclusioni. Questa revisione riassume gli articoli più recenti e indica un'adeguata adesione complessiva alle raccomandazioni per la PAP, sottolineando la necessità di sviluppare e implementare le strategie per migliorare l'adesione alla PAP. Diversi interventi si sono dimostrati efficaci nel migliorare l'aderenza a un'appropriata somministrazione della PAP.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 27-32)

Parole chiave: profilassi antibiotica perioperatoria, infezioni del sito chirurgico, sorveglianza, adesione, linee guida

INTRODUCTION

Surgical Site Infections (SSIs) are common surgical complications and Perioperative Antibiotic Prophylaxis (PAP) contributes to the reduction of the associated risk.^{1,2} Guidelines with specific recommendations are available about the appropriate decision-making, choice, and dose of the antibiotic, timing, and duration of PAP. A technical report and systematic review conducted by the European Centre for Disease Prevention and Control (ECDC) identified the key PAP modalities to be implemented in order to improve compliance with PAP practices for the prevention of SSIs.² Briefly, the following points were identified:

- establishing a multidisciplinary team;
- ensuring administration of PAP within 60 minutes prior to incision;
- assigning responsibility for timely administration of PAP to the anaesthesiologist;
- administering only a single dose of PAP;
- suspending PAP at the end of the procedure.

However, implementation of PAP guidelines is a true challenge, and failure to adhere with such standard of care has been reported, indicating that there are opportunities for improvement in many settings. Furthermore, the European report identified barriers to wide implementation of PAP practices.² Different studies have reported successful interventions to improve PAP compliance, however, methodology and reporting of studies is often suboptimal, and caution in applying the results of these studies to the general practice is needed.³

The aim of the present review article is to summarize the most recently published studies, with a special focus on challenges, strategies, and quality indicators of PAP.

METHODS

Literature searches in the Medline database, using PubMed, were carried out for relevant studies published from January 2011 to April 2015. The searches were limited to papers written in English and were conducted independently by two Authors. The keywords used in combination were: «perioperative antibiotic prophylaxis», «compliance», «adherence», and «intervention». Inclusion criteria were all types of epidemiological studies investigating:

- the compliance with PAP recommendations at different levels by using process indicators;
- the effect of different interventions conducted in order to improve PAP compliance.

No limits were stated for healthcare setting and type of surgical procedures investigated. Only studies whose full-text articles met the inclusion criteria were retained for review. Studies were excluded from review if:

- antibiotics were administered as treatment;
- publications were conference papers or articles without detailed descriptions of methods and results.

Moreover, the reference lists from selected articles were checked to search for further relevant studies.

A total of 28 studies were retrieved. Authors independently re-

viewed all the eligible studies and abstracted the following information in two standard formats. In the first format (**table 1**) the following information was included: first Author's last name, year of publication, study design, surgical procedures investigated, indicators used to assess compliance with PAP guidelines and results. In the second format (**table 2**) the information included was: first Author's last name, year of publication, study design, surgical procedures investigated, interventions to improve compliance with PAP guidelines and their effects.

RESULTS

Compliance with PAP guidelines

Several studies have evaluated current practices of PAP in patients undergoing different types of surgical procedures. **Table 1** reports a summary of study design, surgical procedures included, and the main results of the 19 recent published papers included in the present review.⁴⁻²²

These studies were carried out in various geographical areas: eight studies were conducted in the United States of America, six in Italy, and one in each of the following countries: Germany, the Netherlands, Turkey, Thailand, and China. The most frequent type of study was prospective (12 out of 19) followed by retrospective studies (5 out of 19). Retrieved articles included various types of surgical units performing different surgical procedures. Two studies included procedures performed on neonates or paediatrics patients.^{6,22}

Compliance was mainly assessed considering specific PAP recommendations developed at the local (or institutional), national, and international level. Furthermore, recommendations for appropriate PAP included in care bundles for the prevention of SSIs were also considered. Specifically, compliance with the World Health Organization's surgical checklist (WHO «Safe surgery saves lives» checklist),²³ which includes methods for preoperative removal of hair, appropriate PAP, avoidance of perioperative hypothermia, management of perioperative blood glucose and effective skin preparation, was evaluated in one study.¹⁸ Furthermore, some studies evaluated compliance with the guidelines of the Surgical Care Improvement Project (SCIP),²⁴ which included other measures for SSI prevention than those specific for appropriate PAP (initiating prophylactic antibiotics within one hour of surgical incision; administering the appropriate antibiotic, and discontinuing antibiotic use within 24 hours).^{12,13,15} Finally, adherence to the SSI care bundle developed by the Dutch Hospital Patient Safety Program (DHPSP), including PAP, hair removal before surgery, perioperative normothermia, and discipline in the operating room was also reported.¹⁷

Generally, in the included studies, compliance of the current PAP practices with guidelines, a process measure, was assessed mainly considering one or more of the following indicators:

- indication (appropriate decision-making regarding the use or non-use of antimicrobial prophylaxis) (8 studies);
- timing of administration (the first dose of antibiotic should be administered immediately prior to anaesthesia: 30 to 60 minutes before incision) (15 studies);

Authors/year	Study design	Surgical procedures	Indicators	Results
Agodi et al., 2015 ^(a)	prospective survey	■ hip or knee replacement	■ indication, timing, antimicrobial agent, total duration of PAP	■ compliance with indication: 99.4%; with antibiotics: 57.7 %; with timing: 73%; with duration: 70.2% ■ overall compliance: 43.6%
Agodi et al., 2015 ^(b)	prospective survey	■ herniorrhaphy, other digestive system, cholecystectomy, other endocrine system, colon surgery, mastectomy, appendectomy, small bowel surgery	■ indication, timing, antimicrobial agent, total duration of PAP	■ overall compliance: 12.4%
Murray et al., 2014	quasi-experimental study	■ cardiac procedures performed on neonates	■ appropriate antimicrobial agent, dose, timing, discontinuation of PAP	■ compliance with the 4 process measures significantly improved after an intervention
Yang Ou et al., 2014	prospective multicenter survey	■ clean or clean-contaminated surgery	■ indication, antimicrobial agent combination, antibiotic choice, dose, dosing interval, route of administration, timing of first administration, duration of prophylaxis	■ compliance with indication: 18.6%; with antibiotics: 30.8%; with dose: 76.4%; with dose interval: 65.3%; with route of administration: 85.3%; with timing: 30.3%; with duration: 26.7% ■ overall compliance: 9.4%
Brubaker et al., 2014	retrospective study	■ cesarean delivery	■ compliance with the recommendation for universal PAP	■ 59.5% of women received PAP
Goede et al., 2013	retrospective charts review	■ cardiac, neurosurgery, orthopedics, general, vascular surgery; colorectal, gynecology, thoracic, and solid organ transplantation	■ according to institutional practice standards, antibiotic selection, dosing, timing, redosing	■ compliance with timing: 57.2%; with antibiotic selection 89.2% ■ overall compliance: 24.4%
Napolitano et al., 2013	prospective study on a randomly selected sample	■ various types of surgery	■ antimicrobial agent, timing, length of the prophylaxis	■ compliance with type of antibiotic: 25.5%; with timing: 53.4%
Bozkurt et al., 2013	two prospective studies before and after an intervention	■ general, thoracic, head and neck, neurosurgery, cardiovascular, plastic, orthopedic, and urological	■ indication, antimicrobial agent, timing, number of doses, duration of treatment	■ compliance with the antibiotic chosen: 91.7% and 99%; suitable antibiotic: 77.6% and 90.6% ■ non-compliance with the duration of PAP: 77.0% and 44.7% ■ overall compliance: 15.4% before and 39.3% after the intervention
van der Slegt et al., 2013	prospective study	■ peripheral or central vascular reconstruction	■ according to SCIP antimicrobial prophylaxis criteria: timing, choice of appropriate antimicrobial agent, duration	■ compliance with administration of antimicrobial agent: 95%; with the appropriate type of antibiotic: 98%; with duration: 87% ■ compliance with all 3 indicators: 80%
Lee et al., 2013	retrospective observational cohort with nested case control study	■ hip or knee replacement, vaginal or abdominal hysterectomy, colorectal surgery, or vascular surgery	■ according to SCIP antimicrobial prophylaxis criteria: timing, choice of appropriate antimicrobial agent, duration	■ compliance with administration of antimicrobial agent: 98%; with timing: 95%; with duration: 80% ■ compliance with all 3 indicators: 6.9%
Durando et al., 2012	observational prospective study	■ general, orthopaedic, ear, nose, and throat, obstetric and gynecologic, cardiac, vascular, and chest, urologic surgeries, neurosurgery, and others	■ indication, antimicrobial agent, timing, number of doses, duration of treatment	■ inappropriate prophylaxis in 55.2% patients
Smith et al., 2012	retrospective review	■ patients who underwent emergency trauma laparotomy	■ according to SCIP antimicrobial prophylaxis criteria: antimicrobial agent, timing, correct antibiotic selection, duration	■ compliance with the four SCIP criteria: 49.3%
Hohmann et al., 2012	prospective review	■ different types of surgery	■ choice of antibiotic drug and the duration of PAP	■ compliance in 70.7% of the cases
Crolla et al., 2012	prospective study	■ colorectal surgery	■ compliance with an SSI bundle including PAP, in repetitive measurements	■ antibiotic prophylaxis had a relative high compliance during the entire study period
Kasatpibal et al., 2012	prospective study		■ compliance with the World Health Organization (WHO) surgical safety checklist	■ PAP had been given within 60 min. before the incision in 71% of the cases
Young et al., 2012	prospective study	■ cesarean deliveries	■ timing of PAP	■ a multidisciplinary approach was successful in achieving 100% adherence to institution policy change regarding timing of PAP
Barchitta et al., 2012	a pilot investigation followed by four 1-day SSI point-prevalence surveys, with a 3 month interval between investigations	■ different types of procedures	■ indication and timing of administration	■ overall compliance: 54.5% (from 44.7% to 32.7%)
Prospero et al., 2011	prospective study	■ general surgery, orthopaedic surgery, neurosurgery, vascular surgery, and other surgery	■ indication, timing, and duration	■ compliance with indication: 65%; with timing: 95%; with duration: 82%
Rangel et al., 2011	retrospective study	■ general and urological procedures in paediatric patients	■ indications for PAP	■ 82% of patients received antibiotics during procedures when PAP was indicated

PAP: perioperative antibiotic prophylaxis; SCIP: surgical care improvement project; SSI: surgical site infection

Table 1. Studies on compliance with PAP guidelines included in the review. / **Tabella 1.** Studi sull'aderenza alle linee guida sulla PAP inclusi nella revisione.

Authors/year	Study design	Surgical procedures	Intervention	Effects
Owens et al., 2015	prospective survey	■ vascular, breast, colorectal, and general surgery educational sessions about PAP recommendations	■ a week-long educational initiative, via poster campaign, and face to face	■ not statistically significant improvement in appropriateness of PAP (timing and duration)
Murray et al., 2014	quasi-experimental study	■ cardiac procedures performed on neonates	■ an interdisciplinary task force developed a standardized PAP protocol	■ compliance with 4 process indicators significantly improved after the intervention
Sutherland et al., 2014	prospective survey	■ different types of surgery of SCIP PAP dosing errors	■ education and direct notification	■ improved compliance
Bozkurt et al., 2014	cross-sectional study	■ general surgery, cardiovascular surgery, neuro-surgery, orthopedics, otorhinolaryngology, plastic surgery, thoracic surgery and urology	■ meetings with the infection control committee; inspections and monthly training seminars	■ inappropriate durations of PAP decreased from 89.7% in 2011 to 40.6% in 2012
Bozkurt et al., 2013	before and after study	■ general, thoracic, head and neck, neurosurgery, cardiovascular, plastic, orthopedic, and urological	■ meetings with the infection control committee; inspections and monthly training seminars	■ after the intervention, the rates of the correct PAP timing increased from 91.7% to 99.0% ($p < 0.001$), while the excessively long administration of PAP decreased from 77.0% to 44.7% ($p < 0.001$) ■ overall compliance with the guidelines increased from 15.5% to 40.2% ($p < 0.001$)
Barchitta et al., 2012	a pilot investigation followed by four 1 day SSI point-prevalence surveys, with a 3 month interval between investigations	■ different types of surgery.	■ specific campaign, including posters, leaflets and brochures providing main information ■ literature was distributed to a wide audience of surgeons attending seminars and workshops	■ rates of non-compliance significantly increased in the first three surveys, then decreased in the last one after the intervention, from 55.3% to 45.5% ($p = 0.002$)
Kim et al., 2012	retrospective study	■ arthroplasty, gastrectomy, and hysterectomy; craniotomy and spine	■ implementation of clinical performance indicators of PAP as a part of the National Hospital Evaluation Program (NHEP)	■ PAP quality significantly improved, especially timing ■ the use of unfavourable antibiotics significantly decreased to 28.9-35.3% overall in 2007-2008 ■ the proportion of first antibiotic doses administered within 1 h before skin incision was almost 100% after the intervention ■ the mean duration of PAP after the end of surgery decreased to 7-10 days in 2007-2008
Young et al., 2012	prospective study	■ caesarean deliveries	■ notification of a policy change in PAP through department-wide e-mails and verbal dissemination at departmental meetings, education sessions, and local champions	■ 100% of compliance with the new policy was achieved in 5 weeks
Benning et al., 2011	retrospective study	■ total hip replacement and open colectomy	■ 2 nd phase of a Safer Patients Initiative (SPI) program (learning sessions with the Institute for Healthcare Improvement; web-based learning; participation in safety culture surveys; creation of a collaborative learning community)	■ the data collected on SPI2 suggest that an additional effect of SPI is difficult to detect over and above the improvements occurring across the health service ■ adherence rates for many of the specific criteria reflecting quality of care remained high over time in both groups of hospitals, possibly reflecting a long history of quality improvement in areas such as perioperative care
McHugh et al., 2011	prospective survey	■ general surgery	■ learning program, over a six-month period, consisting of online education, lectures and posters for surgical trainees to improve infection control practices in the areas of SSI and catheter-related bloodstream infection	■ a significant improvement in the administration of PAP prior to incision and a significant decrease in inappropriate dressing changes during the initial 48 hours following surgery ■ the proportion of prophylactic antibiotics administered prior to incision increased from 30.0% to 59.1% ($p < 0.001$)
Haynes et al., 2011	quasi-experimental study	■ different types of surgery.	■ a computer-based order system designed to avoid excessive duration of PAP	■ the computer-based order intervention significantly improved the proportion of procedures with timely discontinuation of antimicrobial agents from 38.8% to 55.7% ($p < 0.001$)
Sun et al., 2011	prospective survey	■ coronary artery bypass grafting	■ regular institutional quality improving activities; regional symposium on PAP; recommendations compatible with adequate references; organizing a team; work flow in administering prophylactic antibiotics	■ instances of prophylactic interval within 1h prior to incision significantly increased from 66.7% to 97.4% ■ rates of prophylactic duration less than 24h significantly increased from 2.8% to 66.1%

PAP: Perioperative Antibiotic Prophylaxis; SCIP: Surgical Care Improvement Project; SSI: Surgical Site Infection

Table 2. Studies on interventions to improve PAP compliance included in the review.

Tabella 2. Studi di intervento per il miglioramento dell'aderenza alle linee guida sulla PAP inclusi nella revisione.

- antimicrobial agent (12 studies);
- dosing of antibiotic administered (5 studies);
- total duration of prophylaxis (discontinuation of the agent within 24 hours after procedure or 48 hours for cardiothoracic procedures) (12 studies).

Cumulative compliance was calculated considering all indicators investigated. The numerator of compliance was the number of patients who appropriately received antimicrobial prophylaxis and the denominator the total number of selected operations performed, multiplied by 100.

In the included studies, overall compliance with all included PAP indicators ranged from 9.4%⁷ to 80%^{12,13} or 100% after an intervention.¹⁹ Compliance with indication ranged from 18.6%⁷ to 99.4%⁴ and with timing from 30.3%⁷ to 95.0%.^{13,21}

Interventions to improve PAP compliance

Table 2 reports a summary of studies conducted in order to assess the efficacy/effectiveness of interventions to improve compliance with PAP guidelines. A total of 12 recent published papers were included in the present review.^{6,11,19,20,25-32}

Different types of surgical procedures, performed in a variety of surgical units, were implemented. One study included cardiac procedures performed on neonates.⁶ The strategy for improvement chosen by almost all investigations was based on education of healthcare workers about appropriate administration of PAP by regular training meetings and through posters, leaflets, and brochures. In two studies strategies included the creation of an interdisciplinary team which aimed to develop a standardized PAP protocol.^{6,32} Furthermore, a computer-based order system to avoid excessive duration of PAP was implemented in one study and a significant improvement of the proportion of procedures with timely discontinuation of antimicrobial agents was demonstrated.³¹ Generally, compliance with the PAP process indicators significantly improved after in-

terventions. Notably, in one study the notification of a policy change in PAP through different tools achieved 100% of compliance in five weeks¹⁹ (**table 2**).

DISCUSSION AND CONCLUSIONS

The optimization of PAP is one of the most important interventions to prevent SSIs. The appropriate administration of PAP has a significant effect on the prevention of SSIs, as reported in a systematic review of 21 meta-analyses.¹ The recent technical report of the ECDC included several studies, published between 2000 and 2011, describing a decrease in SSI rates when an increase in compliance with PAP guidelines was observed.² The present review summarizes the recent published studies and indicates an overall inadequate compliance with PAP recommendations, underlining the need to develop and implement successful strategies to improve PAP compliance. A multimodal approach is considered the current challenge for the effective control of SSI risk; different interventions were found efficacious in order to increase adherence with appropriate PAP administration. However, the previously described obstacles and barriers for the implementation of appropriate PAP should be addressed.²

A limitation of our review is that the papers included were very heterogeneous in the study design and methods used to assess PAP compliance and evaluate interventions to improve it; in addition, studies were performed in different healthcare settings and considered heterogeneous surgical procedures. Further systematic reviews and meta-analyses are needed in order to assess the effect of changes on SSI rates in the compliance with PAP guidelines, to inform appropriate policies and programs. Indeed, infection control education and training are the focus of increasing attention in Europe and the basis of all patient safety and infection control programs.³³

Conflicts of interest: none declared

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WORKING GROUP SIH
PROMOZIONE DELLA SALUTE
Wednesday 14 October
h. 14.00-16.00
Amber Room 2

Professional competencies in health promotion and public health: what is common and what is specific? Review of the European debate and perspectives for professional development

Competenze professionali in promozione della salute e in sanità pubblica: cosa è comune e cosa è specifico? Revisione del dibattito europeo e prospettive per lo sviluppo professionale

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Abstract

According to the *Nairobi Call to Action*, the growth of practitioners' skills can be favoured by setting accreditation standards and by reorienting professional competencies of current and future health workers. This will make it possible to develop a critical mass of competent practitioners, foster training, and increase visibility of the professional field. Through a review of the literature, the authors offer an overview of competency-based strategies for professional development in health promotion. The main research questions discussed were as follows: Is there a shared definition of public health?; Is there a shared definition of health promotion?; Who are the main stakeholders for public health and health promotion in Europe?; What is the meaning of professional competencies in education and practice for public health and health promotion?; Is there a shared system of professional core competencies in public health and health promotion?; What is common and what is specific between the two systems of professional competencies?; Is it useful and feasible to create specific strategies of professional development for public health and health promotion? A transformative use of competencies makes it possible to inform students, professionals, employers, and political decision-makers about what is expected from a specific profession and its values.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 33-38)

Key words: health promotion, public health, competencies, professional development

Riassunto

In accordo con la *Nairobi call for action* lo sviluppo delle competenze dei professionisti può essere favorito stabilendo standard di accreditamento e riorientando le competenze professionali degli operatori sanitari. Ciò consentirà di sviluppare una massa critica di professionisti competenti, per promuovere la formazione e la visibilità di tale campo professionale. Attraverso la revisione della letteratura, gli autori offrono un ampio panorama sulle strategie delle competenze di base per la crescita professionale in promozione della salute. Le principali domande discusse sono state: Esiste una definizione condivisa di sanità pubblica?; C'è una definizione condivisa di promozione della salute?; Quali sono i principali *stakeholder* di sanità pubblica e promozione della salute in Europa?; Qual è il significato di competenze professionali in materia di formazione e l'attività in sanità pubblica e promozione della salute?; Esiste un sistema condiviso di competenze professionali di base in sanità pubblica e promozione della salute?; Che cosa è comune e cosa è specifico tra i due sistemi di competenze professionali?; E' utile e fattibile creare strategie specifiche di sviluppo professionale per la sanità pubblica e promozione della salute? Un uso potenzialmente trasformativo delle competenze permette di informare studenti, professionisti, datori di lavoro, e decisori politici su cosa ci si aspetta da una specifica professione e sui suoi valori.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 33-38)

Parole chiave: promozione della salute, sanità pubblica, competenze, sviluppo professionale

INTRODUCTION

Many countries have moved from a medically dominated public health and health promotion to a multidisciplinary workforce, whose limits are difficult to define. In addition to public health specialists, focused on public health work, the potential for public health and health promotion includes other health and non-health professionals. Investing in a competent workforce, therefore, constitutes an indispensable resource for health improvement and workforce development is encouraged by a number of international statements.

According to the *Nairobi Call to Action*, the growth of practitioners' skills can be favoured by setting accreditation standards and reorienting professional competencies of current and future health workers. This makes it possible to develop a critical mass of competent practitioners, foster training, and increase visibility of the professional field.

As a result of this trend, European professional organizations developed a number of competency-based strategies for professional development. The process, defined independently in the public health setting and in health promotion and by a professional audience, is challenged with different and sometimes competitive proposals.

The main research questions discussed in this review can be formulated as follows: «What is common and what is specific between professional competencies in health promotion and professional competencies in public health?» and «How can a shared system of specific professional competencies influence the perspectives of professional development in health promotion and public health in Europe?». In order to explore the research questions, the following sub-research questions will be discussed:

- Is there a shared definition of public health?
- Is there a shared definition of health promotion?
- Who are the main stakeholders for public health and health promotion in Europe?
- What is the meaning of professional competencies in education and practice for public health and health promotion?
- Is there a shared system of professional core competencies in public health and health promotion?
- What is common and what is specific between the two systems of professional competencies?
- Is it useful and feasible to create specific strategies of professional development for public health and health promotion?

The literature research is mainly based on – as much as possible freely available – Internet documents .

Is there a shared definition of public health?

The EUPHA defines public health as «the science and art of preventing disease, prolonging life and promoting health and wellbeing through the organized efforts and informed choices of society, organizations, public and private, communities and individuals, and includes the broader area of public health, health services research, health service delivery and health systems design».¹

According to the *WHO Glossary of globalization, trade and health terms*, «public health activities aim to provide conditions in which people can be healthy and focus on entire popula-

tions, not on individual patients or diseases».² «Main public health functions are the assessment and monitoring of the health of communities and populations at risk to identify health problems and priorities and the formulation of public policies designed to solve identified local and national health problems and priorities».³

Public health professionals are defined as «all professionals that monitor and diagnose the health concerns of entire communities and promote healthy practices and behaviours to ensure that populations stay healthy. This definition specifically includes health services researchers».¹

Is there a shared definition of health promotion?

The most prominent definition of health promotion comes from the Ottawa Charter. «Health promotion is the process of enabling people to increase control over, and to improve, their health. To reach a state of complete physical, mental and social wellbeing, an individual or group must be able to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is a positive concept emphasizing social and personal resources, as well as physical capacities».⁴

«Health promotion is not just the responsibility of the health sector, but goes beyond healthy life-styles to wellbeing», making health promotion a social and political process, which includes not only actions directed at the individuals, but also actions directed towards changing social and environmental conditions.⁴ Its basic strategies are advocacy, empowerment, and partnership. A health promotion practitioner is defined as «a person who works to promote health and reduce health inequities using the actions described by the Ottawa Charter».⁵

According to an earlier vision «health promotion consists of activities to improve or protect health and to prevent disease».⁶ This approach includes health education (increasing awareness and influencing attitudes and knowledge to improve health), health protection (policies and activities, including legislation, designed to promote healthier environments where healthy choices are easier), and disease prevention.⁷⁻¹⁰

The two definitions of health promotion represent two different visions, holding the tension between bottom-up and top-down programming. The Ottawa vision aims «to enable people to increase control over their health» emphasizing the principles of empowerment and the bottom-up approach.⁴ This vision implies community ownership, explicitly aims at social and political change, and recognizes that empowerment challenges power balance between professionals and citizens. The second vision, more oriented to disease prevention, involves specific groups or individuals in issues and activities largely defined by health agencies, and regards improvement in particular behaviours as the main outcome. Empowerment is viewed more instrumentally as a tool for health behaviour change.⁴

Who are the main stakeholders for public health and health promotion in Europe?

The European Public Health Association (EUPHA) is an international, multidisciplinary, scientific organisation for public health associations and institutes in Europe, and represents the

largest network of public health professionals. The EUPHA's vision is «to improve health and wellbeing and narrow health inequalities for all Europeans, aiming to improve health in Europe, adding value to the efforts of national and international organizations, and individual public health professionals». The EUPHA's mission is to facilitate and activate a strong voice of the public health network by enhancing visibility of the evidence and strengthening the capacity of public health professionals.

It has three main goals:

- to be a leading scientific, independent voice in the field of public health research and policy;
- to build capacity and knowledge in the field of public health research, with the aim of supporting evidence-informed practice and policy decisions;
- to prepare future generations of engaged and connected public health professionals for their leadership role in public health.¹

The International Union for Health Promotion and Education (IUHPE) is a unique global, independent professional association of individuals and organisations committed to improving the health and wellbeing of people through education, community action, and the development of healthy public policies.¹¹ The IUHPE's vision is a world where all people achieve optimum health and wellbeing. The values critical to the achievement of this vision include:

- respect for the innate dignity of all people, cultural diversity, and natural resources and the environment;
- involvement of people in making the decisions that shape their lives and impact upon their health and wellbeing;
- social justice and equity.

The IUHPE aims to achieve the following goals:

- greater equity in the health of populations between and within countries;
- effective partnerships to produce optimal health promotion outcomes;
- broadly accessible evidence-based knowledge and practical experience in health promotion;
- excellence in policy and practice;
- high levels of capacity in individuals, organizations, and countries to undertake health promotion activities.²

The Association of Schools of Public Health in the European Region (ASPHER) is an independent organization dedicated to strengthening the role of public health by improving education and training of professionals for both practice and research.

ASPHER has over 100 institutional members and is located in 42 European countries, with more than 5,000 academics and experts employed in its member institutions. It also has strong links with similar associations in other regions of the world, and with other European and international organisations active in the field of public health.¹²

What is the meaning of professional competencies in education and practice for public health and health promotion?

Over the years there has been an increasing amount of activity to systematize and describe the knowledge and skills required by

various groups of professionals to carry out their specific tasks. In particular, a strong movement has grown that seeks to align the education curriculum as an instrument of learning to achieve requisite competencies as the educational goal.¹³

Competencies are defined as «a combination of the essential knowledge, abilities, skills and values necessary for the professional practice». A competency-based approach specifies the problems to be addressed, identifies the competencies required, tailors the education curriculum to achieve competencies, and assess achievements and shortfalls.¹⁴

Core competencies are «the minimum sets of competencies that constitute a common baseline for all professional roles and are what all practitioners are expected to be capable of doing to work efficiently, effectively and appropriately in a field».⁵

A potentially transformative use of competencies makes it possible to inform students, professionals, employers, and political decision makers about what is expected from a specific profession and about its values and expectations. This could lead to a new objective classification of health professions, which, over the present arbitrary borders, would assign roles and responsibilities according to what professionals are able to offer.

The core competencies for public health reflect foundational skills desirable for professionals engaging in the practice, education, and research of public health. They support workforce development within public health and can serve as a starting point for public health professionals and organizations as they work to better understand and meet workforce development needs, improve performance, prepare for accreditation, and enhance the health of the communities they serve. The core competencies have been integrated into curricula for education and training, provide a reference for developing public health courses, and serve as a base for sets of discipline-specific competencies. The core competencies grew from a desire to help strengthen the public health workforce by identifying basic skills for the effective delivery of public health services.¹⁵⁻²⁶

Is there a shared system of professional core competencies in public health and health promotion?

In 2006, ASPHER decided to take the lead in the development of a system of core competences which could be applicable to public health education, research, and practice throughout Europe. The dialogue between education providers, political decision-makers and employers resulted, even through conferences and workshops, in reports of competencies at intermediate stages of development.

The process made it possible to firmly establish concepts and terms, and define the whole spectrum of competences expected in public health professionals as well as a shorter lists for master of public health (MPH) education.

The final list of competences was disseminated across stakeholders, and, in September 2012, endorsed by all European WHO member states: «National governments should make efforts to ensure that the core competences for public health, recently revised by ASPHER, are being taken into account in na-

tional and subnational educational and training programmes for the public health workforce». ^{15,27-32}

The 2008 Galway Consensus Conference, organized by IUHPE and other partners, launched a participative process aiming to promote exchange and greater collaboration on the development of core competencies in health promotion and the strengthening of common approaches to capacity building and workforce development.

A consensus draft statement, identifying eight domains of core competency for health promotion practice, was produced and offered to the international health promotion community.

In Europe the statement gave birth to the CompHP project «aiming to develop competency-based standards and an accreditation system for health promotion practice, education and training». The project ran from 2009 to 2012. ³²

A phased, multiple-method approach was employed to facilitate consensus building with key stakeholders in health promotion across Europe. Consultation processes included focus and discussion groups at European and country levels, an online survey, a web-based consultation, and testing in academic and practice settings. Successive drafts of the framework were revised based on the feedback from each consultation stage.

As a result of the CompHP project, IUHPE developed and established the European Health Promotion Accreditation System, which to date is fully functioning in Europe, and is set to expand globally. ³³

What is common and what is specific between the two systems of professional competencies?

Since the nineties, in Europe, training programmes have been structured around key areas of competencies (from five to seven according to various documents). ¹⁴ The ASPHER competencies can be summarized as follows. The public health professional shall be able to:

Methods in public health. Understand definitions, models and concepts in health, public health, philosophy of science, sociology, social psychology, and anthropology; apply epidemiological, statistical, and qualitative methods to concrete settings, including IT handling, needs assessment, and literature search and evaluation.

Population health and its determinants. Analyze the impact of environmental and social determinants on health and diseases; identify groups with elevated risk, and recognize their needs; perform risk assessment and management.

Health policy, economics, and management. Plan, implement, manage and evaluate public health programs, including identification of stakeholders and establishment of partnerships; perform health economic and health impact assessment, SWOT analysis, organization analysis; have insight into own leadership style.

Health education and promotion. Know and apply main health promotion concepts (empowerment, holism, community development, participation, capacity building, social marketing, health advocacy); identify population health challenges; effectively communicate public health messages to different audiences, by using modern media; plan, imple-

ment, manage, and evaluate strategies of health protection and communicable disease control; environmental health management, disease prevention (primary, secondary, tertiary).

Ethics. Identify ethical aspects of public health interventions, strategies, and policies; ensure the implementation of basic ethical principles in public health strategy, such as a non-discriminatory approach; respect and adhere to ethical principles and confidentiality regarding any professional activity. ¹⁸

The CompHP competencies are summarized in domains as follows. A health promotion practitioner is able to:

- be rooted in a belief in **ethical values**, especially equity and social justice, respect for the autonomy and choice of both individuals and groups, and collaborative work;
- draw on a multidisciplinary **knowledge base** of the core concepts, principles, theory, and research of health promotion and its application in practice;
- **enable change** with individuals, groups, communities and organizations to build capacity for health promotion action to improve health and reduce health inequities;
- **advocate for health** with, and on behalf of, individuals, communities and organizations to improve health and well-being and build capacity for health promotion action;
- **mediate through partnership** working collaboratively across disciplines, sectors, and with partners to enhance the impact and sustainability of health promotion action.
- **communicate** health promotion effectively, using appropriate techniques and technologies for diverse audiences;
- contribute to **leadership** with the development of a shared vision and strategic direction for health promotion action;
- conduct **assessment of needs and assets** in partnership with stakeholders, in the context of the political, economic, social, cultural, environmental, behavioural, and biological determinants that promote or compromise health;
- develop **planning**, with measurable health promotion goals and objectives based on assessment of needs and assets in partnership with stakeholders;
- **implement** effective and efficient, culturally sensitive, and ethical health promotion action, in partnership with stakeholders;
- use appropriate **evaluation and research** methods, in partnership with stakeholders, to determine the reach, impact, and effectiveness of health promotion action. ^{26,32-34}

The two systems share:

- an attention to **ethical values** like equity and social justice, respect for the autonomy and choice of both individuals and groups and the leadership styles;
- the **planning and implementation** approach, based on needs assessment and partnership with all stakeholders;
- the crucial role of **needs assessment** in the context of the whole spectrum of determinants and of appropriate **evaluation and research and communication**.

The ASPHER system, intended for general public health, is more oriented toward epidemiology, statistics, risk assessment and management, prevention, and health protection. Health promotion appears as an instrument «to improve or protect health and to prevent disease».

The COMPHP system, specific for health promotion, is more oriented toward enabling change, advocacy, and partnership. According to the Ottawa Charter its focus is «enabling people to take control of their health», and therefore stakeholder involvement, empowerment, and equity play a central role and represent the ultimate goals of the strategy.

Is it useful and feasible to develop specific strategies of professional development for public health and health promotion?

The success of core competencies and accreditation systems ultimately depend on the extent to which they are included in a strategy of professional development aiming to:

- attest the quality of workforce and workforce education;
- ensure accountability, including through clear and agreed guidelines and quality standards for knowledge, skills, and values for effective, ethical professional practice;
- facilitate employability by standardizing job descriptions and providing a reference point for employers in recruitment and selection;
- facilitate movement across roles, organizations and countries;
- increase recognition and visibility of discipline and practitioners.

The professional status of people working in public health and health promotion across Europe is characterized by a wide diversity, according to national laws, traditions, and power relationships and systems.

In several countries health promotion is not recognised as a specific profession, and examples of professionals working exclu-

sively on health promotion are extremely rare, with training and practice embedded in public health.

The challenge is therefore stronger for health promotion, seen by some stakeholders «as an approach rather than a profession». They «perceive professionalization as a risk of introducing “experts” contrary to the underpinning principles of health promotion» and «foresaw the risk that the establishment of a profession could mean allocating the role to one profession with the risk of excluding many practitioners who have been working in the sector for years». Others consider «the standards too demanding» and «think that only a few experienced experts would fully qualify on all points».

An alternative vision sees a profession as «necessary to make concrete the concepts of health promotion, to act and advocate as professional body, to stimulate individuals and education, to obtain recognition». «Without an accreditation, everybody can say that they meet standards, whilst actually conceiving very differently what they can do, what they are meant to do, or what they want to do». ³⁵⁻³⁷

An effective strategy of professional development should take into account the differences in health and education contexts and develop flexible competencies and accreditation systems that can empower and gradually incorporate professionals and education providers. A flexible, synergic relationship will enable public health and health promotion professions to avoid unnecessary conflicts and to change or cope with the professional and educational environment.

Conflicts of interest: none declared

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WORKING GROUP
Siti HTA
Wednesday 14 October
h. 14.00-16.00
Amber Room 3

How to choose health technologies to be assessed by HTA? A review of criteria for priority setting

Come scegliere le tecnologie sanitarie da sottoporre a HTA? Una revisione dei criteri usati per il *priority setting*

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Abstract

Introduction. Health Technology Assessment (HTA) plays a key role in the policy and decision-making process. Nevertheless, it is time- and resource-consuming, and therefore requires proper resource allocation. Priority setting, as a best way to organize effective and explicit resource allocation systems, may be applied even in this field.

Objective. The aim of this study was to provide an overview of criteria used for priority setting in HTA at European level.

Methods. A systematic review of the scientific literature was performed through PubMed alongside consultation of the websites of the European HTA Agencies belonging to the INAHTA. The search was limited to papers written in English and provided with the full text. Documents were considered eligible if providing criteria for priority setting in HTA.

Results. Seven scientific articles were retrieved from PubMed and 14 European HTA Agencies released prioritization criteria were analyzed. The most relevant criteria were: frequency/burden of disease, economic impact and costs, potential benefits, impact on ethical, social, cultural and/or legal aspects.

Conclusion. This work is meant to contribute to supranational discussion on priority setting at European level and shows that, despite the available evidence, work still needs to be done toward harmonization and sharing of the criteria to adopt.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 39-44)

Key words: health technology assessment, priority setting, resource allocation

Riassunto

Introduzione. La valutazione delle tecnologie sanitarie (HTA) riveste un ruolo chiave nel processo di policy e decision-making. L'HTA è tuttavia time- and resource-consuming e, pertanto, richiede strumenti per una corretta allocazione delle risorse. Il priority setting, inteso proprio come strumento per la definizione dell'uso efficiente ed esplicito delle risorse, trova spazio anche in tale ambito.

Obiettivo. Obiettivo del lavoro è stato fare una revisione dei criteri di prioritarizzazione proposti a livello europeo per l'HTA.

Metodi. È stata condotta una revisione sistematica della letteratura scientifica attraverso la consultazione di PubMed e sono stati consultati i siti web delle agenzie europee di HTA aderenti all'INAHTA. La ricerca è stata limitata ai documenti in lingua inglese e disponibili in full text e sono stati inclusi nella review gli studi che hanno fornito criteri per il priority setting nell'HTA.

Risultati. La revisione ha preso in considerazione 7 lavori scientifici e i documenti di 14 Agenzie europee di HTA. I criteri di prioritarizzazione più comunemente riportati sono stati: frequenza/carico di malattia, costi e impatto economico, benefici potenziali della tecnologia e suoi impatti/aspetti etici, sociali, culturali e/o legali.

Conclusione. Questo lavoro ha inteso contribuire alla discussione sul priority setting a livello europeo e ha messo in luce che, nonostante le evidenze, è necessario continuare a lavorare per l'armonizzazione e la condivisione dei criteri da adottare.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 39-44)

Parole chiave: health technology assessment, priority setting, allocazione delle risorse

INTRODUCTION

According to the International Network of Agencies for Health Technology Assessment (INAHTA) and the Health Technology Assessment international society, health technology assessment (HTA) is «the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies».¹

Assessing the efficacy, cost-effectiveness, safety, and organizational as well as ethical issues of available drugs, devices, and practices has become necessary because of the increasing costs of health care and inappropriate use of technology in medicine.²

New technologies are increasingly available today, but time and human and economic resources for HTA are limited and HTA agencies must therefore choose which research projects to undertake.³ Technologies to be studied are not equivalent in terms of potential impact on public health and the economy. Different diseases have, indeed, different burdens, and their management with different technologies or protocols has different costs. Moreover, the pressure of stakeholders (including the varied and varying value systems of public opinion and the ruling political forces) may sometimes make it mandatory for HTA agencies to focus on current “hot topics” in health and, consequently, on certain research projects rather than others. However, choosing the technologies on which to focus efforts should retain a scientific and systematic approach, hence HTA agencies need to develop, implement, and disclose valid methods for priority setting.

The first priority setting models became available in the 1990s and include the well-known Donaldson method (adopted by many HTA agencies) and practical approaches which were developed within the EUR-ASSESS Project.³⁻⁴ Even though it soon became clear that no standard method of prioritization will ever be universally valid, prioritization processes usually follow a few widely accepted rules. In particular, those involved in the priority setting should always review available health technologies, health policies, and clinical practices; identify issues that are relevant for decision-makers and technologies potentially to be assessed; set priorities; inform the institutions and agencies involved in HTA; keep monitoring and reviewing assessments and priorities.^{3,5} Criteria for priority setting have a central role in every model and are different or show different weights in the various methodologies.⁶

Noorani et al. reviewed the criteria for priority setting in 2007.⁶ HTA agencies usually used criteria taking into account clinical and economic impact and the burden of the disease, but they generally ignored the potential availability of new technologies in the near future, the variation in their rates of use, and their ethical, legal, or psychosocial implications. Above all, the review from Noorani et al. highlighted the limited participation of stakeholders in most of the analyzed prioritization processes.⁶ In fact, only the US Agency for Healthcare Research and Quality (AHRQ) explicitly involved stakeholders (a volunteer group including clinicians, re-

searchers, third-party payers, consumers of Federal and State beneficiary programs, and healthcare industry professionals) in their priority setting methods.⁶

These considerations eventually led many HTA agencies to renew and improve their priority setting methods and, among others, even the Donaldson method was updated.⁵

How and how much have these criteria changed in Europe in recent years? Aim of this review is to provide an overview of criteria for priority setting in HTA, either published in the literature or promoted by the European HTA agencies that are members of the INAHTA.

METHODS

In order to identify criteria used for priority setting in Europe, a systematic literature review was performed on PubMed and on the websites of HTA Agencies belonging to the INAHTA. The literature review on PubMed was carried out without any starting date and up to 30 November 2014. The algorithm for the search was as follows: (priority setting OR setting priorities OR priority setting criteria OR prioritisation criteria) AND (health technology assessment OR Technology assessment OR HTA OR technologies evaluation) AND (“Europe”[MeSH Terms] OR Europ* OR Austria OR Belgium OR Bulgaria OR Croatia OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Finland OR France OR Germany OR Greece OR Hungary OR Ireland OR Italy OR Latvia OR Lithuania OR Luxembourg OR Malta OR Netherlands OR Norway OR Poland OR Portugal OR Romania OR Russia OR San Marino OR Serbia OR Slovakia OR Slovenia OR Spain OR Sweden OR Switzerland OR United Kingdom). The search was restricted to full-text articles published in English. Articles found on PubMed were screened according to titles and abstracts with respect to the following inclusion criteria:

- setting of the study: European countries;
- objective of the study: provision of criteria for priority setting in HTA.

Articles were excluded if they addressed only methods used to develop priority setting criteria or dealt with priority setting in fields other than HTA (clinical research, public expenditure, adoption of technologies, health care organization, etc.). Reviews were also excluded, even though their references were checked for potential eligible primary studies. The full text of potential eligible articles was retrieved and assessed for final inclusion in the review. The screening process of eligible articles was performed by two researchers independently and disagreements were solved with the involvement of a third one. From articles finally included in the review the following data were extracted and reported in **table 1**: author, country, objective, methods, identified criteria.

The websites of European HTA Agencies were accessed through the INAHTA platform. Each website was screened through the use of the following key words in the query box: priority setting, prioritization, decision making, horizon scanning, HTA. Each report or documentation dealing with priority setting frameworks and prioritization criteria applied in

the selection of the technologies submitted to HTA was read and assessed for eligibility. Tables were used to report both information about agencies (country, date of foundation, population served) and suggested criteria.

RESULTS

The search on PubMed identified a total of 121 articles, of which seven^{5,7-12} satisfied the inclusion criteria and were considered in the qualitative review (figure 1).

The included articles involved a total of 6 European countries: the Netherlands (2 articles), Germany, Hungary, Lithuania, Spain, and the UK. All articles dealt with the development of a theoretical framework which resulted in procedures and criteria for the priority setting process.

From a methodological point of view, a Delphi technique with weighting of criteria was adopted by Jankauskiene et al.⁷ and Berra et al.⁵ Oortwijn et al.^{11,12} used a rating and weighting system based on both scientific and societal criteria in order to propose a new multi-steps procedure for prioritization. A theoretical priority-setting framework was developed by Bastian et al.⁸ using a poll and the principles of multi-criteria decision analysis and involving patients and the general public. Finally, Gulacsi et al.⁹ and Townsend et al.¹⁰ drew on international experiences to develop their models.

The prioritization criteria resulting from the articles are summarized in table 1. The most reported criteria were: potential benefits; costs/cost effectiveness associated to the introduction of the new technology; burden of disease.

The search on the European HTA agency websites showed 14 reported prioritization criteria out of 30 (table 2). Five agencies also reported the description of the priority setting process (GÖG, LBI-HTA, AETS, AVALIA-T, OSTEBEA). AVALIA-T reported a scoring and weighting process, as well.

Twelve out of 14 agencies considered as criteria the «economic impact/costs/maintenance costs» and 11 the «impact on ethical, social, cultural and/or legal aspects» (table 3). «Frequency of disease» was reported by 9 out of 14, «burden of disease» by 8, and «impact on clinical practice» by 7. All other criteria were adopted by less than 50% of agencies (table 3).

DISCUSSION

Priority setting has been defined as the best way to organize effective and explicit resource allocation systems.¹³ Growing attention has been paid to this issue over time because of its relevance for decision making. In fact, priority setting is used as a tool for rationing resources in several contexts, from public policies and economy to healthcare. With respect to the latter, priority setting is considered necessary to fairly allocate resources in the delivery of healthcare.¹⁴ It is also needed in order to appropriately allocate resources for the assessment of health technologies, given the fact that this is a time- and resource-consuming process and that more and more health technologies enter the market each year.

Demographic and epidemiological changes and consumer empowerment have determined an increase in health demand and pressure and competition among companies is rising. Nevertheless, although a standardization of criteria and methods has been developed for the application of HTA,¹⁵ the same is not completely true for priority setting in HTA. At any rate, the interest and experiences available in the field are growing both nationally and internationally. In particular, at the international level, methodological efforts are being made to define recommendations and frameworks for proper priority setting that emphasize transparency.³⁻⁴ Application of the different methodologies has led to the development and definition of several criteria as shown by Noorani et al.⁶ and by our review. Noorani et al.⁶ also grouped criteria used by HTA agencies for priority setting in categories which could represent the starting point for an in-depth discussion involving all relevant stakeholders. This discussion should be conducted by a multidisciplinary group representative of all the European countries and including public participation and citizen involvement.^{16,17} It should also rely on a structured and standardized approach calling for the identification of criteria for priority setting and the role to be played by the various stakeholders. These two issues have been addressed by the Health Policy Forum (HPF) of the Italian Society of HTA (SIHTA) in a paper contributing to the definition of priority setting in the Italian National Health Service.¹⁸

The final aim of the multidisciplinary European discussion should be the delivery of a shared document encompassing categories of criteria to be considered as pillars of the priority setting process across Europe. This is particularly relevant in consideration of the EU 24/2011 directive on the cross-border

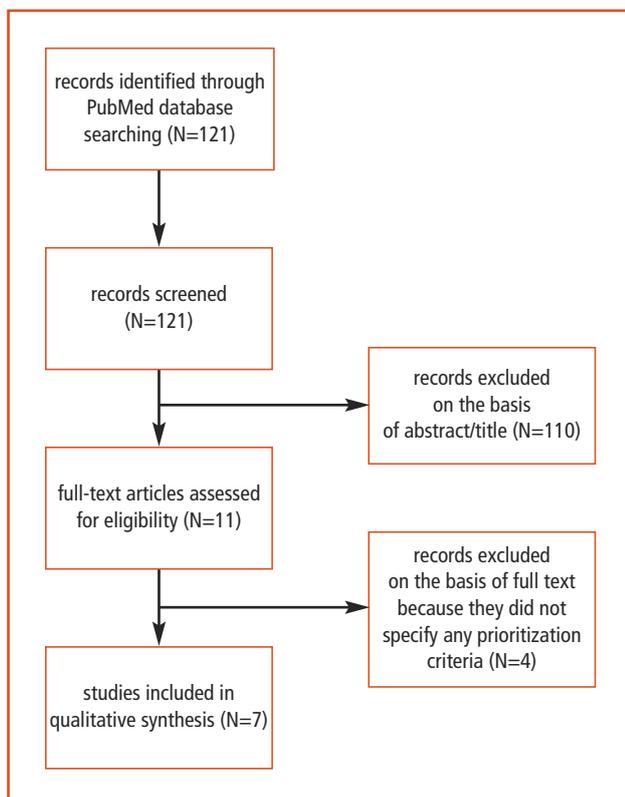


Figure 1. Flow chart of study selection.

Figura 1. Flow chart della selezione degli studi.

First author/ publication date	Objective	Methods	Identified criteria
Jankauskiene D 2013 ⁷	To design a model for HTA priority setting, which would address national needs for a country with little experience in the field of HTA, and assess its feasibility for the health system.	A three-round Delphi study was conducted in the form of an electronic questionnaire distributed to a panel of national experts.	<ul style="list-style-type: none"> ■ health benefit ■ evidence ■ timeliness ■ expected level of interest from policy makers ■ ethical, legal, and social implications
Bastian H 2011 ⁸	To develop a priority-setting framework based on the interests of patients and the general public.	A poll was used to determine level of lay and health professional interest and needs.	<ul style="list-style-type: none"> ■ patients' concerns ■ patients' information seeking ■ patients' use
Berra S 2010 ⁵	To review the set of criteria of the Institute of Medicine (IOM) for priority-setting in research with identification of potential new criteria, and to develop and evaluate the reliability and validity of the final priority score.	A three-round modified Delphi technique was used to identify, rate, and weigh criteria for priority setting.	<p><i>Traditional criteria</i></p> <ul style="list-style-type: none"> ■ prevalence of the condition (or use of service) ■ cost of services to manage the condition ■ variation in use of the service ■ burden and importance of the illness ■ potential to change health outcomes ■ potential to change costs ■ potential to inform ethical, legal, or social issues <p><i>New criteria</i></p> <ul style="list-style-type: none"> ■ financial opportunity ■ potential to translate new knowledge into clinical or health service practice ■ political interest ■ need for knowledge about the problem
Gulacsi L 2004 ⁹	To outline the needs and current development of the "fourth hurdle" (i.e., requirement of effectiveness and cost-effectiveness data for drug coverage policy decisions) in Hungary.	International experiences were considered.	<ul style="list-style-type: none"> ■ evidence ■ effectiveness ■ cost-effectiveness
Townsend J 2003 ¹⁰	To develop a method of economic evaluation and triage for prioritization, before the funding decision.	Existing models were reviewed on the basis of the EUR-ASSESS project and authors' previous experience.	<ul style="list-style-type: none"> ■ impact of research results on policy and practice ■ effects on health benefits ■ costs ■ cost-effectiveness
Oortwijn WJ 2002 ¹¹	To provide a new procedure and one of the first examples of the application of theoretical principles for priority setting.	Different procedures for categorizing, scoring, and weighting policy criteria were defined and different classification strategies were explored.	<ul style="list-style-type: none"> ■ burden of disease ■ benefit for the patient ■ number of patients ■ direct costs of the intervention per patient ■ financial consequences of applying the intervention over time (impact on total costs of health care) ■ additional aspects with an impact on health policy (i.e., rapid uncontrolled diffusion)
Oortwijn WJ 1999 ¹²	To describe a new model proposed by the Health Insurance Council for the definition of priorities based not only on scientific criteria but also on societal criteria.	Different procedures for categorizing, scoring, and weighting policy criteria were defined and different classification strategies were explored.	<ul style="list-style-type: none"> ■ burden of disease ■ Uncertainty about the (cost-)effectiveness of the intervention ■ potential benefits of the research project ■ potential impact on healthcare

Table 1. Characteristics of studies included from PubMed.

Tabella 1. Caratteristiche degli studi inclusi da PubMed.

der healthcare, which entails harmonization of practices.¹⁹ In order to comply with the EU directive, the HTA network was established: it aims to facilitate an efficient use of HTA resources in Europe, create a sustainable system of HTA knowledge sharing, and promote good practice in HTA methods and processes.²⁰ In our view, the first goal entails working on the development of a structured and shared approach to priority setting. Our focus on Europe was justified by these recent developments in the HTA landscape. However, the extra-European perspective and priority setting systems – such as those

reported by Noorani et al.⁶ from several extra-European agencies belonging to Canada, USA, and Israel – may also be taken into consideration in the discussion.

Categories and criteria resulting from the multidisciplinary discussion should undergo a validation at European level so they may be adopted and tailored to each specific context for – as also stated in the SIHTA HPF document – prioritization criteria may assume different weight according to the specific health system model and the level of evaluation.¹⁸

In this process of drawing up a shared document, assessment

Country	HTA agency	Year of foundation	Description of population served
Austria	GÖG – Gesundheit Österreich GmbH	2006	National
	LBI-HTA – Ludwig Boltzmann Institute for Health Technology Assessment	2006	National
Belgium	KCE – Belgian Health Care Knowledge Centre	2002	National
Denmark	HTA-HSR/DHTA – HTA & Health Services Research	1999	National
Finland	FinOHTA – Finnish Office for Health Technology Assessment	1995	National
France	CEDIT – Comité d'Évaluation et de Diffusion des Innovations Technologiques	1982	Paris region
	HAS – Haute Autorité de Santé	2005	National
Germany	DAHTA @ DIMDI- German Agency for HTA at the German Institute for Medical Documentation and Information	2000	National
	G-BA – The Federal Joint Committee (Gemeinsamer Bundesausschuss)	2004	Germans with public health insurance
	IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	2004	*
Ireland	HIQA – Health Information and Quality Authority	2007	National
Italy	Agenas – Agency for Regional Healthcare	1993	*
	ASSR – Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care)	1998	Regional (Emilia-Romagna)
	UVT-HTA Unit in A. Gemelli Teaching Hospital	2001	*
Lithuania	VASPVT – State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	1996	National
Luxembourg	CEM – Inspection générale de la sécurité sociale (IGSS) Cellule d'expertise médicale	2010	*
Norway	NOKC – Norwegian Knowledge Centre for the Health Services	2004	National
Poland	AHTAPol – Agency for Health Technology Assessment in Poland	2005	National
Spain	AETS – Agencia de Evaluación de Tecnologías Sanitarias	1994	National
	AETSA – Andalusian Agency for Health Technology Assessment	1996	Andalusian Region
	AQuAS – Agència de Qualitat i Avaluació Sanitàries de Catalunya	2010	Catalonian Region
	AVALIA-T – Galician Agency for Health Technology Assessment	1999	Galician Region
	OSTEBA – Basque Office for Health Technology Assessment	1992	Basque Region
Sweden	SBU – Swedish Council on Technology Assessment in Health Care	1987	National
The Netherlands	ZonMw – The Netherlands Organisation for Health Research and Development	2001	The Netherlands
	ZIN – Zorginstituut Nederland	2001	*
United Kingdom	CRD – Centre for Reviews and Dissemination	1994	England, Northern Ireland and Wales
	HIS – Healthcare Improvement Scotland	*	National
	NIHR – National Institute for Health Research	2008	United Kingdom

*no available data

Table 2. HTA agencies consulted.

Tabella 2. Agenzie di HTA consultate.

of priority setting efforts and results should also be considered. It should be based on criteria such as those proposed by Sabik and Lie.¹⁴ According to their publication, the first criterion might be ensuring adequate public input in the process, which calls for public participation.^{16,17} The second might be the adoption of appropriate principles, including the evaluation of costs and benefits.¹⁴ In this respect, although the EUR-ASSESS project³ recommended to evaluate the costs and benefits of the assessment process, the latter were not well represented in the priority setting frameworks identified by the literature review.⁶ The third criterion concerns the impact on policy and practice.¹⁴ The SIHTA HPF addressed the requisites needed to have an impact on HTA with priority setting.¹⁸ Among them, the following have been reported and, in our view, may play an important role:

clearness of the question to be addressed, accountability and sharing of methods and results of priority setting, and timeliness of the evaluation.

Aim of this review has been to contribute to the supranational discussion on the topic and to posing the challenge of harmonization and sharing of priority setting practices. Our search, performed by assessing both the scientific literature and the deliverables of HTA agencies, has shown that available evidence cannot be considered particularly copious and definitive. On the other hand, as the results of the literature review performed on PubMed show, there is a considerable interest of the scientific community in the topic. It is therefore time to come to an agreement and to put it in practice.

Conflicts of interest: none declared

Criteria	A G E N A S	A E T S	A E T S A	A H T A P O I	A V A L I A	C E D I T	D A H T A	F I N O H T A	G O G	L B I - H T A	O S T E B A	S B U	N I H R - H S C	Z O N M W	Total (%)
disease frequency	x	x			x		x	x	x	x	x	x			9 (64%)
burden of disease	x	x			x		x		x	x			x	x	8 (57%)
patient preferences					x										1 (7%)
public interest	x						x		x						3 (21%)
frequency of use of the technology					x				x	x				x	4 (29%)
controversial nature of the technology		x							x	x					3 (21%)
technical performance									x						1 (7%)
efficacy/effectiveness/validity	x		x		x	x				x					6 (43%)
Impact on health/quality of life	x	x	x							x	x	x			6 (43%)
risks/safety					x	x									2 (14%)
economic impact/costs/maintenance cost	x	x	x	x	x	x	x		x	x	x	x		x	12 (86%)
organizational impact	x	x	x	x							x	x			6 (43%)
impact on clinical practice	x			x			x	x			x	x		x	7 (50%)
risk of inappropriate use of the technology	x		x												2 (14%)
impact on ethical, social, cultural and/or legal aspects	x	x	x		x	x	x			x	x	x	x	x	11 (79%)
likelihood that HTA results are going to be implemented									x						1 (7%)
impact of HTA results/dissemination of technology			x						x		x		x		4 (29%)
availability of scientific evidence	x	x						x	x		x			x	6 (43%)
number of criteria proposed by agency	11	8	7	3	8	4	6	3	10	8	8	6	3	6	

Table 3. Prioritization criteria proposed by HTA agencies. / **Tabella 3.** Criteri di prioritizzazione suggeriti dalle agenzie di HTA.

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WORKSHOP 7
Thursday 15 October
h. 14.00-15.30
Brown Room 1

Genetic testing and economic evaluations: a systematic review of the literature

Test genetici e valutazioni economiche: una revisione sistematica della letteratura

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Abstract

Objectives. To identify those studies in which economic analysis of predictive genetic and pharmacogenetic testing programs have been carried out. Since the Italian National Prevention Plan 2014-2018 foresees the implementation of genetic testing for inherited breast cancer, special attention was given to the cost-effectiveness of *BRCA1/2* testing programs.

Methods. A systematic review of primary economic evaluations (EEs) of predictive genetic and pharmacogenetic testing programs and an overview of previously published systematic reviews of economic evaluations (ERs) was performed.

Results. Overall 128 EEs and 11 ERs were identified. The methodological quality of both EEs and ERs was good on average. Both predictive genetic and pharmacogenetic testing programs were mainly concerned with oncological diseases. Seventeen percent of genetic testing programs are cost-saving, while a further 44% of cost/QALY ratios fall under the commonly used threshold of €37,000 per QALY. For *BRCA1/2* testing, only cascade genetic screening programs, targeted to close relatives of carriers, show clear evidence of cost-effectiveness.

Conclusion. Despite some limitations, EEs and ERs are powerful tools that provide indications to policy-makers on which genetic testing programs might be introduced into health care systems and public health practice.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 45-50)

Key words: genetic tests, pharmacogenetic tests, *BRCA1/2*, cost-effectiveness, systematic review

Riassunto

Obiettivi. Identificare le analisi economiche dei programmi sanitari dei test genetici predittivi e farmacogenetici. Particolare attenzione è stata data ai test genetici *BRCA1/2*, in quanto il Piano Nazionale della Prevenzione 2014-2018 prevede la realizzazione di programmi di prevenzione del carcinoma ereditario della mammella.

Metodi. È stata svolta una revisione della letteratura economica di studi primari (valutazioni economiche, EE) e secondari (revisioni sistematiche, ER) finalizzata alla valutazione dei programmi sanitari genetici.

Risultati. Sono state identificate 128 EE e 11 ER. Sia gli studi primari sia i secondari hanno una buona qualità metodologica. I programmi genetici più frequentemente analizzati sono quelli relativi a patologie oncologiche. L'analisi dei rapporti costo-utilità ha evidenziato che il 17% dei programmi sono cost-saving e il 44% risulta sotto la soglia di €37.000 per QALY. Lo screening genetico *BRCA1/2* "a cascata" sui parenti dei portatori ha chiare evidenze di costo-efficacia.

Conclusione. Nonostante alcune limitazioni, EE e ER sono potenti strumenti di guida per l'implementazione di programmi di screening genetico.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 45-50)

Parole chiave: test genetici, test farmacogenetici, *BRCA1/2*, costo-efficacia, revisione sistematica

INTRODUCTION

As genomic technologies develop and groundbreaking research is translated into a better understanding of its implications for clinical practice, public and policy-makers' interest increases and effective genetic testing is carving out a thriving piece in

health care systems and public health policies. For example, in Italy, the National Prevention Plan 2014-2018 has recently introduced genetic testing for *BRCA* as a preventive strategy aimed at reducing the incidence of inherited breast and ovarian cancer, delegating to Italian Regions the most appropriate

local planning of *BRCA* genetic testing programs.¹ Thus the promise of predictive medicine is gradually becoming a reality in public health care and this trend is likely to increase for the foreseeable future.

Despite the prominence of frontline research, the vast majority of potential genetic/genomic applications (tests or interventions) have not yet been implemented into clinical practice; indeed, it is estimated that not more than 3% of published research focuses on the translation from experimental genetic/genomic applications to evidence-based guidelines and health care practice.² Thus, this “implementation research” receives relatively little attention, with few genetic and genomic applications actively considered for introduction into clinical practice.^{2,3} One barrier to such implementation is a lack of appreciation of the cost-benefit of new testing regimes, particularly pertinent nowadays, when health care systems are under financial pressure. Therefore, economic evaluations of candidate technologies should benefit clinicians and public health officials when deciding which genetic tests to introduce, how to manage carriers and non-carriers, and how to assess the impact of testing on health-related quality of life.⁴ In fact, economic analysis allows one to collect and integrate all relevant factors linked to genetic testing (prevalence of disease and mutation, specificity and sensitivity of the test, association between genotype and phenotype, efficacy of interventions in preventing disease) and to estimate the benefits and costs of an entire health care program, beginning with the characteristics of a target population and continuing with preventive surveillance, prophylactic treatments and consequent follow-up.^{4,5} This review aims to map which economic studies have been conducted concerning genetic and pharmacogenetic testing programs. Since the Italian National Prevention Plan 2014-2018 foresees the implementation of nationwide genetic testing for inherited breast cancer, special attention is given to full economic evaluations of *BRCA1/2* testing programs.

METHODS

We performed a systematic review of primary economic evaluations (EEs) of predictive genetic and pharmacogenetic testing programs and an overview of previously published systematic reviews of such economic evaluations (economic reviews, ERs).

Literature search and eligibility criteria

Two investigators independently searched Medline, Embase, NHS Health Economic Evaluations Database, the HTA database, the Cost-effectiveness Analysis (CEA) Registry, and the Cochrane database of systematic reviews from inception to the end of 2012 for EEs and ERs of genetic testing programs, using the following search terms: “genetic* OR pharmacogenetic*”, “economic evaluation* OR cost-effectiveness OR cost-utility OR cost-benefit OR cost-minimization OR QALY* OR LYG*”, “systematic review”. A manual review of references from eligible EEs and ERs was also performed. Titles, abstracts and full texts of the resulting papers were examined in detail, and discrepancies were resolved by consensus. Articles were considered eligi-

ble if the authors had performed a full economic evaluation (for primary studies, EEs) or they had included only full economic evaluations (for systematic reviews, ERs) related to the implementation of genetic tests in health care programs.

Data extraction and quality assessment

For each EE, in addition to information on authors, journal, funding declaration and year of publication, the following data were recorded: type of economic evaluation (cost-utility, cost-effectiveness, cost-benefit, or cost-minimization analysis), analytical approach, outcome measures, study perspective, collection of cost and effectiveness data, time horizon, discounting, sensitivity analyses, setting, target population, gene and clinical condition, testing scope, health care pathways triggered by test results. The quality of the studies was assessed independently by two raters using the Quality of Health Economic Studies (QHES) scale.⁶

From each eligible ER, two investigators abstracted information independently on first author, year of publication, outcomes examined, number of included studies, and reported summary results (target population, gene and clinical condition, testing scope). Since no quality assessment checklists exist in the literature to evaluate ERs, the methodological quality of each ER was assessed with a tool developed from three available methodological handbooks that deal with the systematic review of economic evaluations.⁷⁻⁹

Data synthesis

Given the considerable heterogeneity of EEs, the combination of results by quantitative meta-analysis was not possible, and therefore a descriptive synthesis was performed. Due to the large quantities of data synthesized and results generated, we have reported here only those details of incremental cost-effectiveness ratios for *BRCA* testing strategies, which thus serve as an example and case study. A descriptive analysis of the ERs of genetic testing programs was also performed.

RESULTS

A total of 758 studies were retrieved from electronic databases; a further 45 articles were obtained from other sources, including a review of references cited in the 758 studies initially identified. After removing duplicates and screening for title/abstract, 190 and 23 full-text articles were assessed for eligibility as EEs and ERs, respectively. Double screening and review of these yielded 128 EEs and 11 ERs that met the inclusion criteria (for the PRISMA flow diagram, see the [Appendix](#), available online).

Economic evaluations (EEs)

The 128 EEs included in this study (see the [Appendix](#) for references) mainly originated from the U.S. (62 EEs, 48%) and Europe (46 EEs, 36%) with only a few carried out in Asian countries (9 EEs), Canada (7 EEs), and Australia (4 EEs). Cost-utility analysis (CUA) was the methodology most frequently used (73, 57%), followed by cost-effectiveness analysis (CEA) (67%). Sixty-seven EEs (52%) adopted the health care system

perspective, 39 EEs (30%) the societal perspective and seven EEs performed the economical evaluation from the perspective of third-party payers; in 15 EEs the analytical perspective was not reported. The time horizon was lifetime in more than half of the studies (69 EEs, 54%); thirteen pharmacogenetic tests adopted a time horizon of less than one year. In terms of effectiveness, outcome measures were different according to the test category: for predictive genetic testing programs the results were mainly presented as LYGs, while for pharmacogenetic testing programs the outcomes most frequently used were QALYs (table 1).

The mean quality assessment score of all 128 EEs was 78, indicating good average quality. Almost 40% of studies were published after 2009 and these were assigned an average score slightly higher than those published prior to that year (81 vs 74). No significant differences in quality were detected between EEs of predictive genetic and pharmacogenetic tests (table 1). Predictive genetic testing programs (66, 52%) were more often studied than pharmacogenetic testing programs (62, 48%). Predictive genetic testing programs were mainly concerned with prevention of oncological diseases (40%), in particular hereditary colorectal syndromes (Lynch syndrome and familial adenomatous polyposis) and hereditary breast and ovarian cancer syndrome. Less studied were genetic tests for some inherited disorders such as hereditary haemochromatosis, cystic fibrosis, chromosomal abnormalities, and thrombophilia. Other disorders such as familial hypercholesterolemia, fragile X syndrome, long QT syndrome, and hypertrophic cardiomyopathy were evaluated in only a few studies (table 1). Most EEs of pharmacogenetic testing programs were concerned with the analysis of genetic information from patients with neoplastic disorders (breast, colorectal, and lung cancer) to target specific drug therapies (23, 37%). Genetic variations associated with anticoagulation treatment for venous thromboembolism were evaluated in nine EEs (14%). Pharmacogenetic tests for chronic viral diseases such as AIDS and hepatitis C were studied in 11 EEs (18%). Six studies assessed pharmacogenetic tests for the detection of thiopurine methyltransferase (TPMT) mutation carriers before therapy with thiopurine drugs; this allowed optimal dosage to be determined and toxicity to be minimized in patients with inflammatory bowel disease, rheumatic conditions, or acute lymphoblastic leukemia. A small number of studies also evaluated pharmacogenetic tests for depression and chronic kidney disease (table 1).

CUA is the most recommended method of economic evaluation according to widely accepted guidelines, because it incorporates quality of life measures and enables standardized comparisons across studies.¹⁰ A total of 73 CUAs were retrieved in this study, of which 66 are also included in the CEA Registry, which is the most comprehensive and recent source of CEAs available.¹¹ From these 66 CUAs, a total of 138 incremental cost-effectiveness ratios were extracted and expressed as 2013 Euros per QALY gained. The majority (68%) of cost/QALY ratios indicate that genetic testing programs provide better health outcomes although at higher cost, with al-

most half the ratios falling below €37,000 per QALY, a commonly used threshold. Seventeen percent of genetic testing programs are cost-saving. Pharmacogenetic testing programs are more likely to be cost-saving, but predictive genetic tests more frequently result in cost-effectiveness ratios below the threshold of €37,000 per QALY (figure 1).

Economic reviews (ERs)

The 11 ERs included in this study were performed in Canada,¹²⁻¹⁵ the US¹⁶⁻¹⁸ and Europe (Netherlands, UK, and Germany),¹⁹⁻²² from 2003 to 2012.^{15,20} Two ERs focused on predictive genetic testing programs,^{15,19} five on pharmacogenetic tests,^{13,17,18,21,22} and three investigated both genetic testing programs.^{12,14,16} The majority of these ERs were conducted to assess the methodological quality of EEs of genetic tests,^{12-16,21} or to simply identify those economic studies conducted in the field,^{17,18,21} since they included a wide range of genetic tests. Only two ERs focused on a specific genetic test.^{20,22}

Almost all ERs evaluated the methodological quality of the primary studies using different standardized tools.^{12-14,16,18-22} The most common limitations of primary studies found by the ERs were: lack of a defined analytical perspective;^{12,14,16,19,21} lack of coherence between perspective of analysis and costs;¹⁹ inappropriate sensitivity analyses;^{12,19,21} no discussion of potential bias.^{12,14,16} Other methodological deficiencies were the absence of definitions of time horizon and discount rate.^{13,14,19,21}

The ERs themselves were of good or moderate quality. Almost all ERs formulated a clear research question and used appropriate eligibility criteria for the inclusion of primary studies, but the methodology for the identification and selection of primary studies was judged appropriate in only half of the ERs (data not shown).

Cost-effectiveness of BRCA genetic testing programs

BRCA1/2 mutations account for about 5-10% of all breast cancers and for around 15% of ovarian cancers overall.²³ Harmful mutations in *BRCA1* and *BRCA2* have high penetrance, dramatically increasing lifetime risk of developing breast and ovarian cancers (45-65% breast and 11-39% ovarian cancer).²⁴ *BRCA* genetic testing is a powerful tool for reducing the incidence of these inherited cancers. Nine EEs that compared different strategies for determining the most efficient use of such tests were retrieved after a systematic search (updated to Jan 2015). Three main programs were analyzed in these EEs: population-based genetic screening,²⁵⁻²⁷ family history (FH)-based screening and,²⁸⁻³⁰ and cascade genetic screening.^{31,32} Population-based genetic screening was assessed for the Ashkenazi Jewish community in three EEs in which *BRCA1/2* tests were offered to all women regardless of their individual or familial risk.²⁵⁻²⁷ Cost-effectiveness results were more favourable if women underwent prophylactic surgery (mastectomy and salpingo-oophorectomy), varying from cost-saving to \$8,300 per QALY. Three EEs described a FH-based screening program in which only high risk women were tested, with the risk assessment based principally on the family history.²⁸⁻³⁰ This ap-

Table 1. Main characteristics of full economic evaluations (EEs) of predictive genetic and pharmacogenetic tests.

Tabella 1. Principali caratteristiche delle valutazioni economiche complete dei test genetici e farmacogenetici.

	Predictive genetic test	Pharmacogenetic test	Total
	EEs (%)	EEs (%)	EEs (%)
Type of economic evaluation			
CUA	20 (30.3)	37 (59.7)	57 (44.5)
CEA	34 (51.5)	16 (25.8)	50 (39.1)
CEA & CUA	9 (13.6)	7 (11.3)	16 (12.5)
CBA	2 (3.1)	1 (1.6)	3 (2.3)
CBA & CEA	1 (1.5)	--	1 (0.8)
CMA	--	1 (1.6)	1 (0.8)
Analytical perspective			
health care system	28 (42.4)	39 (62.9)	67 (52.3)
societal	22 (33.3)	17 (27.4)	39 (30.5)
third-party payer	5 (7.6)	2 (3.2)	7 (5.5)
n.r.	11 (16.7)	4 (6.5)	15 (11.7)
Time horizon			
lifetime	39 (59.1)	30 (48.4)	69 (53.9)
>1 year	7 (10.6)	13 (21.0)	20 (15.6)
≤1 year	4 (6.1)	13 (21.0)	17 (13.3)
n.r.	16 (24.2)	6 (9.6)	22 (17.2)
Outcome measures of effectiveness			
LYGs	24 (36.4)	2 (3.2)	26 (20.3)
QALYs	21 (31.8)	37 (59.7)	58 (45.3)
LYGs & QALYs	7 (10.6)	5 (8.1)	12 (9.4)
cases detected	8 (12.2)	1 (1.6)	9 (7.0)
disease-free newborns	2 (3.0)	--	2 (1.6)
cancer-free years	1 (1.5)	--	1 (0.8)
adverse effects avoided	1 (1.5)	8 (13.0)	9 (7.0)
monetary units	1 (1.5)	1 (1.6)	2 (1.6)
patients cured	--	1 (1.6)	1 (0.8)
others	--	4 (6.4)	4 (3.1)
n.r.	1 (1.5)	3 (4.8)	4 (3.1)
Quality score (QHEs scale)			
0-25	--	--	--
26-50	4 (6.1)	4 (6.4)	8 (6.3)
50-75	27 (40.9)	19 (30.6)	46 (35.9)
76-100	35 (53.0)	39 (63.0)	74 (57.8)
type of disease			
hereditary colorectal cancer	17 (25.7)	--	17 (13.3)
hereditary breast/ovarian cancer	9 (13.6)	--	9 (7.0)
hereditary haemochromatosis	6 (9.1)	--	6 (4.7)
cystic fibrosis	6 (9.1)	--	6 (4.7)
chromosomal abnormalities	6 (9.1)	--	6 (4.7)
thrombophilia	5 (7.6)	--	5 (3.9)
familial hypercholesterolemia	3 (4.5)	--	3 (2.3)
fragile X syndrome	2 (3.0)	--	2 (1.6)
long QT syndrome	2 (3.0)	--	2 (1.6)
hypertrophic cardiomyopathy	2 (3.0)	--	2 (1.6)
breast cancer	--	15 (24.3)	15 (11.7)
venous thromboembolism	--	9 (14.5)	9 (7.0)
AIDS	--	8 (12.9)	8 (6.3)
colorectal cancer	--	5 (8.1)	5 (3.9)
inflammatory bowel disease	--	4 (6.5)	4 (3.1)
chronic hepatitis C	--	3 (4.8)	3 (2.3)
lung cancer	--	3 (4.8)	3 (2.3)
major depressive disorder	--	3 (4.8)	3 (2.3)
chronic kidney disease	--	2 (3.2)	2 (1.6)
acute lymphoblastic leukaemia	--	2 (3.2)	2 (1.6)
rheumatic diseases	--	2 (3.2)	2 (1.6)
others	8 (12.3)	6 (9.7)	14 (10.9)
Total	66 (100)	62 (100)	128 (100)
CUA: cost-utility analysis; CEA: cost-effectiveness analysis; CBA: cost-benefit analysis; CMA: cost-minimization analysis; EE: economic evaluation; n.r.: not reported; LYGs: life years gained; QALYs: quality-adjusted life years gained			

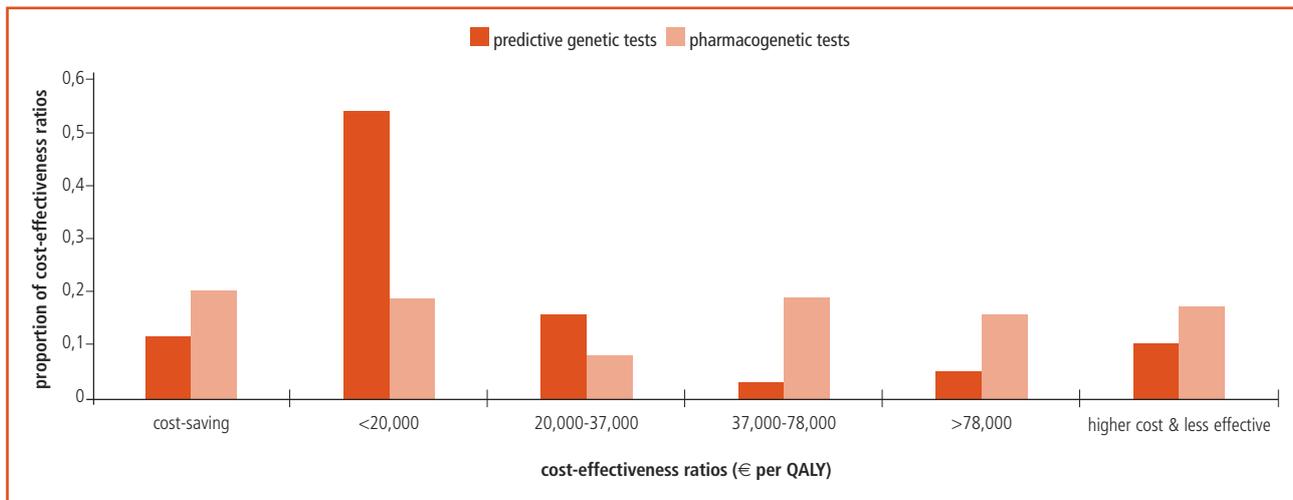


Figure 1. Distribution of cost-effectiveness ratios (€ per QALY gained) for genetic and pharmacogenetic tests (N=138 ratios).

Figura 1. Distribuzione dei rapporti di costo-efficacia (€ per QALY guadagnato) per i test genetici e farmacogenetici (N=138 rapporti).

proach proved cost-effective (\$4,294 per LYG, \$3,500-5,000 per QALY), but the costs of the identification of high-risk women were not considered. In both of the two EEs that focused on cascade genetic screening, BRCA tests were offered to close relatives of previously identified carriers (known familial mutation) and were cost-effective (\$32,670 per QALY, €832 per LYG).³¹⁻³² Finally, one EE investigated genetic screening among women with breast cancer to prevent both ipsilateral (if they were treated with breast-conserving therapy) and contralateral cancer recurrence, in addition to ovarian cancer.³³ This strategy was cost-effective only for particular conditions.

DISCUSSION

The results of the exercise conducted in this study clearly show that genetic testing is a major theme in health economics, with many examples in the literature of full EEs and ERs covering a wide range of diseases. Nevertheless, a remarkable number of genetic tests have not yet been evaluated, including some with demonstrated clinical utility that are related to diseases with high health burden and/or high expenditure (e.g., melanoma, congenital disorders assessed using a newborn screening panel, epilepsy, trigeminal neuralgia, chronic gout, Huntington's disease).³⁴ However, since the economic health literature was only searched for papers published up to the end of 2012, it is possible that many emerging tests and currently available tests are not included in the present review. By contrast, most genetic tests assessed by EEs have not been evaluated for clinical effectiveness;^{35,36} this could prematurely move genetic testing toward practice with potentially adverse effects for patients and the health care system.³⁷

Only 12% of predictive genetic tests and 21% of pharmacogenetic tests are cost-saving. The majority of the cost-utility ratios indicate that these tests provide better health care, but at higher cost. These results are consistent with the findings of a previous review of EEs of personalized medicine tests,³⁵ indicating that genetic testing can save money only in a small minority of cases. However, these results are in line with those

from other fields, where it was shown that less than 20% of preventive measures and treatments for existing conditions are cost-saving.³⁸ Of more concern is the absence of demonstrated clinical utility for a significant proportion of genetic tests. Therefore, some genetic tests may not be cost-effective because of a lack of demonstrated clinical utility.^{35,36} On the other hand, more reassuring is the methodological quality of the economic evaluations retrieved, which is good on average and may be improving over time.

The principal limitations of conducting a systematic review of economic evaluations derive from their high degree of heterogeneity, meaning that results cannot be pooled across studies and are difficult to investigate with current statistical methods.^{13,14,16,17} Nevertheless, even using descriptive approach only, exhaustive reviews of economic evaluations may usefully inform stakeholders and policy-makers of the potential for cost-effectiveness interventions.^{14,15,18} Thus, in the example we used, *BRCA1/2* genetic testing, a systematic review of cost-effectiveness analyses clearly illustrates that there is evidence of cost-effectiveness only for genetic testing targeted to populations at high risk, such as the close relatives of carriers (cascade genetic screening programs). Despite these findings, FH-based screening programs are very promising, but the published EEs did not include the costs of the selection process of high-risk women through a familial risk assessment. Therefore, at least in Italy, only cascade genetic screening programs can be considered ready at present for a full implementation in health care.

In conclusion, full EEs of genetic tests and ERs are potentially very useful for providing indications to policy-makers by which genetic applications could be introduced into general health care and public health practice. However, many genetic tests have not yet been subjected to formal EE and, perhaps most importantly, many genetic tests have not been demonstrated to have clinical utility. EEs, particularly those using rigorous modelling exercises, could also be useful for the selection of genetic/genomic applications that are most promising in terms of value for money and may thus direct and prioritize research efforts.

Conflicts of interest: part of the work described in this paper is connected to the project «L'impatto economico dei test genetici sul Servizio Sanitario Nazionale (SSN): valutazione dei percorsi diagnostico-assistenziali, stime di costi-efficacia e costi-utilità e analisi delle politiche sanitarie a livello europeo» (The

economic impact of genetic testing on the National Health Service: evaluation of diagnostic care pathways, estimates of cost-effectiveness and cost-utility and investigation of health policies at European level), funded by the Italian Ministry of Health.

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COMMUNICATIONS C17
Thursday 15 October
h. 11.30
Amber Room 1

HPV vaccination for boys? A systematic review of economic studies

Vaccinazione anti-HPV anche per i maschi? Una revisione sistematica degli studi farmaco-economici

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Abstract

Introduction. HPV vaccination is recommended in many countries, including Italy, for girls in their twelfth year of age. In some countries, the goal of vaccination coverage has not been reached, and extension to boys has thus been debated.

Objective. Aim of this study is to perform a systematic review of pharmaco-economic studies considering the extension of HPV vaccination to boys.

Methods. An electronic literature search was performed on Pubmed to identify studies published from 2005 to 2015 in English and Italian. Four search strategies were used, including the terms «HPV», «boys», «vaccination», «economic evaluation», «cost effectiveness», and «epidemiological impact». Screening of titles, abstracts, and full texts was conducted, and economical evaluation of the extension of HPV vaccination to males was considered a criteria of inclusion. A total of 289 articles were identified. Only 15 articles were finally considered pertinent.

Results. The extension of HPV vaccination to boys was cost-effective or potentially cost-effective in 53% and 7% of the studies, respectively. Six studies did not positively evaluate the implementation of this intervention. However, taking into account both the new two-dose vaccination schedule available for all subjects ≤ 13 years, and the dramatic reduction in the price of vaccines in the last few years, the advantages of universal vaccination are more consistent.

Conclusion. The extension of HPV vaccination to boys is therefore foreseen to become increasingly implemented in the near future.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 51-58)

Key words: HPV, boys, cost-effectiveness

Riassunto

Introduzione. La vaccinazione anti-HPV è raccomandata in molti Paesi, tra cui l'Italia, alle ragazze nel dodicesimo anno di vita. In diverse nazioni l'obiettivo di copertura vaccinale non è stato raggiunto e l'estensione ai maschi è in discussione.

Obiettivo. Scopo dello studio è stato quello di effettuare una revisione sistematica degli studi farmaco-economici che valutano l'estensione della vaccinazione anti-HPV ai maschi.

Metodi. È stata condotta una ricerca sugli studi pubblicati dal 2005 al 2015 in inglese e italiano su Pubmed, utilizzando 4 stringhe di ricerca che includevano i termini «HPV», «boys», «vaccination», «economic evaluation», «cost effectiveness», «epidemiological impact». Gli articoli sono stati inizialmente selezionati se nel titolo, nell'abstract e nel testo esaminavano a livello economico l'estensione della vaccinazione anti-HPV ai maschi. Sono stati individuati 289 articoli: solo 15 sono stati ritenuti infine pertinenti.

Risultati. L'estensione della vaccinazione anti-HPV ai maschi risulta costo-efficace o potenzialmente costo-efficace rispettivamente nel 53% e nel 7% degli studi. Sei articoli, in base alle loro assunzioni, non valutano positivamente l'implementazione di tale intervento. Tuttavia, considerando la nuova schedula vaccinale a due dosi disponibile per tutti i soggetti di età ≤ 13 anni e la notevole riduzione del prezzo del vaccino intervenuta negli ultimi anni, si rende necessario aggiornare tali valutazioni utilizzando i nuovi dati di input.

Conclusioni. L'estensione della vaccinazione anti-HPV anche ai maschi sembra essere un intervento destinato a sempre più ampia applicazione nel prossimo futuro.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 51-58)

Parole chiave: HPV, maschi, costo-efficacia

INTRODUCTION

Infection due to high-risk *Human papillomavirus* (HPV) is the main cause of cervical cancer in women.^{1,2} Usually, HPV infections are cleared quickly within 1-2 years. Persistence of an oncogenic HPV infection is the first step towards cervical precancerous lesions and, more rarely, cervical cancer.³ The public health impact of HPV infections is more evident in women; however, high-risk HPVs are also responsible for other significant cancers like ano-genital and head-and-neck cancers, not necessarily correlated to female gender.^{4,5} In USA, during 2004-2008, 33,369 HPV-associated cancers (with a rate amounting to 10.8 cases per 100,000) were notified annually: 12,080 cases were among males (8.1 per 100,000) and 21,290 among females (13.2 per 100,000), according to data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results program.⁶ Cervical cancer was the most frequently notified, with about 11,967 cases per year, immediately followed by oropharyngeal cancer, with 11,726 cases per year. Furthermore, 2,370 head-and-neck cancers were registered among females and 9,356 among males. Particularly, the rate of head-and-neck cancers among males was four times higher than that among females (6.2 *versus* 1.4 per 100,000). Finally, anal cancer was more common among females (1.8 per 100,000) than among males (1.2 per 100,000).⁶

Two vaccines, the bivalent HPV-16/18 and the quadrivalent HPV-16/18/6/11, are currently available and recommended for protection against HPV infection. The main goal of current vaccination programs is the prevention of cervical cancer in females by reducing infections and precancerous lesions caused by high-risk HPV types in naïve girls. A cross-protective efficacy against four oncogenic non-vaccine HPV types (HPV 33/31/45/51) was reported for the bivalent HPV 16/18 vaccine, while the quadrivalent HPV 16/18/6/11 vaccine, in addition to the same cross protection, especially against HPV 33 and 31, also protects directly against genital warts caused by the low-risk HPV 6 and 11.⁷⁻¹⁰

HPV vaccination is usually recommended for 12-year-old girls. However, in many countries the goal of vaccination coverage (>70-80%) has not been reached in the target cohorts. In Italy, vaccination coverage with the complete schedule was 71% for the 1997-2000 girl cohorts in 2014, with wide regional variability, and did not show the expected increase in the last invited cohorts.¹¹ HPV vaccination coverage of girls was also lower than expected in other European countries.¹²

In order to improve the impact of HPV vaccination (reducing HPV transmission and, consequently, incidence of infections, disease, and cancer in females through herd immunity and reduction of HPV infections in males), some countries with low vaccination coverage for the main target population (e.g., USA, with 49% of adolescent girls with at least the first of three HPV doses in 2010) have recently extended HPV vaccination offer to boys in a universal immunization program.^{13,14}

Universal HPV immunization, including boy cohorts, could determine benefits by direct boys' immunization, but also by indirect protection of unvaccinated girls.

Therefore, while clinical benefits of adding vaccination to boys

has been clearly demonstrated, the most debated issue is the cost-effectiveness profile of universal vaccination. In the last ECDC guidance on the introduction of HPV vaccination in European Union countries, universal HPV immunization programs including boys were considered too expensive compared to the potential benefits. This was in accordance with several original studies and review articles on the economic impact of HPV vaccination already published at the time the guidance was issued.¹² The aim of the present study was to perform an updated systematic review on economic studies related to the extension of HPV vaccination to boys, considering also the more recent indications (like the reduction to a 2-dose vaccination schedule for subjects aged <14 years) and the reduced vaccine costs.

MATERIALS AND METHODS

Search strategy

A systematic review of economic studies considering HPV vaccination and strategies including boys was performed. PubMed was searched for articles and reviews pertaining to cost-effectiveness evaluation of HPV vaccination.

A search was made for the following headings: «HPV», «boys», «vaccination», «economic evaluation», «cost effectiveness», «epidemiological impact». Four search strategies were adopted:

- search strategy 1: «vaccin*» AND («human papillomavirus» [MeSH] OR «HPV») AND («ICER» OR «cost effectiveness» OR «economic evaluation» OR «model*») AND («male» OR «males» OR «boy*» OR «men») – only free open access results;
- search strategy 2: «HPV vaccination AND («economic evaluation» OR «cost effectiveness») AND («male» OR «men» OR «boys»);
- search strategy 3: («HPV vaccination» OR «human papillomavirus vaccine») AND («economic evaluation» OR «cost effectiveness» OR «pharmacoeconomics» OR «modelling» OR «cost-utility analysis» OR «incremental cost-effectiveness ratio» OR «cost-benefit» OR «epidemiological impact» OR «economic impact» OR «mathematical model») AND («male» OR «men» OR «boys»);
- search strategy 4: «HPV vaccination AND («economic evaluation» OR «cost effectiveness» OR «pharmacoeconomics» OR «modelling» OR «cost-utility analysis» OR «incremental cost-effectiveness ratio» OR «cost-benefit» OR «epidemiological impact» OR «economic impact» OR «mathematical model») AND («male» OR «men» OR «boys») NOT women».

The identified articles were compared in order to exclude duplicate studies. Articles were selected if first in the title, then in the abstract, and finally in the text they evaluated the economic extension of HPV vaccination to boys. A general research on Pubmed was also conducted in order to increase the review sensitivity. In addition, a research of published reviews was performed in order to identify other articles and compare their outcomes. **Figure 1** shows the flow diagram of the literature search.

Inclusion criteria

The economic studies searched for were original articles in English or Italian, published between 2005 and 2015, evaluating the

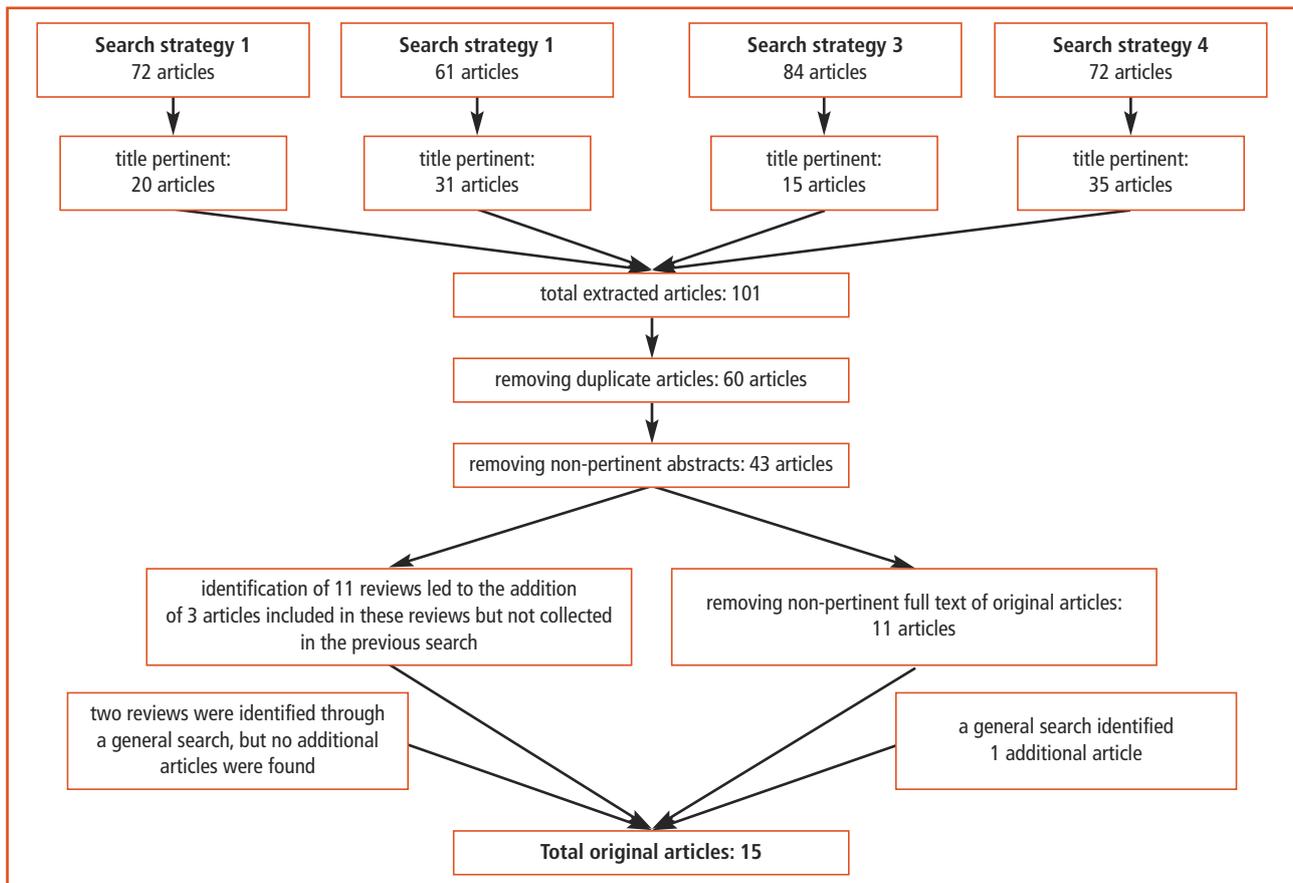


Figure 1. Flow diagram of the literature search and studies included or excluded in the review.
Figura 1. Diagramma di flusso della ricerca di letteratura e studi inclusi od esclusi nella review.

cost-effectiveness of the extension of HPV vaccination to boy cohorts compared with female-only adolescent immunization (standard target population for vaccination). All articles were assessed for methodological quality and data extraction was performed by 4 reviewers. In case of doubt, the topic was discussed together by all authors.

Data extraction

A table including the main relevant data of each study (authors, year of publication, country, period of analysis, mathematical model used, vaccine, price per dose and schedule, discounted rate, population, age of vaccination and catch-up, comparator, clinical outcomes considered, vaccine efficacy, duration of protection, assumptions on vaccination coverage, screening status, sensitivity analysis, economic outcomes – cost/QALY, cost/LYG – and other outcomes and conclusions) was created.

RESULTS

A total of 289 articles were identified: 246 articles were excluded because inconsistent with the research topic in the title or in the abstract, and as a consequence of duplicate removal. After assessment of the remaining 43 full-text articles, 11 were eventually considered suitable for inclusion in the present review because the other 32 articles did not focus on economic evaluation. In addition, 11 reviews were identified which allowed for the

identification of three more articles not collected through the applied search strategies. Finally, another article identified through general search in PubMed was included. Other two reviews were found through general search, but no additional articles were retrieved. A total of 15 original economic studies were examined (table 1).

All studies were published in the period 2007-2015; most of them referred to high-income countries (USA, UK, Australia, etc.), while two articles referred to middle-income countries (Mexico¹⁷ and Brazil¹⁶).

The bivalent vaccine was analyzed in three studies^{16,18,21} while the quadrivalent vaccine (HPV 6/11/16/18) was analyzed in the other 12 studies. Age at vaccination ranged from 9 to 26 years, but immunization was more frequently administered in the twelfth year of age. Some studies also considered a program of catch up for females and/or males aged 12-25 year in addition to universal vaccination. All studies took into account a three-dose schedule, except Laprise et al., which also considered a two-dose schedule.²⁶ Vaccine cost ranged between EUR 110-139 and USD 59-133. Vaccination coverage rate considered in the studies varied between 20% (Chesson et al.,²⁴ resulting in USD 23,600/QALY) and 90% (Kim et al.,¹⁶ resulting in I\$ 136,910/QALY).

According to WHO recommendations, a health intervention is considered cost-effective when cost/quality adjusted life

Author year/ country	Model/ period of analysis	Vaccine used/ vaccine cost/ schedule	Disc. rate	Model population	Morbidities	Vaccination age/ catch up	Comparator	Vaccine efficacy	Duration of protection
Elbasha 2007 ¹⁵ USA	dynamic 100 y	HPV 6/11/16/18 USD 360 (2005) 3 doses	3%	cohort based on US population	CIN 2/3 CC, GW	12 y no CU or 12-24 y F&M	F only	90%	lifelong
Kim 2007 ¹⁶ Brazil	dynamic n.a.	HPV 16/18 I\$ 25-400 (2000) 3 doses	3%	cohort based on Brazilian population associated only)	age-specific cancer incidence rates (HPV16-18	12 y n.a.	F only vs F&M	100%	lifelong
Insinga 2007 ¹⁷ Mexico	dynamic 62 y	HPV 6/11/16/18 USD 240 3 doses	3%	cohort based on Mexican population	CIN 2/3 CC, GW	12 y no or CU 12-24 for F&M	F only F only + CU for F F&M + CU for F	90%	lifelong
Kulasingam 2007 ¹⁸ Australia	Markov n.a.	HPV 16/18 AUD 115/dose (2005) 3 doses	5%	cohort based on Australian population	all HPV 16/18 associated diseases	12 y no	screening only	100%	lifelong
Jit 2008 ¹⁹ UK	dynamic 100 y	HPV 6/11/16/18 GBP 60-80.50/dose (2006-2007) 3 doses	3.5%	cohorts based on UK population	CIN, CC, GW HPV-related	12-25 y no	F only + CU 12-25 y	100% vs vaccine type HPV infection	lifelong 10 y
Kim 2009 ²⁰ USA	hybrid/dynamic n.a.	HPV 6/11/16/18 USD 120/dose (2006) 3 doses	3%	cohort based on US population	all HPV-related diseases	12 y n.a.	F only	vs infection: F 100% M 85% vs disease F 100% M 90%	lifelong
Zechmeister 2009 ²¹ Austria	dynamic 52 y	HPV 16/18 EUR 100/dose (2007) 3 doses	5%	cohort based on international epidemiological data	CC, CIN 1/3	12 y no	F only	90%	lifelong (booster at 10y)
Olsen 2010 ²² Denmark	dynamic 62 y	HPV 6/11/16/18 EUR 415 (2007) 3 doses	3%	heterosexual	CC, CIN 1/3, GW	12 y scenario CU for F to 15-26 y	F+CU to 15 y vs F+CU to 26 y	100%	n.a.
Elbasha 2010 ²³ USA	dynamic n.a.	HPV 6/11/16/18 USD 400 (2008) 3 doses	3%	cohort based on US population	CC, ANA, VAG, VUL,PEN, H&N, CIN 1-3, GW, RRP	9-26 y no	F only	90%	lifelong
Chesson 2011 ²⁴ USA	hybrid 100 y	HPV 6/11/16/18 USD 116/dose (2008) 3 doses	3%	cohort based on USA population	GW, CC, VAG, VUL, ANA, PEN, ORPH	F 12-26 y M 12 y annual CU for F 13-26 y	F only increased coverage in F	F: 95% M: 90%	lifelong
Pearson 2014 ²⁵ New Zealand	Markov n.a.	HPV 6/11/16/18 USD 59/dose (2011) 3 doses	3%	cohort based on New Zealand and Australia population	CIN 1/3, GW, CC, ANA, VUL, ORPH	12 y no	F only	99%	20 y
Laprise 2014 ²⁶ Canada	dynamic 70 y	HPV 6/11/16/18 CAD 85/dose (2010) 2/3 doses	3%	cohort based on Canadian population	GW, CC, VUL, VAG, ANA, PEN, ORPH	9 y CU 14 y	F only	2-dose: 90% 3-dose: 95%	2-dose: 10-30 y 3-dose: 20 y-lifelong
Burger 2014 ²⁷ Norway	dynamic lifetime	HPV 6/11/16/18 USD 75/dose (2010) 3 doses	4%	cohort based on Norwegian population	GW, CC, VUL, VAG, ANA, PEN, ORPH	12 y n.a.	F only	F: 100% M: 90%	lifelong
Bresse 2014 ²⁸ Austria	dynamic 100 y	HPV 6/11/16/18 EUR 120/dose (2012) 3 doses	3%	cohort based on Austrian population	GW, CC, VUL, VAG, ANA, PEN, ORPH	9 y no	no vaccination	F: 76-100% M: 41-96%	lifelong 20 y
Olsen 2015 ²⁹ Denmark	dynamic 62 y	HPV 6/11/16/18 EUR 417 (2008) 3 doses	3%	heterosexual	GW, CIN, CC, ANA, VAG, VUL, PEN, H&N	12 y n.a.	F only	100%	lifelong

F: female, M: male; Y: years; CC: cervical cancer; GW: genital warts; VAG: vaginal cancer; VUL: vulvar cancer; ANA: anal cancer; PEN: penil cancer; H&N: head and neck cancer; ORPH: oropharynx cancer; RRP: re

Table 1. Cost-effectiveness studies on HPV vaccination including boys. / **Tabella 1.** Studi di costo-efficacia sulla vaccinazione anti-HPV nei maschi.

	Coverage	Screening status	Sensitivity analysis			Outcome cost/QALY cost/LYG	Other outcomes and conclusions
			natural history	vaccine parameters	economic parameters		
	70%	current	n.a.	one-way	one-way	Vaccination F&M: dominated Vaccination F&M + CU 12–24 y for F: USD 41,803 ICER of most effective strategy (F&M12+CU F&M): USD 45,056/QALY	Quadrivalent vaccine can substantially reduce genital warts, CIN, and cervical cancer
	25-90%	n.d.	multi variate	multi variate	multi variate	The ratio for vaccinating both girls and boys increased from I\$ 810/LYG to I\$8,650/LYG, as coverage increased	Adding boys to a vaccination programme may not be cost-effective in Brazil, unless the cost per vaccinated person is well below I\$50, coverage in girls is well below 50% and could not be increased.
	70%	current	one-way	one-way	one-way	Vaccination F&M: dominated compared to F only. Vaccination F&M+CU for F: incremental USD 16,663/QALY compared to vaccinating F+CU for F Further incremental USD 16,702/QALY if CU for F&M	The most clinically effective strategy was vaccination of 12-year-old females and males combined with a temporary female and male 12-24-year-old catch-up program
	80%	current	no	one-way	one-way	AUD 33,644 compared to no vaccination program	In a setting with effective screening program, vaccinating boys is likely to be cost-effective when the morbidity of the screening program is taken into account (QALY), but not when only mortality associated with CC is considered (LYG).
	80%	current	multi variate	one-way	multi variate	Incremental GBP 113,846 if 10 years' vaccine protection is assumed Incremental GBP 172,892 if 20 y vaccine protection is assumed Incremental GBP 520,255 if lifetime vaccine protection is assumed	Adding boys is unlikely to be cost-effective, even if vaccination results in lifelong protection. This is because at 80% coverage it is likely that most HPV 16-18 related CC along with many cases of GW (in both sexes) will be prevented. Therefore the additional benefits from vaccination of boys are few.
	75%	current	multi variate	multi variate	multi variate	Independently from clinical outcomes considered, universal vaccination is not cost-effective (cost/QALY: USD 290,290 - 90,870)	Our results suggest that if vaccine coverage and efficacy are high among preadolescent girls (12 years), then including boys in an HPV vaccination program is unlikely to provide good value for resources compared with vaccinating girls only.
	65%	biannual screening	one-way	one-way	one-way	The additional vaccination of boys increases the ICER to EUR 311,000/LYG and EUR 299,000/LYG in a public care perspective or a societal one, respectively	Vaccinating boys may not be cost-effective without reducing the vaccine price.
	70%	current	multi variate	multi variate	multi variate	As scenario (12-year-old F and M vaccination at 70% coverage rate) ICER: EUR 18,677/QALY	HPV type 6-11-16-18 were estimated to be eliminated after 50 years of vaccination.
	75%	current	no	one-way	one-way	USD 25,700 if vaccination protects against all HPV-6/11/16/18 associated diseases USD 69,000 if it only protects against diseases currently in the vaccine indication	Adding quadrivalent vaccination to M 9-26 years potentially has substantial public health and economic benefits. The inclusion of M would further reduce HPV-related morbidity and is cost-effective at commonly cited thresholds.
	25-30-75%	current	multi variate	multi variate	multi variate	The incremental cost per QALY gained was USD 23,600 in the lower female coverage scenario (20% coverage at 12 years) USD 184,300 in the higher female coverage scenario (75% coverage at 12 years)	HPV vaccination of M might potentially be cost-effective, if F coverage is low and if all potential health benefits are included. In the long term, adding M to vaccination reduces HPV-related CC in the three coverage scenarios.
	45-56% / 73%	current, but cost excluded	no	efficacy and coverage considered as independent variables	one-way	Vaccination of M to achieve the current coverage for F would not be cost-effective, at USD 61,400/QALY gained compared to the current F-only program An intensified F-only program would give USD 17,400/QALY gained Adding M to this program was also not cost-effective (USD 128,000/QALY)	Vaccination of boys was not found to be cost-effective, even with very low vaccine or program administration costs. In order for vaccination of males to become cost-effective in New Zealand, the vaccine would need to be supplied at very low prices and administration costs would need to be minimized.
	80%	current	multi variate	multi variate	multi variate	Vaccinating boys with 2 or 3 doses was not cost-effective (always above USD 100,000/QALY)	The price for M would need to be reduced by more than half to make a 2-dose F&M strategy cost-effective vs 3-dose F-only. Adding M to an HPV vaccination program would extend benefits to MSM, who do not benefit from the herd effects of F-only vaccination.
	71%	current	multi variate	multi variate	multi variate	USD 81,700/QALY considering only cancer for F&M USD 60,100/QALY when considering all HPV-related conditions	At the anticipated tender price, expanding the HPV vaccination program to boys may be cost-effective. Increasing coverage in F is uniformly more effective and cost-effective and should be considered a priority.
	65%	current	one-way	one-way	one-way	Cost-effective with base case analysis of EUR 26,701/QALY gained for CC only, EUR 15,820/QALY also including VAG, VUL and GW, EUR 10,033/QALY also considering ANA, PEN, ORPH	Decrease in infections (about -70% in F + M) reducing HPV 16/18-related cancers in both sexes. An increase of vaccine coverage among F + M from 65% to 80% would accelerate and increase the reduction in the prevalence of HPV 16/18-related infections by 10 and 14 points in F and M, respectively.
	85% (and 70%)	current: F 23-64 y every 3-5 y	one-way	multi variate	multi variate	Vaccination of F and M vs vaccination of F only: ICER: EUR 28,031/QALY (2-dose regimen) ICER: EUR 41,636/QALY (3-dose regimen)	Extension of the current HPV program in Denmark to include boys and girls is a cost-effective preventive intervention.

current respiratory papillomatosis; CU catch up; AUD: Australian dollars; CAD: Canadian dollars; EUR: Euros; GBP: British pounds; I\$: International dollars; USD: US dollars

Authors	Year	Number of evaluated articles (year range)	Main conclusions
Newall et al. ³⁰	2007	4 (2003-2004)	The additional vaccination of boys was found to be unattractive under most plausible scenarios.
Kim et al. ³¹	2008	6 (2004-2007)	Vaccination of boys is unlikely to be cost-effective if reasonable levels of coverage are achieved in girls. Increasing vaccine coverage of girls is always more cost-effective than extending coverage to boys.
Brisson et al. ³²	2009	12 (2003-2008)	If vaccine coverage is high in girls, including boys in a vaccination program will not be cost-effective.
Marra et al. ³³	2009	13 (2003-2008)	The cost effectiveness of a male and female vaccination program is generally not cost-effective compared with female-only vaccination.
Jeurissen et al. ³⁴	2009	11 (2003-2008)	Vaccinating boys is not cost-effective.
Garland et al. ³⁵	2010	5 (2002-2009)	Inclusion of males in an HPV vaccination program is likely to have significant health and economic benefits. Comprehensive cost-benefit analyses are needed to determine the efficacy of these programs in the overall population.
Seto et al. ³⁶	2012	29 (2007-2010)	It appears that the addition of boys to a vaccination program generally exceeds traditional cost-effectiveness thresholds. The MSM population represents a potential additional target for routine HPV vaccination.
Low et al. ³⁷	2012	18 (2000-2010)	Models currently show that vaccination strategies with high female coverage enjoy the same benefits with greater savings than strategies that include males. Benefits of vaccinating males often do not warrant the high cost when considering only prevention of cervical cancer. Authors suspect that once adequate adequate cost-effectiveness modelling of HPV-related morbidities in males is completed, data will support vaccination in men at that time.
Canfell et al. ³⁸	2012	3 (2009-2011)	Although the inclusion of males in HPV vaccination programs can be cost-effective in some circumstances, increasing coverage in males is unlikely to be associated with a more attractive cost-effectiveness ratio than increasing coverage in females, if this can be achieved.
ECDC ¹²	2012	11 (2004-2011)	Universal HPV vaccination may not be cost-effective. The cost-effectiveness can be re-assessed if vaccination costs are significantly reduced in the future, especially if regimens of less than 3 vaccine doses are proven to be just as efficacious as the current standard vaccination protocols.
Jiang et al. ³⁹	2013	9 (2004-2011)	More favourable cost-effectiveness appeared when all HPV-related disease outcomes were considered, a suboptimal vaccine coverage among girls, and/or lower vaccine prices were assumed.
Fasenfeld et al. ⁴⁰	2013	25 (2007-2012)	Two study considering vaccination in males, contrasting conclusions due to different assumptions (GW included, higher threshold and lower vaccine efficacy in the favourable study).
Marsh et al. ⁴¹	2014	8 (2004-2011)	Current studies of the cost-effectiveness of universal HPV vaccination suffer from a number of limitations. Decisions to invest in universal HPV vaccination need to be based on a complete assessment of the value that it generates. This is not provided by existing economic evaluations.

Table 2. Reviews of cost-effectiveness studies on HPV vaccination including boys. / **Tabella 2.** Review di studi di costo-efficacia sulla vaccinazione anti-HPV nei maschi.

year (QALY) is less than 1 out of 3 times the Gross Domestic Product (GDP) per capita and very cost-effective if less than one GDP per capita. Therefore, the cost-effectiveness threshold is related to the specific economic background of each country. Based on this assumption, 8 studies (53%) considered adding boys to the female vaccination program a cost-effective intervention, with a cost/QALY ranging from EUR 10,033 (Bresse et al.,²⁸ assuming a 65% coverage) to USD 81,700 (Burger et al.,²⁷ assuming a 71% coverage). Chesson et al. considered adding boys to the vaccination program to be cost-effective under some assumptions: universal vaccination is cost-effective if immunization coverage in girls is less than 30%, but with a vaccine price of USD 116 per dose (\$23,600/QALY).²⁴

On the other hand, 6 studies (40%) indicated that universal vaccination is not cost-effective. Among these studies, Laprise et al. showed that a two-dose vaccination series for girls and boys compared to a three-dose series with girls-only vaccination would become cost-effective if the vaccine price for boys were reduced by more than half.²⁶ Zechmeister et al. suggested that vaccinating boys with 3 doses of bivalent vaccine may not be cost-effective without reducing the vaccine price (price considered: EUR 110 per dose) and when the economic evaluation is limited to only direct benefits related to cervical carcinoma prevention.²¹

In the analysis performed by Kim et al., universal vaccination did not turn out to be cost-effective for prevention of HPV 16 and 18 related cancers in a limited-resource setting unless the cost of vaccination is well below USD 50 and vaccine coverage in girls is well below 50%, with no possible increase.¹⁶ Pearson et al. admitted that vaccination of boys may become cost-effective only if a very low vaccine price (about USD 30) and lower program administration costs are achieved in the future.²⁵ The high vaccination coverage rate for girls (80%) assumed in Jit et al. was bound to determine the lack of cost-effectiveness of male vaccination.¹⁹ Finally, like others, in a study performed by Kim et al. considering a cost per vaccine dose of USD 120, which is far higher than the current cost, boys' vaccination was not economically favourable.²⁰

Table 2 shows the 13 reviews identified through the literature search. The oldest reviews concluded that universal vaccination was not cost-effective compared to female-only vaccination or increasing coverage among girls.³⁰⁻³⁴ The most recent reviews, instead, suggested that adding boys could become cost-effective in the future if vaccine costs are reduced, if coverage among girls does not increase, and if all HPV-related disease are taken into account.^{12,39,41} These statements are in agreement with the findings of our review.

DISCUSSION AND CONCLUSIONS

The previous published reviews showed that the cost-effectiveness of universal vaccination with the old parameters was controversial and generally unfavourable.

The results of this review, instead, show that many studies have a favourable cost-effectiveness profile, while others indicate that it could be cost-effective only with a low vaccination coverage in girls and with lower vaccine costs. However, in the last years, vaccine cost has decreased greatly worldwide compared to the price assumed in the analyzed studies. For example, the current cost per dose is about EUR 35 in Italy: this parameter surely has a great effect on the total costs of a universal vaccination program. In addition, the European Medicine Agency (EMA) authorized a two-dose schedule for both vaccines when used in younger subjects (≤ 13 and ≤ 14 years for the quadrivalent and bivalent vaccines, respectively).⁴² Indeed, considering the input parameters in studies not favourable to universal vaccination, and their conclusions, at the current price of EUR 35 per dose and a two-dose schedule instead of a three-dose regimen, results would become cost-effective in all studies (Laprise et al.,²⁶ Zechmeister et al.,²¹ Jit et al.,¹⁹ Kim et al.²⁰), except Kim et al.¹⁶ and Pearson et al.,²⁵ whose conclusions would remain unfavourable to universal adolescent vaccination strategy. If Chesson et al.²⁴ had considered a price per dose of USD 38.11 (about EUR 35) instead of 116, and a two-dose regimen, their conclusions would have been favourable, too. In the other studies, with updated parameters, the results would be even more favourable for universal vaccination. These two parameters (price and number of doses) are a crucial change for the economic sustainability of universal vaccination. Therefore, economic studies should be updated assuming more recent

vaccination costs and immunization schedules, so that the cost-effectiveness profile of universal vaccination would most likely be significantly improved.

In addition, as reported by Marsh et al.,⁴¹ all HPV-related clinical outcomes should be included in economic studies in order to obtain a more accurate cost-effectiveness profile. Lastly, new economic evaluation on HPV universal vaccination should also be performed considering the availability of a 9-valent HPV vaccine in the near future.

Therefore, many issues are still open and should be further analyzed. For example, no evaluation on universal immunization policies is available for the scenario where vaccine coverage is 70% (a value that Kim et al.³¹ recognize as insufficient). However, compared to previous reviews, our findings show better results in the economic evaluation of adding boys to vaccination, especially with updated economic parameters (12 studies out of 15 would confirm cost-effectiveness).

A possible limitation of our review is the use of a single electronic database (PubMed). We cannot rule out the possibility that a few articles on the subject may have been missed.

In conclusion, a universal HPV vaccination program could greatly reduce the incidence of new HPV infections in the population, and is likely to be cost-effective and economically sustainable, considering current vaccine prices and the two-dose schedule. Taking into account that several recent epidemiological studies and reviews have highlighted that HPV-related diseases pose a substantial burden even on males, the extension of HPV vaccination to boys is highly desirable and should become a reality in many countries in the next few years

Conflicts of interest: none declared

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COMMUNICATIONS C24
Friday 16 October
h. 8.30
Amber Room 1

Antimeningococcal and antipneumococcal vaccination determinants: a European systematic literature review

Analisi dei determinanti associati con la vaccinazione antimeningococco C e antipneumococco: risultati di una revisione sistematica di letteratura condotta in Europa

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Abstract

Background. ESCULAPIO is a multicenter project, funded by the Italian Centre for Disease Prevention and Control, aimed at implementing communication strategies to improve vaccination knowledge and attitudes among different target populations.

Objective. The objective of the Sicilian research unit was, in the first phase, to identify, through systematic literature revision, which vaccination determinants play a role in the uptake of recommended vaccines included in the Italian Vaccination Plan.

Design. A systematic literature review was carried out on studies describing the determinants underlying pneumococcal and meningococcal vaccination uptake. The analysis was limited to papers published in English from 2000 to date.

Results. A total of 188 (meningococcal) and 731 (pneumococcal) papers were found. After selection by publication data, country (Europe), article type (original article), target population (healthy subjects), 7 (meningococcal) and 4 (pneumococcal) manuscripts were finally included in the analysis. For meningococcal vaccination a better socioeconomic status is related to vaccination acceptance, whereas distance from immunization service is a negative determinant. For pneumococcal vaccination the determinants related to vaccination uptake are older parental age and a strong vaccine recommendation. Conversely, when the vaccine needs to be paid for, a refusal is more likely

Conclusions. Our results show that payment for vaccination is a major barrier and communication about meningococcal and pneumococcal vaccination should be targeted towards specific population groups, especially through the counseling activities by health professionals.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 59-64)

Key words: systematic literature review, meningococcal vaccination, pneumococcal vaccination

Riassunto

Introduzione. ESCULAPIO è un progetto multicentrico, finanziato dal Centro per la prevenzione e il controllo delle malattie, che ha tra i suoi obiettivi quello di sviluppare strategie per implementare le conoscenze vaccinali in differenti target di popolazione.

Obiettivi. L'U.O. della Sicilia aveva il compito di identificare i determinanti associati con l'adesione vaccinale delle vaccinazioni raccomandate presenti nel Piano nazionale vaccini.

Disegno. Sono state condotte due revisioni sistematiche di letteratura sui determinanti associati con le vaccinazioni anti-meningococco e anti-pneumococco.

Risultati. Attraverso le stringhe di ricerca specifiche sono stati trovati 188 (meningococco) e 731 (pneumococco) articoli. Selezionando per data di pubblicazione (dal 2000 a oggi), nazione (Europa), tipologia di articolo (articoli originali), popolazione target (no soggetti a rischio), sono stati inclusi nell'analisi 7 (meningococco) e 4 (pneumococco) lavori. Per il meningococco il principale fattore pro-vaccinazione è un migliore status socioeconomico, mentre la distanza dai servizi vaccinali è un determinante negativo. I determinanti associati con la vaccinazione antipneumococcica sono una maggiore età dei genitori e la raccomandazione alla vaccinazione da parte dell'operatore sanitario. Viceversa, il pagamento del vaccino implica un rifiuto vaccinale.

Conclusioni. I risultati dimostrano che il pagamento della vaccinazione costituisce una barriera fondamentale e che gli sforzi informativi/comunicativi in tema vaccinale devono essere rivolti prevalentemente alle fasce di popolazione che necessitano di un maggiore supporto, specialmente attraverso l'attività di counselling vaccinale da parte dell'operatore sanitario di riferimento.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 59-64)

Parole chiave: revisione sistematica di letteratura, vaccinazione antipneumococcica, vaccinazione antimeningococcica

BACKGROUND

In 2012, the Italian Centre for Disease Prevention and Control (CCM) of the Ministry of Health, funded a multicenter research project presented by researchers of six Italian regions (Toscana: leading proponent; Liguria, Puglia, Sardegna, Sicilia, Veneto) entitled *Development of health communication strategies and interventions on preventable diseases and vaccination to increase vaccine coverage in the general population*. For every region, a research unit constituted by researchers from universities or Local Public Health authorities was identified, with specific population targets. The project was finally renamed with the acronym ESCULAPIO. The target for the Sicilian research unit was the evaluation of the determinants related with vaccination uptake among the general population. In particular, in a first phase of the study, the Sicilian Unit conducted systematic literature reviews (SLR) for the most important optional vaccinations recommended by the Italian National Vaccination Plan (*Human papillomavirus*, influenza, measles, mumps and rubella, meningococcal, pneumococcal).¹

In this manuscript, data on studies describing the determinants underlying pneumococcal and meningococcal vaccination uptake among the general population are reported.

Meningococcal vaccination

Meningococcal vaccination is a relatively recent public health acquisition. Despite meningococcal polysaccharide vaccines having been available for several decades, effectiveness was not satisfactory.² The first conjugate vaccine against *Neisseria meningitidis* serogroup C was approved only in 1999.² In the following years, the introduction of the quadrivalent conjugate vaccine against *Neisseria meningitidis* serogroups A, C, W135, and Y improved the vaccination offer. Nevertheless, for many years the meningococcal quadrivalent vaccine was recommended only for some groups of the population, according to socio-occupational (e.g., soldiers, males who have sex with males, travelers in high risk areas) or clinical (e.g., thalassemia, asplenia, chronic liver disease, chronic renal failure, AIDS) characteristics.³ Only in 2014, recommendations for quadrivalent meningococcal vaccination was extended for routine infant vaccination (<2 years old).⁴ Moreover, in 2013 a vaccine against *Neisseria meningitidis* serogroup B in infants was finally licensed.⁵ Therefore, in the international scientific literature, determinants associated with meningococcal A, B, W135, and Y serogroups vaccination were not analyzed, limiting available data to meningococcal C vaccination.⁶⁻¹²

Pneumococcal vaccination

The history of pneumococcal vaccination began more than 30 years ago in the USA, where the 23-valent pneumococcal polysaccharide vaccine (PPSV23) was licensed. Nowadays, PPSV23 is currently recommended in people aged ≥ 65 years and in high-risk adults aged 19-64 years.¹³ However, PPSV23 has limited effectiveness against invasive pneumococcal disease, especially among immunocompromised adults, and PPSV23 protection is short-lived, with a rapid waning of antibody concentrations and with a lack of memory B-cell production following immunization.¹⁴⁻¹⁶

Since 2000, the offer of pneumococcal vaccine has been enriched by a conjugate 7-valent vaccine (PCV7) for all children aged 2-23 months.¹⁷ In 2010, PCV7 vaccine was replaced by a 13-valent vaccine (PCV13) with six additional serotypes.¹³⁻¹⁸ Both conjugate vaccinations demonstrated good efficacy and effectiveness in invasive pneumococcal disease (IPD) prevention.¹⁹⁻²⁰

On August 2014, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of PCV13 even among adults aged ≥ 65 years, extending the vaccine indication to community-acquired pneumonia.¹³

MATERIAL AND METHODS

An SLR was carried out on determinants associated with meningococcal and pneumococcal vaccination compliance, considering key terms used in combination and referred to vaccine/immunization, uptake/coverage, determinant/factor, and *Neisseria meningitidis*/meningococcal/meningococcus or *Streptococcus pneumoniae*/pneumococcus/pneumococcal, with medical subject headings (MeSH) and MeSH major topics included in the syntax. The PubMed/MEDLINE, SCOPUS, EMBASE, and ISI Web of Science online databases were considered, as well as the grey literature, and a manual search was performed based on the references of the articles retrieved. Original articles published from January 2000 to December 2014 were collected (figure 1).

Qualitative and quantitative studies describing the determinants underlying meningococcal or pneumococcal vaccination uptake among parents of children or adolescents/adults were included in the review. Exclusion criteria applied during title and abstract screening were: articles published in a language different from English, Italian, or French, studies conducted in non-European countries, studies reporting vaccination information on non-healthy populations, studies other than original articles (e.g., review) (figure 1). Other exclusion criteria were applied during full text analysis: assessing only vaccination coverage; reporting uptake determinants not in first person or not by parents; not reporting direct linking with uptake (e.g., linking with adverse publicity or with information-seeking) (figure 1).

Variable extraction was conducted on the basis of potential classes of determinants identified in previous SLRs, that included among others: knowledge, beliefs, and perceptions (both on vaccines and diseases); attitudes/behaviours; demographics (such as ethnicity, mother's age, child's age, gender, geographic location); socioeconomic status (SES) (including education level, employment, family income, number of children in the household).²¹

The literature search and systematic review were conducted by two independent investigators. In case of any incongruity, the two investigators came to an agreement after further analysis and discussion.

RESULTS

Meningococcal vaccination

As shown in figure 1, through the standardized database searching, 144 records were identified. After duplicates were removed, 135 records were screened and 125 records were excluded on the basis of title and abstract screening (based on language, study setting, methodology, or target population).

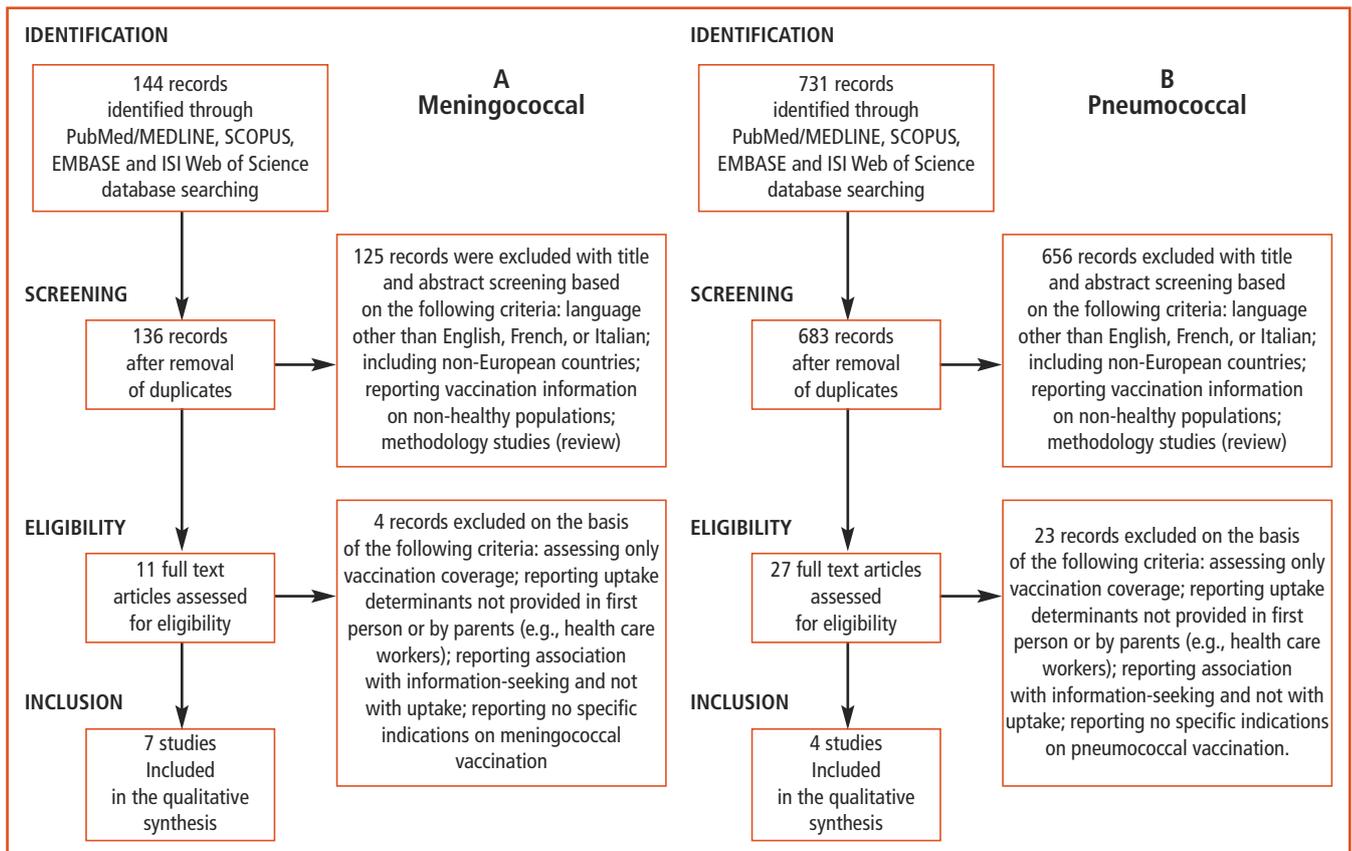


Figure 1. Flow SLR diagram of the determinants of pneumococcal (A) and meningococcal (B) vaccination.

Figura 1. Diagramma di flusso delle RSL relative ai determinanti delle vaccinazioni antimeningococco (A) e antipneumococco (B).

Finally, among 11 articles assessed for eligibility, 4 were excluded on basis of exclusion criteria and 7 were analyzed in the qualitative synthesis.

Manuscripts included in the meningococcal vaccination SLR are summarized in [table 1](#).

In particular, the first European experience analyzing vaccine status and determinants of British undergraduates in South Wales (mean age in years 18.9, 51% females), showed that the supply of meningococcal C vaccination through school-based campaigns (93% vaccinated *vs* 19% vaccinated without an active vaccination offer) was the most important determinant for vaccination acceptance.⁶

A study conducted in 2005 among 1,763 Dutch parents of children aged 6 to 14 years old demonstrated that ethnicity, religion (not practicing), and a higher parent education level were related with vaccination acceptance.⁷

Vaccination coverage (VC) reported in the study was 84%. Considering the diversity of the Dutch population, analysis of the different ethnicities showed there was better information, risk awareness, and critical attitudes towards meningococcal vaccination among Dutch parents compared to parents of different ethnicity (e.g., Turkish, Moroccan, Surinamese).⁷

Perceptions, attitudes, and behaviour regarding meningococcal vaccination were also analyzed in the Netherlands among the same group of parents.⁹ Specifically, a higher perceived vulnerability of their own child contracting meningococcal disease and

a perceived control of vaccination in preventing meningococcal C infection were strongly related with vaccination acceptance.⁹ In 2005, a retrospective study conducted in Belgium (EPI-survey), reported coverage and predictive factors associated with childhood vaccination compliance. In particular, for meningococcal vaccination (VC=94%), using the paediatrician as a referent for vaccination counselling in the multivariate analysis, a better vaccination attitude was shown to be related with “well-baby clinic” or “daycare” vaccination counseling (OR 1.9; 95%CI 1.2-2.8).⁸ Conversely, a family physician vaccination counseling represents a barrier for meningococcal vaccination (OR 0.4; 95%CI 0.2- 0.8).⁸

Results of the EPI-survey study among parents of 14- and 7-year-old Belgian children were also reported.¹⁰⁻¹¹ In particular, among 14-year-old children, the determinants associated with vaccination uptake were mother’s education (secondary school or higher: OR 1.7; 95%CI 1.0-2.9) and employment (part-time work: OR 1.9; 95%CI 1.4-2.7), whereas the determinants associated with vaccination refusal were the adolescent’s school career (repeated 1 year: OR 0.6; 95%CI 0.4-0.8; special education: OR 0.4; 95%CI 0.2-0.7), mother’s ethnicity (non European: OR 0.4; 95%CI 0.3-0.7), and father’s employment (part-time work: OR 0.2; 95%CI 0.0-0.8).¹⁰

Among parents of 7-year-old children, vaccination uptake was strongly related with higher family income (>€3,000/month: OR 2.92; 95%CI 1.39-6.09).¹¹

Finally, a cross-sectional survey conducted in Poland among parents of 0-5 years olds children highlighted lower meningococcal VC than the Netherlands and Belgium.¹²

Vaccination compliance was related with older parental age (>25 years: OR 2.60; 95%CI 1.03-6.83), higher socio-economic status of the family (OR 3.46; 95%CI 1.95-8.48), number of children (one: OR 3.64; 95%CI 1.96-7.14), and area of family physician practice (town: OR 3.94; 95%CI 1.95-8.48).¹² High cost of the vaccine was associated with vaccination refusal (OR 0.18; 95%CI 0.09-0.36).¹²

Pneumococcal vaccination

For pneumococcal vaccination, 731 records were identified through the database search (figure 1). After duplicates were removed, 683 records were screened and 656 records were excluded on the basis of title and abstract screening (based on lan-

guage, study setting, methodology or target population). Finally, among 27 articles assessed for eligibility, 23 were excluded on the basis of the exclusion criteria and 4 were analyzed in the qualitative synthesis. Manuscripts included in the pneumococcal vaccination SLR are summarized in table 2.^{12,22-24}

The first article analyzed was a survey conducted in 2002 on a sample of adults ≥65 years of age conducted in 11 Italian regions.²² Vaccination coverage reported for PPSV23 was only 5%. Factors associated with vaccination uptake were a strong recommendation by the family general practitioner (GP), free-of-charge vaccination, and perception of the danger of pneumococcal disease.²²

In 2009, a cross-sectional study was conducted among parents of 0-5 year old Polish children to measure coverage and determinants of self-paid vaccinations.¹² Factors associated with PCV7 pneumococcal vaccination uptake were the same as

Manuscript (1 st author, journal, publication date)	Geographical setting/ target population	Adolescents (own vaccination)		Parents (vaccination on their child)		Type of determinant
		facilitator	barrier	facilitator	barrier	
Thirlaway K ⁶ <i>Commun Dis Public Health</i> 2003	UK undergraduates (18-21 years old)	<ul style="list-style-type: none"> ■ UK residence ■ living in student accommodation ■ school-based vaccination program 	Irish residence			<ul style="list-style-type: none"> ■ demographic factors (residence) ■ socio-economic factors (accommodation type) ■ vaccination strategies
Timmermans D et al. ⁷ <i>Vaccine</i> 2005	Netherlands parents of children 6-14 years old			<ul style="list-style-type: none"> ■ ethnicity (Dutch); ■ religion (not practicing) ■ higher parental education level 		<ul style="list-style-type: none"> ■ demographic factors (ethnicity, religion) ■ parents' education level
Theeten H et al. ⁸ <i>Vaccine</i> 2007	Belgium parents of children 18-24 months			main vaccinating physician: well-baby clinic or daycare (referent: pediatrician)	main vaccinating physician: family physician (referent: pediatrician)	type of health care workers recommending vaccination
Timmermans D et al. ⁹ <i>BMC Public Health</i> 2008	Netherlands parents of children 6-14 years old			<ul style="list-style-type: none"> ■ perceived vulnerability of their own child ■ perceived control in preventing meningococcal infection 	psychosocial factors	(perceptions, attitudes, and behaviours)
Vandermeulen C et al. ¹⁰ <i>Pediatrics</i> 2008	Belgium parents of adolescents 14 years old	school career of adolescent (repeated 1 year, special education)		<ul style="list-style-type: none"> ■ higher mother's education ■ mother's employment (part-time work) 	<ul style="list-style-type: none"> ■ race of the mother (non European) ■ father's employment (part-time work) 	<ul style="list-style-type: none"> ■ demographic factors (race) ■ education level (parents) ■ employment type (parents) ■ education-related factors (adolescent)
Theeten H et al. ¹¹ <i>Acta Paediatr</i> 2009	Belgium parents of children 7 years old			higher socioeconomic status (family income)		socioeconomic factors (family income)
Ganczak M et al. ¹² <i>Vaccine</i> 2013	Poland parents of children 0-5 years old			<ul style="list-style-type: none"> ■ age ≥25 years old ■ number of children in the family (one) ■ higher socioeconomic status (family income) ■ area of family physician practice (town) 	<ul style="list-style-type: none"> ■ number of children in the family (more than one) ■ high cost of the vaccine 	<ul style="list-style-type: none"> ■ demographic factors (parents' age, number of children) ■ socioeconomic factors (family income) ■ family physician related factors (area of practice) ■ cost of the vaccine

Table 1. Determinants for meningococcal vaccination reported in the manuscripts included in the systematic literature review.

Tabella 1. Determinanti associati con la vaccinazione antimeningococcica inclusi negli articoli della revisione sistematica di letteratura.

Manuscript (1 st author, journal, publication date)	Geographical setting; target population	Adolescents (own vaccination)		Parents (vaccination on their child)		Type of determinant
		facilitator	barrier	facilitator	barrier	
Sammarco S et al. ²² <i>Annali di Igiene</i> 2004	Italy people aged ≥65 years old	<ul style="list-style-type: none"> ■ strong vaccine recommendation ■ free vaccination ■ perceived dangerous disease 				<ul style="list-style-type: none"> ■ psychosocial factors (perceptions, attitudes, and behaviours) ■ vaccination strategies
Ganczak M et al. ¹² <i>Vaccine</i> 2013	Poland parents of children 0-5 years old			<ul style="list-style-type: none"> ■ age ≥25 years ■ number of children in the family (one) ■ higher socioeconomic status (family income) 	<ul style="list-style-type: none"> ■ high cost of the vaccine 	<ul style="list-style-type: none"> ■ demographic factors (parents' age, family composition) ■ socioeconomic factors (family income) ■ family physician related factors (area of practice) ■ cost of the vaccine
Lode H et al. ²³ <i>Advances in Therapy</i> 2013	13 Western European countries adults aged >50 years	<ul style="list-style-type: none"> ■ perception of vaccine efficacy and effectiveness ■ health care worker recommendation 	<ul style="list-style-type: none"> ■ lack of physician recommendations ■ vaccine awareness ■ not being concerned about pneumococcal infections 			<ul style="list-style-type: none"> ■ psychosocial factors (perceptions, attitudes, and behaviours)
Robert E et al. ²⁴ <i>BioMed Research Intern</i> 2014	Belgium parents of children aged 18-24 months			<ul style="list-style-type: none"> ■ attending Mother & Child clinics or a daycare ■ number of children 		<ul style="list-style-type: none"> ■ vaccination strategies ■ demographic factors (number of children) in the family (one)

Table 2. Determinants for pneumococcal vaccination reported in the manuscripts included in the systematic literature review.

Tabella 2. Determinanti associati con la vaccinazione antipneumococcica inclusi negli articoli della revisione sistematica di letteratura.

those reported above for meningococcal vaccination.¹² A multicenter survey carried out in 13 Western European countries investigated attitudes to vaccination in people aged >50 years.²³ As reported in **table 2**, the principal determinants for pneumococcal vaccination uptake were perception of vaccination efficacy and effectiveness and a strong recommendation from the GP. Similarly, factors associated with vaccine refusal were: lack of physician recommendation or vaccine awareness, and not being concerned about pneumococcal infections.

Finally, the results of two cross-sectional studies performed in 2012 in two Belgian regions among parents of 18-24 months-old children were reported.²⁴

The predictor most often and most strongly associated with PCV7 vaccination was Mother and Child clinic attendance (Wallonia region: OR 2.8; 95%CI 1.5-5.1; Brussels-Capital region: OR 4.8; 95%CI 2.4-9.4).²⁴ In Wallonia, having only one child was related with higher vaccination uptake (OR 2.8; 95%CI 1.3-6.0). Higher vaccination rates were also observed in Brussels-Capital Region among children who attended a daycare centre (OR 2.1; 95%CI 1.0-4.5).²⁴

DISCUSSION

Meningococcal vaccination

Meningococcal C vaccination is a fundamental measure to prevent invasive meningococcal disease (IMD) among children and adolescents.²⁵ According to our revision, in countries with an active universal meningococcal vaccination program like the Netherlands and Belgium, uptake among parents of European children is strongly related with higher education level and socioeconomic status of the parents.^{7,10-12,26}

Probably, in these cases, parents have higher awareness regarding meningococcal vaccination.⁹ In particular, parents in Belgium can choose to have their child immunized in Mother and Child health or well-baby clinics, which are public organizations, or by a practitioner. Administration is free of charge when performed at the clinics, while a fee must be paid if the vaccine is administered by a GP or a pediatrician.²⁶ For these reasons, appropriate counseling about vaccination strategies represents an essential determinant for parents of 18-24 month old children in Belgium.⁸ Conversely, in Poland pneumococcal vaccine is not included in the national immunization program.²⁶

Nevertheless, in addition to free-of-charge vaccines listed in the mandatory immunization schedule, self-paid vaccinations are also recommended for Polish children (pneumococcal, meningococcal, rotavirus, etc.).²⁶ Indeed, in this context, determinants of vaccination uptake/refusal were mainly socioeconomic (family income, cost of the vaccine).²⁶

Moreover, older parent age and a small number of children in the family, predictors that are already known in the literature and may be associated with higher socioeconomic status, were related with higher vaccination coverage.^{26,27}

Among adolescents, a British study demonstrated the benefit of a school-based vaccination program.⁷ In particular, UK students demonstrated better meningococcal vaccination coverage and attitudes compared to Irish student (no school-based vaccination strategy was implemented in Ireland).⁷

Pneumococcal vaccination

The value of pneumococcal conjugate vaccination in IPD prevention is recognized worldwide.^{19,20} Nonetheless, in some Eu-

European countries this is a recommended self-paid vaccination for children.²⁶ Therefore, in Poland the principal determinants related with vaccination uptake were socioeconomic (family income, cost of vaccination, etc.), similarly to those observed for meningococcal vaccination in the same country.¹² Likewise in Belgium, where pneumococcal vaccination was fully offered only in mother and child clinics or in daycare centres, vaccination coverage was higher precisely in these contexts.^{24,26} Moreover, like in Poland, having only one child was a socioeconomic determinant associated with vaccination adherence.^{12,24}

Conversely, among healthy European adults PPSV23 vaccination uptake was related with a strong recommendation by their own general practitioner.^{22,23} Furthermore, the perception of pneumococcal disease danger and the perception of vaccination efficacy and effectiveness were factors strongly linked with adequate counseling by health care professionals.^{22,23}

CONCLUSIONS

Our results show that communication and information about meningococcal and pneumococcal vaccination for newborns and children should be targeted towards specific groups of par-

ents (low income or cultural level, younger age, different ethnicity). Moreover, it is essential to organize universal free-of-charge vaccination strategies. For healthy adults, conversely, the health professional's counseling activities on PPSV23 and in future on PCV13 vaccinations should be targeted on pneumococcal disease danger and pneumococcal vaccination efficacy and effectiveness. A strong recommendation for pneumococcal vaccination from general practitioners and a free-of-charge vaccination plan would also be important strategies.

Conflicts of interest: none declared

Funding: The working group and the project receive financial support from the Italian Centre for Disease Prevention and Control.

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CONTRIBUTIONS
INTERVENTI

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From surveillance to development of nutritional guidelines

Dalla sorveglianza allo sviluppo di raccomandazioni nutrizionali

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PLENARY SESSION 4
Saturday 17 October
h. 10.00-11.30
Brown Room 3

Abstract

In Italy, like in most parts of the world, 30% of children and almost 50% of adults are overweight. This condition is one of the causes of non-communicable diseases responsible for over two thirds of DALYs, deaths and costs for healthcare. Current surveys confirm that overweight and obesity are associated with food habits which have changed, in Italy, in the last fifty years. Fewer and fewer people have been following a Mediterranean diet, which is considered an effective diet for the prevention of many diseases. The consumption of fruit, vegetables, legumes, whole cereals, and EVO oil has decreased, while the consumption of food with high energetic density and rich in sugar, salt, and added fat has increased, especially when eating out.

Schools and workplaces are the best places to promote healthy food habits and an active lifestyle. The aim is to involve families (including low-income families), educators, and catering services.

This type of intervention is not new to the National Health System and has already led to improvements: however, it is still possible to improve the use of resources and coordination between social, educational, and health services bringing the community to become its own health promoter.

Health operators have to be more aware of overweight as a health threat. The National Health Plan represents a commitment for Italy, the country hosting EXPO 2015, to fulfill the targets of the «Action Plan European Strategy for the Prevention and Control of Non-communicable Diseases 2012–2016» entrusting the Departments of Prevention with the interventions and development of a network of stakeholders.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 66-70)

Key words: food, nutrition, health, survey, Mediterranean diet

Riassunto

Le sorveglianze PASSI e Okkio alla salute rivelano che in Italia un terzo dei bambini e quasi la metà degli adulti sono in sovrappeso. Una condizione nota per essere causa di malattie croniche non trasmissibili che sono responsabili di oltre 3/4 delle morti premature e di quasi la metà del peso delle malattie. Le sorveglianze confermano, inoltre, l'associazione di sovrappeso e obesità con stili alimentari che negli ultimi 50 anni si sono allontanati dal modello mediterraneo. Penalizzato è soprattutto il consumo di frutta e ortaggi, legumi, cereali integrali, olio EVO, sostituiti da alimenti a crescente densità energetica, ricchi di zuccheri, grassi e sale consumati in fretta e sempre più fuori casa.

Scuola e mondo del lavoro sono contesti importanti per promuovere un'alimentazione salutare e una vita attiva coinvolgendo i diversi soggetti interessati: la ristorazione, gli educatori, le famiglie (anche quelle più penalizzate perché di basso livello socio-economico).

Si tratta di interventi non nuovi per il Servizio sanitario nazionale e che hanno già dato qualche risultato. Restano comunque ampi margini di miglioramento circa l'uso delle risorse, il coordinamento fra gli assi sanitari, educativi e sociali, anche nell'ottica di coinvolgere l'intera comunità come imprenditrice della propria salute. Per parte loro, gli operatori sanitari devono essere consapevoli della grave minaccia per la salute rappresentata dall'eccesso ponderale (consapevolezza che secondo le sorveglianze è troppo bassa e in riduzione).

Il Piano nazionale della prevenzione 2014-18 impegna tutte le politiche e l'intero Paese, sede di *Expo 2015*, dedicato all'alimentazione, nella sfida per il raggiungimento degli obiettivi del «Piano di azione globale OMS per la prevenzione delle malattie croniche non trasmissibili 2013-2020», affidando ai Dipartimenti di prevenzione la *governance* degli interventi con l'impegno a sviluppare una rete integrata tra portatori di interessi (istituzionali e no).

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 66-70)

Parole chiave: alimenti, nutrizione, salute, sorveglianza, dieta mediterranea

INTRODUCTION

The *2013 Global Burden of Disease* highlighted that, for the first time in the world, the number of diseases due to insufficient caloric intake (868 million malnourished people) was overcome by the number of diseases related to wrong dietary habits (1.5 billion of overweight/obese people),¹ a phenomenon involving even Italy.

Surveillance systems used in Italy, in particular «Okkio alla salute» (Take care of your health)^a 2014² and PASSI (Steps)^b 2010-2013³ pointed out that 30% of teenagers and almost 50% of adults are overweight and, in every class of age, overweight, lack of physical activity, and sedentary lifestyle were more frequent in the groups of population with lower educational and socio-economic level. For this reason we need interventions to support social equity. People often have a wrong perception about their weight and lifestyle. This phenomenon is common even among parents of overweight or obese children and it must be taken in account, since awareness is a key factor in changing inadequate lifestyles.

Surveillance data pointed out that wrong food habits were associated with overweight, and they were included among the main health threats by the *2013 Global Burden of Disease*. In particular, in Italy dietary factors represented the first risk factor (13% of the burden of disease expressed in terms of DALYs) for the most important chronic-degenerative diseases: cardio-cerebrovascular diseases, cancer, type II diabetes. A low fruit diet ranked fifth in the risk factor list. The 2014 «Okkio alla salute» surveillance pointed out that in Italy barely 8% of children 9 years old consumed the suggested five-a-day portions of fruit and vegetables, while one quarter of children did not eat any at all. Even the percentage of adolescents eating fruit and vegetables at least once a day was too low.⁴

As far as adults were concerned, the situation was quite similar. The 2010-2013 PASSI surveillance showed that, on average, in Italy only 10% of adults ate five-a-day portions of fruit and vegetables (48% of them consumed at least three portions). Women (11%), adults 50-69 years old (13%), educated (11%) and well-off (11%) people were more frequent consumers of fruit and vegetables.

There was even a geographic pattern: compliance to the five-a-day was higher in the northern regions (Liguria 18%) than in southern ones (Basilicata/Calabria 5%), in spite of the greater abundance of vegetables in the traditional meals of the latter regions.

From 2008 to 2013 there was a decrease in the consumption of fruit and vegetables throughout Italy (from 10.2% to 9.1%); the decrease was more evident in the central regions (from 10% to 8.5%), perhaps partly due to the economic crisis of the last few years.

According to the Nomisma study,⁵ in 2014 the yearly consumption of fresh fruit and vegetables was 130 kg per capita, not more than 360 g per day (it had been 400 g in 2000), with a decrease of 15% of fruit and 6% of vegetables in the last 15 years. Even though the economic crisis has certainly contributed to reducing the consumption of fruit and vegetables, it is in any case true that there was already a trend of progressive detachment of Italian people from the Mediterranean diet pattern: indeed the Mediterranean Adequacy Index moved from 10 (1960) to 0.5-1.5 (2013) and, paradoxically, this trend was more evident in those southern regions where the Mediterranean diet was born.⁶ On the other hand, there is growing evidence of the positive role that the Mediterranean diet has on the prevention of chronic diseases (cardio-cerebrovascular diseases, cancer, diabetes, neuro-degenerative diseases). The introduction of food and beverages with higher energetic density and richer in sugar, fat and salt, on the market is a major culprit. These kinds of food are promoted by aggressive marketing strategies, offering greater portions at lower cost, and are especially popular among poorer and less educated consumers, who represent the best target for junk food advertising campaigns. In addition, the import of food patterns like fast food, the decreasing time dedicated to the purchase, preparation, and consumption of food, the dramatic growth in the number of people eating out (12 million Italian eat out, Fipe 2012)⁷ for various reasons like study, work or leisure time, has led to the development of catering.

SCHOOL SETTING

However, catering represents an amazing context to promote a healthy education (decrease use of salt, increase consumption of fruit/vegetables and of all other food useful to fight obesity and chronic diseases) and it is a strong opportunity to develop health education, even at school. The *Osservasalute* report (2009-10)⁸ indicated that those attending a school canteen consume more fruit and vegetables. Services of Food Hygiene and Nutrition of the Department of Prevention are active in the field of health protection related to food through initiatives of nutrition surveillance like «Okkio alla salute», food safety and promotion of healthy lifestyles in different settings like schools, workplaces, and other public places.

The result of this commitment was confirmed by «Okkio alla salute» reporting in 2014 a decrease in the percentage of overweight children 8-9 years old: 20.9% were overweight (23.2% in 2008) and 9.8% were obese (12% in 2008). Furthermore, the improvement of food (reduced consumption of heavy snacks and carbonated and carbohydrate-rich beverages) and physical activity habits were reported.² The 2014 Italy HBSC (Health Behaviour in School-aged Children) surveillance regarding school teenagers (11, 13, and 15 years old) showed a decrease

^a OKkio alla SALUTE ("Take care of your health") is a surveillance system focusing on the weight of primary school children (6-10 years of age), their diets and the physical activities they perform (or any connected risk behaviour). It was started in 2007 within the framework of the "System to investigate behavioural risks of children aged 6-17", promoted and financed by the Ministry of Health/CCM, and it is coordinated by the National Centre of Epidemiology, Surveillance and Health Promotion (CNESPS) of the Advanced Health Institute (ISS), in collaboration with Regions, Local Health Units (AUSL), the Ministry of Education, universities and research bodies.

^b PASSI ("Steps") (Progress of health companies for health in Italy) is a health surveillance program which collects, on a continuous basis and through samplings, information about adults in Italy (18-69), about their lifestyles and behavioural risk factors connected with the onset of non-transmissible chronic diseases and the degree of knowledge and compliance with the action plans the state has been implementing for their prevention. Coordinated by the (CNESPS) of the Advanced Health Institute (ISS), it is managed by Local Health Companies directly, in cooperation with the regions and autonomous provinces.

in overweight in all ages, more evident among those aged 11 years (from 23.3% to 19.9% in males and from 17.1% to 13.5% in females) if compared to 2010. Even obesity decreased, especially among those aged 13 (from 4.5% to 3.3% in males and from 2.4% to 1.3% in females). Even in this case, like for the younger children, there was a geographic pattern showing higher percentages of overweight and obesity among central and southern regions. As far as food habits were concerned, it was shown that only a low percentage of students consumed fruit and vegetables at least once a day, even though the trend was growing if compared to 2010: the highest value was among 15-year-old girls.⁴ In spite of some data suggesting a trend inversion about overweight, which seem to support strategies used so far, there are still worrisome data indicating higher percentages of overweight and obesity among school children particularly in southern regions. That is why it is necessary to improve food habits and promote a more active physical lifestyle.

It will be essential to carry out programs within the 2014-2018 National Health Plan and related Regional Health Plans, according to scientific conclusions expressed by the «Okkio alla salute» technical committee (Report ISTISAN 15/1).⁹

The interventions in schools and catering are the most important, because these settings play an essential role in improving food habits.

In a context marked by a progressive reduction of economic and human resources, it is more and more important to develop comprehensive initiatives among ministries, local and regional health authorities, education, university, agriculture and environment sectors so as to avoid projects which are repetitive, redundant or – even worse – incoherent, like some interventions recently carried out in school settings. It is especially important to ensure continuity to interventions by including them in the school curricula.

The recent agreement between Health and Education Ministers, promoted by the General Direction of Health Prevention, is a right step in this direction. Besides, it is necessary to improve the coordination with the Minister of Agriculture, responsible for funds and achievement of the «Fruit in school» program, financed for the 2013-2014 edition (the fifth consecutive one) with over €20 million, according to the CE Regulation 1234/2007.¹⁰

These are important economic resources not only for fruit suppliers, but above all for the educational target of promoting consumption of fruit and vegetables among children, which, as previously described, is still inadequate. Since the «Okkio alla salute» project, which targets the same years and people as the fruit intervention, assesses the situation as unsatisfactory, assessment tools should be designed through common work between the Education and Health sectors. This initiative is also necessary to prevent criticism about catering services like those voiced, at times, by parents and confirmed by health authority checks. In other words, it is necessary to provide for new terms of contract in school catering, requiring meals consistent with the new LARN (*Dietary Reference Values for Italian Population*, edited by SINU, the Italian Society of Human Nutrition) and guidelines.

We should deliver few but clear messages and we should involve school catering (starting from day-care centres and kindergartens), educators, children themselves while they are eating meals and snacks. The reduction of heavy snacks from 80% (2008) to 50% (2014), recorded by «Okkio alla salute» is another important result.

The involvement of families is also essential as far as school catering is concerned. According to the Eurobarometro (EUFA 2010)¹¹ and PASSI (2012)¹² surveys and to the current experience of Food Safety and Nutrition services, such as that in Bologna, families are more and more careful about the quality of food, focusing particularly on pesticide pollution and preservatives. Consequently, families now demand organic food even though their belief is more based on some regional and national laws tending to promote regional products with a reduced environmental impact than on a proven health benefit.¹³

It should be noted that organic products have a cost that is 50% higher than conventional ones, in a context where official inspections show that pollution levels are very limited even for “conventional” fruit and vegetables: 0.4% were irregular *vs* 1.6% in the EU, with over 60% without any residual of pesticides, (source: *Health Minister – Official control on food pesticides 2012*).¹⁴

The choice of organic food, which is the right choice in the presence of sufficient economic resources, becomes questionable when needy families are not able to pay for the canteen fee and would prefer to give a sandwich prepared at home to their child to replace the meal that they cannot afford, with all the negative educational and managerial consequences that may derive from this situation. At times, as happened in Bologna, parents demand organic food, while, at the same time, requesting a replacement of fruit, vegetables, fish, and legumes that their children don't like simply because they are not provided in their home menu.

We should not forget that Bologna does not have a traditional Mediterranean diet, indeed its nickname is «fat Bologna» and its most traditional salami, «mortadella», is known abroad as «bologna» sausage. In fact, when people heard about the (moreover unfounded) possibility that, according to regional guidelines, «bologna» would be excluded from school catering there was a public debate on mass-media that lasted 4 months in 2012. In spite of this situation, in the territory of the Bologna AUSL (Local Health Authority) which includes 45 municipalities, we have already achieved a number of results. One hundred percent of students has access to a canteen, attended by the 90% of them, with a menu that is verified by the Food Safety and Nutrition service according to regional and national guidelines. The percentage of overweight 9-year-old children is below the cut-off of 25% (8.5% overweight and 5.9% obese *vs* 21% and 7.7% of the Emilia Romagna regional percentages and 20.9% and 9.8% of the national percentages), confirming a declining trend for obesity since 2010.

As far as food habits are concerned, the mid-morning snack is adequate in 74.4% of cases (*vs* 44.6% in Italy), while the 5 daily portions of fruit and vegetables are consumed by 13.2% of children (*vs* 8.1% in the entire Italy) (Okkio alla salute 2014).

This result was partly fulfilled thanks to the distribution of fruit, milk, or yoghurt, mainly in the mid-morning, in schools (69% of classes involved), while 52% of classes took part in initiatives of promotion and consumption of healthy food («Okkio alla salute 2014»).

In 2015, a survey on children's satisfaction with catering started in some primary schools, targeting children, teachers, and parents, and representing an important educational tool for all the people involved. This experience confirmed the following opinions, which moreover have already been scientifically acknowledged:

- school meals are the best occasion to promote correct nutrition;
- teachers' behaviour in school makes the difference between acceptance and refusal (as does parents' behaviour at home);
- children are actually able to judge themselves and are prone to change idea if they are listened to and motivated;
- an experience like this is able to involve even the most sceptical parents, focusing particularly on the environmental impact of food, as well as on promoting further considerations by consumers, public and catering services, and the entire community.

COMMUNITY SETTING

This experience was also included in a community project on healthy nutrition and active life for all ages, from day care centres for toddlers to social centres for the elderly. The name of this project is: «Cheers! Citizens as entrepreneurs of their quality of life».

The 2014-2015 project, carried out in a neighbourhood of Bologna (Navile), involved health (Local Health Authorities), education (university, schools), and social services (public services, and non-profit organizations).

Needs, resources (including already existing projects) and synergies were identified to develop a context enhancing healthy nutrition and active lifestyle. Process and outcome assessment tools were provided for each single step and at a community level. In the first 16 months, meetings and cooking workshops were held in 10 day care centres/kindergartens. Outdoor education with teachers, children, and parents was promoted in 33 primary school classes. The empowerment pathway involved parents, teachers, and children as active protagonists. Food education was included in literacy courses for foreign women, inter-generational cooking workshops were held in social centres, games and non-competitive sport activities were fostered within replanned green areas, parents and senior citizens became promoters of vegetable gardens in kindergartens, even a jail was included in interventions on food education, involving inmates who were also canteen cooks. Journals, participation to special events (white night, spring festival), and other activities were all documented with videos, photos, and interviews. As we wait for the project to end (December 2016), it is possible to disclose some considerations concerning an experience which confirms the usefulness of promoting community health, inter-generational bridges, and contrast of inequalities. The major challenge of the project is to achieve a

stable change in the community, one that will persist even after the conclusion of the project.

WORKPLACE SETTING

Another important setting for the enhancement of a proper nutrition style is the workplace, as highlighted by the most important international health agencies and the National Prevention Plan 2014-2018.¹⁵

The workplace is for an adult what school is for a child. It is a context in which even those penalized for cultural and social reasons can be involved, along with their family.

Another example concerning the Bologna AUSL (Local Health Authority) in the period 2012-2013 regarded construction workers, with structural interventions carried out in canteens and through cooperation with the vocational schools for construction workers of the Bologna province, local media, occupational physicians, manufacturer associations. As previously seen for schools, even in this case the actions were evidence based.

This is also true for actions performed in the healthcare sector. Many AUSLs, within their social accountability, have promoted actions in favour of their employees, taking into account proper nutrition, customer satisfaction, and environmental protection within the catering service.

On the other hand, it is essential that every health operator becomes a testimonial of healthy nutrition. In this sense, it is urgent to invert the trend showing insufficient attention to overweight by health workers, as described in the 2010-2013 PASSI surveillance report. Only 50% of overweight or obese people interviewed said they had received advice from a health operator about starting a diet to lose weight. Among those advised, 37% actually started a diet, while only 13% of those that didn't receive any advice did. In the period 2008-2013 the percentage of overweight people who were advised to follow a diet decreased by 5.5 % in all areas (-4.4% in the North and Centre and -8% in the South).

Last but not least, it is necessary to act on salt consumption, which in Italy is double the recommended daily intake,¹⁶ in order to reduce the occurrence of hypertension, defined as the first health threat in the *2013 Global Burden of Disease*.

An agreement like that achieved in some Italian regions (Lombardia, Emilia-Romagna)¹⁷ with bakers' representatives to reduce salt in bread should be extended to the entire country. A global policy of diminution in the use of salt (preferring in any case iodized salt) in catering, commercial, and domestic settings should be fostered.

CONCLUSIONS

This document's proposals concerning the complex issue of prevention of chronic diseases through lifestyle improvement, although not exhaustive, can help to set up a framework in which the targets of the «Action Plan European Strategy for the Prevention and Control of Non-communicable Diseases 2012-2016»¹⁸ may be fulfilled in Italy within National Health Plan 2014-2019 and the Regional Health Plans.

Departments of Prevention have a double role: implementation

of their own preventive interventions and governance of the interventions performed by other agencies and services, so it is possible to amplify the network of stakeholders by linking local communities to regional and national governments in a bidirectional manner.

Departments of Prevention are recognized to have «a leadership based upon the prevention culture of public health operators and enhanced by the previous National Prevention Plans». This leadership, as far as food and nutrition are concerned, belongs to Food Safety and Nutrition Services.

To fulfill the ambitious targets of the Prevention Plans it will

be essential to guarantee economic resources in terms of at least 5% of the National Fund for Healthcare, i.e., the amount allotted by law for all prevention. The percentage actually available for the entire Department is not more than 4.2%, and for Food Hygiene and Nutrition Services alone a scarce 0.29%.²⁰

In Italy, the country hosting «EXPO 2015 - Feeding the planet energy for Life», the Food Safety and Nutrition Services will starve in the near future without these economic resources.

Conflicts of interest: none declared

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WORKSHOP 8
Thursday 15 October
h. 14.00-15.30
Brown Room 2

The importance of indicators in monitoring water quality according to European directives

Importanza dell'utilizzo di indicatori per il monitoraggio della qualità dell'acqua secondo la normative europea

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Abstract

Directive 2000/60/EC and subsequent legislation provide a list of priority substances to be measured and monitored in EU water bodies and require the adoption of analytical methods that ensure comparability of the data collected in all Member States. These regulations and standards have gradually improved water quality in the EU. However, new drugs, whose effects on ecosystems and health are still to be determined, are detected with growing frequency. The Member States are now called upon to characterize and monitor these pollutants in view of their possible inclusion in the priority substance list.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 71-75)

Key words: water, monitoring, European directives, priority pollutants

Riassunto

La Direttiva 2000/60/CE e le successive normative in materia hanno individuato un elenco di sostanze prioritarie da misurare e monitorare nei bacini acquiferi dell'Unione europea, con l'adozione di metodologie che rendano i dati confrontabili in tutti gli Stati membri. Con l'introduzione di tali norme la qualità delle acque dell'UE ha subito un progressivo miglioramento, sebbene nuove sostanze, i cui effetti non sono stati al momento accertati, siano riscontrate frequentemente richiedendo l'impegno degli Stati membri per la caratterizzazione di tali inquinanti e per il loro monitoraggio al fine di inserirle a pieno titolo tra le sostanze prioritarie.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 71-75)

Parole chiave: acqua, monitoraggio, direttive europee, inquinanti prioritari

INTRODUCTION

Surface waters receive large quantities of hazardous substances, which mainly derive from industrial, agricultural, domestic sources, and municipal sewage-treatment plants as well as surface runoff and atmospheric deposition. In this context, the Water Framework Directive (WFD; Directive 2000/60/EC) laid down criteria to protect inland surface waters, transitional waters, coastal waters and groundwater, to prevent their ecological decline, protect and enhance the status of aquatic ecosystems, promote sustainable water use based on long-term protection of available water resources, and contribute to mitigating the effects of floods and droughts. The Directive provides for the first time a list of substances, defined as priority pollutants (PPs), whose presence and levels need close monitoring, and lays down the methods to be applied to achieve compliance with legal PP levels to protect ecosystems and human health.

In addition to the PPs listed in Directive 2000/60/EC, public

health bodies are also required to monitor a multitude of new substances, which over the past decade have been demonstrated to exert harmful effect on the environment and human health. At least two significant directives have amended Directive 2000/60/EC: Directive 2008/105/EC sets environmental quality standards (EQSs) for 30 PPs listed in Decision 2455/2001/EC and for eight other pollutants that were already regulated at EU level; and Directive 2009/90/EC sets technical specifications for chemical analysis and monitoring of water status, and minimum performance criteria for the analytical methods applied, which must be sufficiently sensitive to ensure that any overrun of EQSs is reliably detected and measured, with a view to providing understandable and relevant monitoring data.

The latest directive on water, 2013/39/EU, updated the list of PPs, which now total 45, redefines the criteria for assessing EQSs, and provides a watch list of substances whose mechanisms of damage to ecosystems and health are still unclear.

EQSs and threshold values for these substances need to be defined, to facilitate planning of priorities for action and to integrate data from the water analysis and monitoring programs implemented so far.

The new regulations reflect a change in focus with regard to the types of substances that are to be sought and monitored, and the main problems in water body management it seems to associate to what are known as emerging pollutants.

The water quality directives have led to the adoption by Member States of monitoring criteria and plans and of risk assessment methodologies for the substances included in the watch list. A key goal of the Water Framework Directive (WFD) and of the latest Directive is to achieve a good chemical status of waters. Comparing different directives with actual water quality, different approaches of standard settings are applied and potential treatment options are discussed. Each Member State has approved a National Implementation Plan (NIP) describing how each will meet the directive goals and the measures that will be implemented to eliminate or reduce the release of PPs into the environment by the use of best available techniques (BATs) and application of best environmental practices (BEPs). The main innovation introduced by the latest directive is a watch list for 10 substances or substance groups, of specific matrices for their monitoring, and a list of methods of analysis that can be adopted, none of which entail excessive cost. The substances included in the watch list are selected from those that, according to available information, may present a significant risk for the aquatic environment and human health and for which monitoring data are currently insufficient. Diclofenac, 17- β -estradiol (E2), and 17- β -ethinylestradiol (EE2) are included in the first list and data are collected to facilitate the determination of measures to address the risks posed by these substances. The new mandate of the Working Group (2013 to 2015), approved by the Water Directors, envisages continuation of the activity on effect-based tools, in particular, in relation to the detection and evaluation of effects caused by mixtures of pollutants.

The aim of this paper is to gain insights into the problems associated with PPs and emerging pollutants at the European level, so as to improve the use of water quality indicators in the light of the new EU legislation.

METHODS

An overview of the literature published since 2000 and reports of international agencies regarding the concentrations of priority pollutants listed in the European directives on water safeguard by the official EU database, was made.

A PubMed search for papers addressing the levels of these chemicals in EU water bodies was conducted using «biomonitoring AND water», «priority pollutants AND water», «heavy metal AND water», «pesticides AND water», «organotin compounds AND water», «endocrine disruptor AND water» as the key words. Only papers with minimum performance criteria for the analytical methods applied were selected. A comparison of the ecological status of aquatic ecosystems with respect to the EQSs or maximum admissible concentrations (MACs)

reported in the Directives for PPs, as well as the best monitoring action that better reflects the ecological risk associated with each class of discussed contaminant, was conducted.

RESULTS

Several methods have been applied to comply with the obligations set by the Directives and Member States have adopted the best technology and monitoring methods to measure PP levels in water basins and reduce them to meet legal targets. Pesticides have long been and still are an important class of contaminants in many EU countries. Their levels in several water samples collected from water mains, dug and deep wells exceeded MACs; in particular, simazine, fenitrothion, and diazinon MACs were exceeded in most samples, whereas those for DDT, methoxychlor, acephate, and atrazine were exceeded less frequently.¹

A ranking index based on the measured concentrations of several priority pesticides in Spanish rivers and its ecotoxicological potential (EC50 values for algae, *Daphnia* sp., and fish), revealed a high risk for the aquatic ecosystems.² Notably, insecticides were identified as most important for *Daphnia* sp. (chlorpyrifos, chlorfenvinphos, diazinon, etc.) with RI up to 37%, followed by alkylphenols including octylphenol, nonylphenol, and related compounds. In Portugal, alachlor, atrazine, chlorfenvinphos, chlorpyrifos, endosulfan, simazine, and terbutryn detected in rivers exceeded their respective EQS values, with implications for the classification of the ecological status of surface water bodies in Portugal.³

Among all priority pesticides, agricultural insecticides constitute a major driver of animal biodiversity loss in freshwater ecosystems, and the global extent of their effects and the spatial extent of exposure remain largely unknown. Unfortunately, Europe – especially the southern and central European countries – represents a hotspot for insecticide contamination, as was pointed out by a predicted model for insecticides in global surface water developed by Ippolito et al.⁴

As regards to metals and metal compounds, cadmium (Cd), lead (Pb), and mercury (Hg) are included in the watch list. Metal contamination of water basins is declining, and although their concentrations are in the range set by the WFD for 2015, in some European water systems they may far exceed (up to 10-fold) the ground content limit set for 2021.⁵ Nevertheless, monitoring programs only based on total metal determination in water have been recognized to be lacking, as metals present even at undetectable concentrations in water are strongly accumulated in fish. Moreover, when high concentrations of Hg are found in sediments, this indicates that the aquatic ecosystem may present pollution problems in regards to this metal, as demonstrated by the high Hg levels found in fish.⁶⁻⁸ In order to evaluate the influence of metal pollution on the aquatic ecological status, several biological indicators, such as macroinvertebrates (IBMWP), diatoms (IPS), and macrophytes (IVAM), have been successfully considered from an integrated point of view.⁸⁻¹¹

Recent data also show the advantage of a multidisciplinary approach based on bioindicator organisms and biomarkers of ex-

posure to monitor the acute and chronic adverse effects of both metals and organochloride compounds.^{6,12,13}

Persistent organic pollutants (POPs) are a group of organic chemicals of special concern for their toxicity, persistence, long-range transport, and bioaccumulative potential. PCB levels often exceed the national EQS, such as data reported in the Venice lagoon (5-2,049 µg/kg and 4.24-239.15 µg/kg),¹⁴ Oslofjord, Norway, (1-764 µg/kg),¹⁵ the Sado River estuary, Portugal (1.3-114 µg/kg),¹⁶ the Scheldt estuary, Netherlands-Belgium (0.47-136 µg/kg),¹⁷ the Thau lagoon, France (2.53-33.32 µg/kg),¹⁸ the intertidal zone of the North Sea (4.11-8.44 µg/kg),¹⁹ the Guadiana estuary, Portugal (0.1-1.8 µg/kg),¹⁶ and the Elbe estuary, Germany (2-85 µg/kg).²⁰ Data available range from heavily polluted to minimally impacted areas. In a wide monitoring study on global distribution of PCBs in the Mediterranean Sea, coastal lagoons reported PCB levels between 0.9 and 5,600 µg/kg.²¹

Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs), despite their global distribution, have never been intentionally produced. However, a variety of chemical and thermal processes, including the manufacture of chlorinated intermediates and the combustion of chlorinated materials, can result in the formation and release of PCDD/Fs. There are some contaminated coastal areas in Europe, e.g., the Venice lagoon (16-126,561 ng/kg),²² the Elbe estuary, Germany (711-169,605 ng/kg),²³ the Norwegian Grenlandsfjords (25,000-730,000 ng/kg),²⁴ and the Finnish Gulf (430-52,900 ng/kg),²⁵ while other areas show moderate contamination, e.g., the Thau lagoon, France (153-1656 ng/kg),¹⁸ the Spanish northern Atlantic coast (0.15-3.99 ng/kg),²⁶ and the intertidal zone of the North Sea (0.124-3.156 ng/kg).¹⁹

Organotin compounds (OTCs) are widespread pollutants, frequently used as additives in antifouling agents for ships, which have contributed to the contamination of surface waters and aquatic systems in the last decades. These compounds exhibit a diversity of physical and chemical properties which offer various fields of application in industry and agriculture. In some European waters OTCs are found to be below the Directive's MAC.²⁷⁻²⁹ Despite its decreasing contamination, TBT is still listed in the new directives, because of its persistent release from sediments, so much so that certain water bodies are still particularly contaminated with concentrations up to 110 ng/l.^{30,31} Sampling of organotins in water is problematic, as normally large volume samples are needed in order to achieve the concentrations necessary to fulfil the current EQS requirements for TBT in the WFD (0.2 ng/l). Ultra-clean sampling containers and laboratories are necessary to achieve low background blanks, along with sensitive and robust instrumental methods. An alternative method for monitoring organotin compounds in water is the use of passive sampling, and this technique has received some attention over the past decade.

In a recent case study of representative Mediterranean rivers, more than 160 chemicals were detected in the Llobregat. Industrial compounds and pharmaceuticals were predominant, followed by personal care products, pesticides, perfluoroalkylated substances and illegal drugs.³² A review on emerging contami-

nants in UK surface water and wastewaters reports approximately 70 pharmaceuticals belonging to a variety of therapeutic classes in UK environmental waters.³³ As regards pharmaceuticals, the latest water Directive (2013/39/EU) prescribes a number of actions for measuring them; once they have been characterized, Member States are required to begin their monitoring. Even though pharmaceutical products have been used for centuries, from an ecotoxicological viewpoint active pharmaceutical ingredients (APIs) are considered emerging environmental contaminants, because suitable and accurate analytical and sampling techniques to quantify them in environmental matrices have only recently been devised.³⁴ In this context, Petrie et al., (2015), highlight the importance of combined use of chemical analysis and biological indicators to better assess environmental impact from ECs, to avoid that transformation products go undetected and to develop a more accurate environmental risk assessment.

DISCUSSION

The present overview of studies, carried out to evaluate EU water policy objectives, which began to be set in 2000, documented only a small improvement in water quality in all Member States. Chemical status of a large proportion of water bodies is unknown due to poor chemical monitoring in many Member States, either because not all PPs are monitored or because few water bodies are monitored. A weak reduction in PP levels has been documented in water bodies across Europe, except those where PPs have been present longest. Nevertheless, organic substances with toxic properties such as pharmaceuticals, biocides, hormones, antibiotics, personal care products, flame retardants, and endocrine active substances, i.e., «emerging contaminants», are increasingly detected in the wider environment. Furthermore, the additive, synergistic, or antagonistic biological effects of those substances are not always clear because many of them are usually present at low or even barely detectable levels in surface waters, thus giving no clear evidence for their environmental risk.³⁵ This gap in knowledge has been covered by the use of both in vitro and in vivo bioassays^{36,37} and by the use of biomarkers^{6,13} for several kinds of contaminants.

Emerging contaminants are characterized by a diffuse presence in the environment, lack of knowledge of their medium- or long-term effects on human health and ecosystems, and poor coverage by current regulations. Among the mechanisms of action hypothesized for these contaminants, the most likely are endocrine disruptor chemicals (EDCs), adversely affecting development and reproduction. The classification criteria adopted for these substances, and for chemicals in general, include not only their environmental and health effects but also their production volumes.³⁸ The last World Health Organization (WHO) report, *State of the Science of Endocrine Disrupting Chemicals*, confirms that exposures to EDCs affect the reproductive health of wildlife species. Over the past 10 years, a high incidence and an increasing trend of many endocrine-related disorders in humans have been observed.³⁹ There has been a dramatic shift in focus from investigating associations between adult exposures to EDCs and disease outcomes to linking developmental exposures to disease outcomes later in life. Chil-

dren are the most vulnerable humans and exposure to EDCs during foetal development and puberty plays a role in the increased incidences of reproductive diseases, endocrine-related cancers, behavioural and learning problems, including ADHD, infections, asthma, and perhaps obesity and diabetes in humans.³⁹ In response to the potential hazard of EDCs in the aquatic environment, several screening programs have been implemented using a variety of chemical analyses. One of the main limitation is the possibility to detect their presence in water bodies at very low concentration levels (from µg/l up to pg/l), prioritizing the development of high-performance analytical techniques.⁴⁰ Analytical methods have been developed to successfully determine ultra-traces of target EDCs in the aquatic environment by gas chromatography coupled to mass spectrometry (GC-MS), or gas chromatography–tandem mass spectrometry (GC-MS-MS), as well as detecting estrogens in different matrices by liquid chromatography–tandem mass spectrometry (LC-MS-MS); recently, a new screening method has been introduced for EDCs employing stir bar sorptive extraction (SBSE). These methods provide the highest certainty of detection and the lowest detection limits, which are in the range of 0.1–0.5 for surface waters and in the range of 1–2 ng/l in sewage effluents. It has to be emphasized that effective concentrations are often in the range of the limit of detection.⁴¹ International literature, in accordance with the Water Directive guidelines, considers bioindicators as the best available means to meet their goals. These organisms are resistant to contamination and can accumulate pollutants, enabling the calculation of a relationship between concentration and the level of environmental alteration that has occurred over time. Bioindicators have the advantage of being easily available, practical to use even in special operating conditions (e.g., canals, drains, wells, etc.), robust, and inexpensive (most artificial supports such as DGT), enabling extensive testing. To date, the adoption of different methods to detect PPs persists, depending on PP type and Member State. These discrepancies were the reason why Directive 90/2009/EC set criteria to ensure data consistency across studies.

Europe is a variegated area where river basin water management has undergone progressive homogenization in terms of both the methods used to measure PPs and water management. Directive 2009/90/EC laid down the criteria for EQS setting according to standard methods and processes across Europe. According to these criteria, high physicochemical water quality is one where synthetic pollutant concentrations are close to zero or below the limit of quantitation (LoQ) of the most advanced methods of analysis, and good if concentrations are lower than the EQSs.

In Italy, the reliability of the monitoring data provided by ARPA is ensured by the ISPRA Environmental Metrology Service through compliance with UNI EN ISO 17025 and uncertainty levels are close to the accepted limits. Data then undergo inter-comparison through collection of information on PP concentrations from various laboratories, to evaluate their overall quality. Directive 2013/39/EC requires member States to analyze the long-term trend of concentrations of PPs that tend to accumulate in sediment and/or biota, and define the frequency of monitoring. Member States may propose analyses to identify new PPs or priority hazardous substances, or to classify certain PPs as priority hazardous substances and, where appropriate, to set EQSs for surface water, sediment, or biota.

CONCLUSION

In conclusion, water pollution caused by wastewater effluents still persists, despite three decades of efforts to clean up European surface waters, the enforcement of anti-pollution laws, and increased monitoring of water bodies. Despite the successful reduction of the levels of some water pollutants, detection of emerging substances entailing public health risks indicates that the fight against water body pollution will have to take on ever newer threats. Even though it is difficult to eliminate the risk arising from exposure, it is possible to reduce its effects through synergistic action and the adoption of reliable detection methods.

Conflicts of interest: none declared

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WORKSHOP 10
Friday 16 October
h. 8.30-10.00
Brown Room 3

Migrant health: the Apulian model

Lo stato di salute degli immigrati: il modello pugliese

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Abstract

Introduction. Since the 1990s Puglia has been totally involved in the reception and assistance of refugees. The prevention of infectious diseases among migrants, especially those residing in communities, is an important concern for public health authorities, since infectious diseases eliminated in Europe may still be widespread in the migrants' countries of origin, and other diseases may have a higher incidence than in European countries. Thus immigrants may contribute to the burden and spread of infectious diseases.

Objective. We describe the Apulian model of management and prevention of infectious disease among the population of Asylum Seeker Centres (CARA). It consists of a number of activities: surveillance of Poliovirus circulation, tuberculosis screening, seroprevalence studies of viral hepatitis and HIV, an immunization program for children, and syndromic surveillance. All the activities are organized and carried out by the Regional Observatory for Epidemiology among refugees hosted in the Bari Palese CARA.

Results. Surveillance of Poliovirus circulation has been carried out periodically since 2008 by assessing the presence of wild poliovirus or Sabin-like poliovirus in stool samples and seroprevalence studies. Data did not show circulation of poliovirus and indicated a good level of immunization against polio among refugees. Seroprevalence studies of viral hepatitis and HIV were carried out in 2008 and involved 529 refugees; 44 individuals (8.3%) were HBsAg positive, 24 (4.5%) were anti-HCV positive, 8 (1.5%) were HIV positive. Tuberculosis screening started in 2009 after a refugee's death due to tuberculosis and has been ongoing since then. The Mantoux tuberculin skin test is used and cutipositive migrants are examined by chest X-ray. Around 50% of migrants have been found to be cutipositive and 10% showed TB sequelae. Syndromic surveillance and an immunization program began in 2011 because of the significant increase in migration flow following civil unrest in North Africa; respiratory tract infection and diarrhoea were the most frequent notified syndromes. The immunization program involved 129 children coming from 23 countries: all received the appropriate vaccinations. The program also includes an annual special session to vaccinate all refugees against flu.

Conclusions. The results confirmed some traditional concerns about migrant health and especially about the control of infectious diseases among these populations and the need, from our point of view, to strengthen screening to aid the development of trust between migrants and resident population.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 76-80)

Parole chiave: health surveillance, infectious diseases, syndromic surveillance

Riassunto

Introduzione. Dagli anni Novanta la Puglia è in prima linea nell'accoglienza e assistenza dei migranti. La prevenzione delle malattie infettive tra i migranti, soprattutto residenti in centri di accoglienza o comunità, è cruciale per le autorità di sanità pubblica, perché nei Paesi d'origine dei migranti potrebbero circolare malattie infettive eliminate in Europa o altre patologie con un'incidenza superiore a quella dei Paesi europei. Per questo gli immigrati possono contribuire al carico e alla diffusione delle malattie infettive.

Obiettivo. Il lavoro descrive il modello pugliese di gestione e prevenzione delle malattie infettive nella popolazione che risiede nei centri per richiedenti asilo politico (CARA), che si compone di diverse attività: sorveglianza della circolazione di poliovirus, screening della tubercolosi, studi di sieroprevalenza di epatite virale e HIV, programma di vaccinazione per i bambini e sorveglianza sindromica. Tutte le attività sono organizzate e svolte dall'Osservatorio epidemiologico regionale presso il CARA di Bari Palese.

Risultati. La sorveglianza della circolazione di poliovirus viene effettuata periodicamente dal 2008 attraverso la valutazione della presenza di poliovirus selvaggio o di poliovirus di tipo Sabin in campioni di feci e con studi di sieroprevalenza. I dati non hanno mostrato circolazione dei poliovirus e indicano un buon livello di immunizzazione per la poliomielite tra i rifugiati. Gli studi di sieroprevalenza di epatite virale e HIV sono stati effettuati nel 2008 e hanno coinvolto 529 profughi; 44 (8,3%) sono risultati HBsAg positivi, 24 (4,5%) anti-HCV positivi, 8 (1,5%) sono risultati HIV positivi. Le attività di screening della tubercolosi sono iniziate nel 2009 dopo la morte per tubercolosi di una rifugiata e, da allora, sono effettuate routinariamente. Viene utilizzato il test di Mantoux e per i cutipositivi è prevista l'esecuzione della radiografia del torace. Circa il 50% dei migranti è risultato cutipositivo e il 10% degli immigrati ha mostrato sequele di tubercolosi. La sorveglianza sindromica e il programma di immunizza-

zione sono stati avviati nel 2011 a causa dell'importante aumento del flusso migratorio seguente disordini in Nord Africa; le infezioni delle vie respiratorie e la diarrea sono le sindromi più frequentemente notificate. Il programma di immunizzazione ha coinvolto 129 bambini provenienti da 23 Paesi, tutti hanno ricevuto le vaccinazioni appropriate. Il programma prevede anche una seduta annuale di vaccinazione contro l'influenza per tutti i rifugiati.

Conclusioni. I risultati hanno confermato alcuni assunti già consolidati sulla salute dei migranti, soprattutto per il controllo delle malattie infettive, e la necessità di implementare l'utilizzo di questi screening che servono a garantire la salute pubblica e a favorire lo sviluppo di un rapporto di fiducia tra i migranti e residenti.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 76-80)

Key words: sorveglianza sanitaria, malattie infettive, sorveglianza sindromica

INTRODUCTION

Italy was historically and until the 1970s a country of emigrants; beginning in the last thirty years of the 20th century, an important demographic change occurred, and the number of immigrants has grown exponentially since then.¹ According to the National Bureau of Statistics (Istat), in 2014 there were nearly 5 million foreign nationals legally residing in Italy, and this number had more than doubled compared to 2007. These are only a part of a multitude of «migrants lacking a regular status» that include undocumented migrants, asylum seekers, and irregular migrants.^{2,3}

Puglia region (also known as Apulia, a region in the South of Italy) has been considered a «border region» because it is wholly involved in the reception and assistance of migrants. In the 1990s, Puglia became the prime transit point for illegal immigrants from Albania arriving in Apulian ports by sea. At that time the Italian Government established three centres located along the Apulian coasts to ensure «first aid» and contrast clandestine migration due to the large number of landings. This was the first Italian experience of a large migratory flow, following which other immigration reception centres were founded and recognized by law in Italy.⁴ Since then, Puglia has remained one of the primary European entry points for immigrants, especially asylum seekers from Africa and Asia. In particular, in the past few years another large flow of refugees has been arriving from North Africa due to the Arab Spring.⁵ The refugees are normally received in ports equipped for the purpose and, following an initial registration and health assessment, are transferred to reception centres for asylum seekers located across the country. They stay in these centres until their migration status is cleared. All immigration centres, whether managed by private or public organizations, are provided with internal, self-managed, outpatient services.² Currently, there are 10 asylum seeker centres (CARAs) in Italy. Three of them are located in Puglia. Illegal migrants or people who commit crimes are transferred to special detention centres (Centres for Identification and Expulsion, CIE) and, after a period of detention, they are repatriated.

The prevention of infectious diseases among migrants, especially those residing in communities, is an important concern for public health authorities; refugees often come from areas where the prevalence of infectious diseases and standards of healthcare might be different compared with their host countries. In their countries of origin, infectious diseases eliminated in Europe

(such as poliomyelitis) could still be circulating, while other diseases (such as tuberculosis, hepatitis C, HIV) may have a higher incidence than in European countries.^{6,7} Immigrants may contribute to the burden and spread of infectious diseases.

Assistance is complicated because migrants are a highly heterogeneous population, with different socio-economic and cultural backgrounds. Moreover, living conditions within semi-open communities, such as immigration centres, could expose them to communicable disease.⁸

Since 2008, the Regional Observatory for Epidemiology (OER) has managed and organized prevention and screening of communicable diseases in the immigration centres in Puglia.⁹⁻¹²

Aim of this paper is to describe the activities (surveillance of Poliovirus circulation, tuberculosis screening, seroprevalence studies of viral hepatitis and HIV, immunization program) that are being carried out in the region's biggest CARA, located in Bari Palese, which houses an average of 1,500 refugees. The paper also describes the epidemiological surveillance system of infectious diseases in all Apulian CARAs.

METHODS

Surveillance of poliovirus circulation

In Apulian centres for asylum seekers, we registered many refugees coming from countries where poliovirus circulation is endemic or sporadic cases and outbreaks of poliomyelitis are notified. A main objective of refugee health surveillance was to assess the possible circulation of poliovirus among asylum seekers and the seroprevalence of poliomyelitis, as recommended by WHO.¹³ The presence of wild *poliovirus* or Sabin-like poliovirus was evaluated in stool samples periodically collected from refugees on a voluntary basis. Two surveys were carried out in September 2008 and March 2011. Faecal samples were analyzed for the presence of enterovirus by nested-polymerase chain reaction (PCR).¹⁴ In 2008 and 2014, two studies were carried out to evaluate the poliomyelitis immunization level by titration of the neutralizing antibody. Signed informed consent to the study was obtained from each participant. A 10 ml blood sample was obtained by venipuncture and the serum was separated by centrifugation. Each serum sample was coded and stored at -20°C. The immunity against poliomyelitis was evaluated as described previously.¹⁵

Tuberculosis screening

On March 9, 2009, the corpse of a 24-year-old Nigerian

woman who resided at the Bari Palese CARA was found on the roadside near the city of Bari. The police investigation revealed that the woman was a prostitute who worked in the countryside around the city. The results of the post-mortem examination indicated that the death was due to worsening of pulmonary tuberculosis (TB). In response to this finding, systematic screening of centre residents was undertaken, to evaluate possible contagion.

Immigrants living in the CARA were screened for TB by the Mantoux method with 5 UI of lyophilized biocine PPD. The population to be screened was identified through the centre's records. The test was evaluated after 72 hours and a subject with an induration >10 mm was considered positive. Cutipositive migrants were examined by chest X-ray. From then on, systematic TB screening is ongoing: a session of screening is organized 4 times a year and involves the newly arrived migrants.

Seroprevalence of viral hepatitis and HIV

Refugee populations are more at risk of having HBV, HCV, HIV, and sexually transmitted infections (STIs), either because they come from countries that are highly endemic for these infections, or because of lack of information on STI prevention directed to the migrant communities in the host country, the predominance of younger and more sexually active persons, the breaking up of couples and other family ties, and the exclusion from normal society, exacerbated by the barriers of language, culture, and socioeconomic conditions. Thus, assessing the prevalence of viral hepatitis among refugees is necessary for the planning of health control measures in primary and secondary prevention.¹⁶⁻¹⁷

The study was carried out in the period May-July 2008 and recruited only voluntarily enrolled healthy refugees. Adhesion was completely voluntary and signed informed consent, written in the immigrants' mother tongue, was obtained. Each migrant was tested for the hepatitis B virus surface antigen (HBsAg), the hepatitis B virus core antibody (anti-HBc), the hepatitis C virus antibody (anti-HCV), and antibodies to HIV (anti-HIV), and underwent venereal Disease Research Laboratory (VDRL) syphilis screening.¹¹ Test results were communicated to refugees and positive cases were treated in the Infectious Disease Unit of the Local Hospitals. Data were stored according to the Italian laws on privacy. Demographic data from the Asylum Centre database and the laboratory exam results were analyzed using the STATA MP11 statistical software.

Syndromic surveillance

Since spring 2011, in the light of the crisis in the Mediterranean and the resulting increase in population movements, the Ministry of Health and the National Institute of Health (ISS), in collaboration with the regions, have set up an ad hoc syndromic surveillance system in all active immigration centres receiving migrants from North Africa, aiming at early detection of potential health emergencies in order to establish appropriate control measures.

According to the protocol, migration centres or regional health authorities must notify daily any cases fitting the case definitions, and also provide details of the population residing in each

centre, stratified by age group, filling in a specific form via email or fax to the ISS, who enters and analyzes the data. The 13 syndromes are:

1. respiratory infection with fever
2. suspected pulmonary tuberculosis
3. bloody diarrhoea
4. gastroenteritis and diarrhoea without blood
5. fever with rash
6. meningitis, encephalitis, or encephalopathy
7. lymphadenitis with fever
8. botulism-like syndrome
9. sepsis or unexplained shock
10. fever and hemorrhage affecting at least one organ or system
11. acute jaundice
12. infestations
13. death from undetermined causes.¹⁸

Puglia, with the coordination of the OER, was the first region in Italy to start surveillance activities. All CARAs send the forms to the OER, which collects the data and provides the transmission to the ISS.

In the present work, we analyzed the database of the syndromic surveillance system of Apulian centres from 2011 to 2015.

Immunization program

Since 2011, the Ministry of Health has recommended that all refugees under 18 years receive the appropriate vaccinations.¹⁹ OER established a protocol for children residing in Bari Palese. The OER established a protocol for children residing in Bari Palese. According to this protocol, health care workers, in collaboration with cultural mediators, examined the health documentation of the children and asked parents about previous vaccinations. The immunization schedule of the country of origin, retrieved from the WHO website, was also studied. Then, a specific schedule was arranged for each child. In case of doubt, serological tests for hepatitis B, measles, rubella, and varicella were carried out. HIV and HCV tests were also performed.

The results of the tests and the vaccinations administered were registered in standardized forms and computerized in a File-MakerPro database. Data were analyzed using STATA MP11. Asylum seeker centres are also at major risk of transmission of respiratory infectious diseases, such as influenza. Thus, in December, the OER organizes a special session of immunization against flu for all refugees housed in the Bari Palese CARA. Cultural mediators are involved in vaccine promotion and acquisition of informed, written consent.

RESULTS

Surveillance of poliovirus circulation

We collected 152 stool samples (76 in 2008 and 76 in 2011), of which 11 samples (5 in the 2008 survey and 6 in 2011) belonged to female subjects. The mean age of participants was 20.8±5.5 years for the survey conducted in 2008 and 23.5±6.3 years in 2011. All stool samples were negative for enterovirus. The serological survey carried out in 2008 involved 573 refugees, 520 (90.8%) males and 53 (9.2%) females coming from Africa (546; 95.3%) and Asia (27; 4.7%). In particular,

20 residents (3.5%) were from Afghanistan and 67 (11.7%) from Nigeria, where poliovirus is still endemic. The average age of the population sample was 24.3 ± 5.4 . An antibody titer $\geq 1:8$ was found in 571 subjects (99.6%) for *poliovirus* type 1, in 572 subjects (99.8%) for *poliovirus* type 2, and in 570 subjects (99.5%) for *poliovirus* type 3. All subjects with an antibody titer of less than 1:8 were males from Africa: specifically, a 20-year-old Nigerian with an antibody titer less than 1:4 for the three types of *poliovirus*; two Somalis, aged 26 and 20, had antibody titres of 1:4 and 1:8, respectively. The second serological survey carried out in July 2014 involved 172 males. An antibody titer $\geq 1:8$ was found in 169 subjects (98.3%) for *poliovirus* type 1, in 160 subjects (93.0%) for *poliovirus* type 2, and in 138 subjects (80.2%) for *poliovirus* type 3.

Tuberculosis screening

In March 2009, when a refugee of the CARA died of tuberculosis, there were 1,007 residents at the Bari Palese CARA; of these, 145 (14.4%) were females. Almost all of the migrants came from Africa, and average age was 25 ± 5.8 years. Screening with the Mantoux test was undergone by 982 (97.5%) migrants; of these, 596 (60.7%) were positive. The proportion of cutipositive subjects was 20% of those aged <6 years, 41.4% of those aged 6-18 years, 62.4% of those aged 19-35 years and 61.4% of those aged >35 years (chi-square=17.1; $p < 0.001$). Chest X-rays were performed in 554 of the 596 cutipositive subjects. Active pulmonary TB was diagnosed in 7 migrants (1.3%) and TB sequelae were diagnosed in 99 others (17.9%).

Seroprevalence of viral hepatitis and HIV

A total of 529 refugees (71.1% of the 744 admitted to the CARA in May-July 2008), 442 males and 87 females, aged between 7 and 52 years (average=23.9; SD=6.7 years), were studied. Forty-four individuals (8.3%) were HBsAg positive and 241 (45.6%) anti-HBc positive. The prevalence of HBsAg positive subjects was significantly higher in males (9.7%) than in females (1.1%; $p=0.008$). The proportion of anti-HBc positive individuals was also higher in males (48.4%) than in females (31%; $p=0.002$).

A total of 24 (4.5%) individuals, 23 males (5.2%) and 1 female (1.1%), were anti-HCV positive. Three males from Africa were found to be HBsAg/ Anti-HCV positive.

Eight refugees (1.5%), 6 males (1.4%) and 2 females (2.2%), all from Africa, were HIV positive. Two African male refugees were HIV/Anti-HCV positive.

Four individuals from Africa of the 269 tested (1.5%) were positive to the VDRL test.

Syndromic surveillance

The results of the syndromic surveillance system are shown in table 1.

Immunization program

From May 2011 to December 2013, 14 immunization sessions were performed. In 2014, the immunization program for children stopped because no families with children were housed in

Number of cases per syndrome	Years				
	2011*	2012	2013	2014	2015**
syndrome 1	633	484	163	47	14
syndrome 2	17	12	18		20
syndrome 3	15	28	45	14	0
syndrome 4	421	334	116	35	21
syndrome 5	11	1	7	21	0
syndrome 6	1	2	0	0	0
syndrome 7	9	4	0		00
syndrome 8	0	0	0		00
syndrome 9	0	0	0		00
syndrome 10	0	0	0		00
syndrome 11	0	1	0		00
syndrome 12	171	236	208	264	46
syndrome 13	4	0	0	0	0
total person-days of observation	625,617	715,291	741,577	894,205	313,768

*the surveillance started on 11/04
**until 15 May

Table 1. Syndromic surveillance in the Puglia region, 2011-2015.

Tabella 1. Sorveglianza sindromica nella Regione Puglia, 2011-2015.

the Bari Palese CARA. In the program, we took care of 129 children coming from 23 countries, with an average age of 7 years; 51.9% (n=67) were female.

Fifty-two (40.3%) children came from the North of Africa, 42 (32.6%) from the South of Africa, and 35 (27.1%) from Asia. Only two children showed their certification of immunization. Serological tests were performed on 70 children aged >3 years: 38.6% (n=27) showed an anti-HBs titre <10 UI and 3 (4.3%) presented an HBV infection; no child was affected by HCV infection and 1 (1.4%) child was HIV-positive; 28.6% (n=20) were susceptible to measles and 34.3% (n=24) to varicella.

All migrants received appropriate vaccination, according to our Regional Immunization Schedule.²⁰

In December 2011, 2012, 2013, and 2014 we carried out four special immunization sessions to vaccinatee against flu, achieving high coverage; results are shown in table 2.

DISCUSSION

The results of our model confirmed some traditional concerns about migrant health and especially about the control of infectious diseases among these populations. Even though the risk of poliovirus re-introduction related to migration seems negligible, refugees are at major risk of tuberculosis, hepatitis B, HCV, and HIV. The prevalence of TB sequelae and people with markers of HBV/HCV/HIV infection is higher than in the Italian and European populations.²¹

Season	Number of refugees	People vaccinated	Immunization coverage (%)
2011-2012	1,193	712	59.7
2012-2013	1,296	628	48.5
2013-2014	1,487	646	43.4
2014-2015	1,626	580	35.7

Table 2. Vaccination against flu in the Bari Palese CARA, 2011-2015.

Tabella 2. Vaccinazione antinfluenzale nel CARA di Bari Palese, 2011-2015.

Syndromic surveillance highlighted that CARA populations are affected by communicable diseases typical of a semi-open community with high-density crowds. Diarrhoea, respiratory tract infections, and infestations (in particular skin infestations, such as scabies) are the most frequent syndromes notified.

Serological tests of migrants showed a lack of immunization: around a third of children missed at least a vaccination appointment in their native country. In relation to their entry into European countries, this is a very important concern, because if their vaccination status is unchecked, migrant children could attend schools and other social communities and cause an outbreak of vaccine-preventable diseases (e.g., measles or varicella).²²

An important strength of our model is the availability of a trained, skilled working group that can speak English and French, and of cultural mediators that speak other languages. The principal limitation of the model is the voluntary nature of participation and the high mobility of refugees. Asylum seekers are free to move in and around the CARA; often they are not present on the days of the screening or it is impossible to reach them and explain the results of the tests. Finally it was not possible to check vaccination history because the great majority of refugees lacked documentation for recommended immunizations; this is a matter of concern both for TB screen-

ing (TST could be falsely positive in subjects who received BCG)²³ and for the immunization program.

Under Italian law, asylum seekers have to undergo mandatory medical check-ups only for scabies and dermatophytosis on arrival; no screening takes place for infectious diseases of sexual and parenteral transmission, neither when they are housed in reception centres nor when they have gained permission to live in Italy or Europe. In other countries, such as the USA, systematic screening on arrival is mandatory for public health protection. Because Italy is the gate of Europe, especially for people coming from the «South of the world», the European Union needs to provide in its regulations a specific law about the screening for infectious diseases among migrants (mandatory showing of immunization schedule or serological tests), following, for instance, the recommendations of the Centres for Disease Control and Prevention protocols, considered key documents by several international health authorities.^{24,25}

Today, there is an important debate on a possible discrimination resulting from this screening but, in our opinion, screening could aid in developing a relationship of trust between migrants and resident population.²⁶

Conflicts of interest: none declared

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WORKSHOP 2
Wednesday 14 October
h. 14.00-16.00
Brown Room 2

Evidence-based approach for continuous improvement of occupational health

L'approccio *evidence-based* per il continuo miglioramento della salute in ambito lavorativo

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Abstract

Introduction. It was recognized early on that an Evidence-Based Medicine (EBM) approach could be applied to Public Health (PH), including the area of Occupational Health (OH). The aim of Evidence-Based Occupational Health (EBOH) is to ensure safety, health, and well-being in the workplace. Currently, high-quality research is necessary in order to provide arguments and scientific evidence upon which effective, efficient, and sustainable preventive measures and policies are to be developed in the workplace in Western countries. Occupational physicians need to integrate available scientific evidence and existing recommendations with a framework of national employment laws and regulations.

Objective. This paper addresses the state of the art of scientific evidence available in the field (i.e., efficacy of interventions, usefulness of education and training of workers, and need of a multidisciplinary strategy integrated within the national PH programs) and the main critical issues for their implementation.

Conclusions. Promoting good health is a fundamental part of the smart, inclusive growth objectives of Europe 2020 - Europe's growth strategy: keeping people healthy and active for longer has a positive impact on productivity and competitiveness. It appears clear that health quality and safety in the workplace play a key role for smart, sustainable, and inclusive growth in Western countries.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 81-85)

Key words: evidence-based medicine, occupational health, health, workplace

Riassunto

Introduzione. Il contributo rilevante dell'approccio *evidence-based medicine* (EBM) applicato alla sanità pubblica è risultato da subito evidente, anche nell'area della tutela della salute in ambito lavorativo (*evidence based occupational health* - EBOH), il cui scopo è garantire sicurezza, salute e benessere nei luoghi di lavoro. Nei Paesi occidentali è necessaria una ricerca di elevata qualità ai fini di supportare scientificamente la scelta di misure e politiche di prevenzione efficaci, efficienti e sostenibili in ambito occupazionale. Il medico competente deve integrare nelle proprie attività le evidenze scientifiche e le raccomandazioni esistenti, nel rispetto di specifiche norme e riferimenti legislativi.

Obiettivo. Questo articolo descrive lo stato dell'arte delle evidenze scientifiche disponibili in materia (es: efficacia degli interventi, utilità dell'informazione e formazione dei lavoratori, necessità di strategie multidisciplinari integrate nei programmi nazionali di salute pubblica) nonché le principali criticità della loro applicazione.

Conclusioni. La promozione della salute costituisce uno dei principali obiettivi della strategia di crescita del progetto «Europa 2020» della Comunità europea: mantenere la popolazione attiva e in salute quanto più a lungo possibile ha indubbiamente un impatto positivo su produttività e competitività. Pertanto, risulta evidente come la qualità della salute e la sicurezza nei luoghi di lavoro siano fondamentali nel promuovere lo sviluppo razionale, sostenibile e solidale dei Paesi occidentali.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 81-85)

Parole chiave: *evidence-based medicine*, occupational health, salute, luoghi di lavoro

INTRODUCTION

Evidence-Based Medicine (universally known as EBM) has become an umbrella term which does not only include the retrieval and translation into practice of high-quality evidence, but also involves production of the evidence, and evaluation of the real-life effect of applied changes.

It was recognized early on that the EBM approach could be applied to Public Health (PH) issues, including the area of Occupational Health (OH). High-quality research can provide evidence upon which effective, efficient, and sustainable policies and prevention measures can be developed, in order to provide helpful tools for the occupational physician at the corporate level:¹ the goal is to ensure safety, health, and wellbeing in the workplace.

OH shares with other areas of healthcare the need to define good practices and check their effectiveness, as well as relying on a framework of employment law, practices, and regulations. A number of differences from other areas of PH can be found in the jeopardized competencies and wide responsibilities following separate organizations involved in its management, and because health maintenance is usually considered an incidental part of business activities, and not the central purpose of the enterprise. While medicine is typically based on the dyadic physician-patient relationship, OH is based on a triadic relationship between employer, physician, and employee.² Thus, while the principles of evidence-based practice will be similar to those of medicine, there are likely different reasons for applying them and different responses to the use of evidence-based information in this specific field.

In the context of OH, whereas the evidence on the association between a number of potential exposures (i.e., chemical, physical, biological, and behavioural or environmental) at the workplace and the onset of some occupational diseases is still scarce or non-existent, still, both occupational physicians and court technical advisers are repeatedly required to perform a complex job retrieving and interpreting the available evidence on disparate questions. The issue is critical, as intuitively confirmed by referring to Brownson's classical questions:

1. Is the exposure that we are considering defined as a risk factor for human health?
2. What are the effective interventions needed to deal with this risk factor?
3. Under the economic, social, and environmental viewpoints in which we are to act, which of the effective interventions is the most suitable?³

The first and third questions are related to appropriateness, while the second to the effectiveness of the preventive interventions. Moreover, it is well known that not every «appropriate» intervention is also «effective» in reducing occupational risk in real life.

STATE OF THE ART OF SCIENTIFIC EVIDENCE AVAILABLE IN THE FIELD OF OCCUPATIONAL HEALTH

An overview of evidence-based methodology applied to essential interventions to prevent occupational diseases and in-

juries, focusing on different aspects, both from the viewpoint of occupational hygiene and occupational medicine, has been recently reported by Verbeek et al.⁴ **Table 1** summarizes the results from 24 systematic reviews in the literature.⁵⁻²⁸

With specific regard to back pain, several Authors investigated its prevention introducing the use of mechanical devices, by either nursing staff or lift teams, to reduce workload in patient lifting:²⁹ even though results repeatedly demonstrated that most staff back injuries were preventable among nurses, leading to substantial savings to employers on medical and compensation costs, a longitudinal study performed in Italy found no effect in the reduction of both low back pain, investigated using an ad hoc symptom questionnaire, and mean length of absenteeism for associated disease.³⁰ Given this scenario, it is clear that further high-quality research is needed, with original studies and systematic reviews focusing on safety and health prevention.

A Cochrane review by Mahmud et al.³¹ showed that pre-employment examination and preventive medical controls can be effective in reducing occupational diseases, injuries, or sickness absence, concerning specific occupational hazards, especially in workers potentially at risk, particularly after the implementation of regulations or limitations, and after specific training activities.

Another issue is that risky behaviour is an extremely significant cause of the large number of occupational injuries, diseases and deaths in the workplace:³² in light of this, adequate information and training of workers about health and occupational safety has been a common approach worldwide for many years. Training should educate professionals to recognize hazards, adopt safe working practices, and improve work-environment and organization, through active, continuous interaction with employers.²⁴

With respect to the effectiveness of training activities to improve health and occupational safety, a recent systematic review³³ demonstrated that strong evidence exists for the effectiveness of training on worker behaviours concerning health and occupational safety, but insufficient evidence was found of its effectiveness on health outcomes (i.e., symptoms, injuries, illnesses): Authors recommended that workplaces continue to deliver training to employees because training positively affects worker practices; however, it was not easy to observe any large impact of this activity on health based on the available research evidence.

Training the PH workforce to practice EBOH (Evidence-Based Occupational Health) can contribute to effectively influence health outcomes in workplaces:³⁴ a qualitative research, exploring the perceptions of occupational physicians regarding evidence-based practices, showed that professionals favourably evaluated the intervention, and job satisfaction, autonomy, and self-confidence rose; studies, however, are often time-consuming, and this was identified as a major barrier.³⁵

INTEGRATION OF EBOH WITHIN PH STRATEGIES

Today, efforts to integrate EBOH interventions within the context of the national PH strategies and programs need to

Work-related disorder to be prevented	Environmental interventions	Behavioural interventions	References
cancer pneumoconiosis asthma chronic obstructive pulmonary disease (COPD)	technical measures <ul style="list-style-type: none"> ■ substitution** ■ enclosure^ ■ local exhaust ventilation[§] ■ special ventilation systems[§] ■ general ventilation^ ■ dust suppression techniques[§] ■ segregation of sources (no studies) ■ separation of the worker[§] implementation measures <ul style="list-style-type: none"> ■ regulation^ ■ economic incentives** 	respiratory protection <ul style="list-style-type: none"> ■ technical properties* ■ implementation* 	Fransman W et al., 2008 LaMontagne AD et al., 2006 Cullinan P et al., 2003 Creely KS et al., 2007 Park D et al., 2009 Symanski E et al., 1998 Elsler D et al., 2010
noise-induced hearing loss	technical measures <ul style="list-style-type: none"> ■ hearing loss prevention program^o implementation measures <ul style="list-style-type: none"> ■ regulation^ ■ incentives* 	hearing protection <ul style="list-style-type: none"> ■ technical properties without instruction** <ul style="list-style-type: none"> with instruction[§] ■ implementation school-based^ <ul style="list-style-type: none"> work-based** 	Verbeek JH et al., 2009 El Dib RP et al., 2009
back pain	technical measures <ul style="list-style-type: none"> ■ ergonomics^o ■ maximum weight lift* implementation measures*	aids <ul style="list-style-type: none"> ■ technical properties* ■ implementation^o instruction manual material handling/lifting ^o <ul style="list-style-type: none"> incentives* 	Rivilis I et al., 2008 Driessen MT et al., 2010 Verbeek J et al., 2011 Martimo KP et al., 2007 Clemes SA et al., 2010 Bigos SJ et al., 2009 Dawson AP et al., 2007
injury prevention	technical measures <ul style="list-style-type: none"> ■ fall prevention* ■ other measures* ■ rollover protection^ implementation measures <ul style="list-style-type: none"> ■ regulation** ■ experience rating[§] ■ enforcement^ ■ inspections^ ■ penalties[§] ■ subsidies* 	safety equipment <ul style="list-style-type: none"> ■ technical measures* ■ implementation* education ^o / training** <ul style="list-style-type: none"> education agriculture^o safety climate* <ul style="list-style-type: none"> worker incentives <ul style="list-style-type: none"> ■ monetary^ ■ praise and feedback^ ■ team competitions^ 	Rautiainen RH et al., 2008 Tomba E et al., 2007 van der Molen HF et al., 2007 Cohen A et al., 1998 Robson LS et al., 2010 Burke MJ et al., 2006 Hartling L et al., 2004 McAfee RB et al., 1989

*no evidence on systematic review.; if evidence available:** some indication of effectiveness;° no indication of effectiveness; ^ indication of effectiveness; § strong indication of effectiveness

Table 1. Evidence for effectiveness of studies included from PubMed (adapted from Verbeek J et al. *Saf Health Work* 2013⁴).
Tabella 1. Livello di evidenza di efficacia in studi pubblicati su PubMed (adattata da Verbeek J et al. *Saf Health Work* 2013⁴).

be improved, especially in developed countries, and should be oriented toward avoiding workers' illness, injury, and disability, and promoting health, function, and wellbeing. The critical issues identified in wellbeing include socioeconomic status, workplace factors, environmental factors, occupational hazards, personal health information, and demographic factors.³⁶

Functions traditionally considered to fall under OH include activities such as compliance with regulations, training programs to learn more about safety, ergonomics, blood-borne patho-

gens, and radioprotection. The aim has been the improvement of individual behaviours to safeguard workers' health through group-based activities, although more recent efforts have focused on changes in organizational frameworks reducing risk exposures in the physical or psycho-social environment.³⁷

A multi-disciplinary approach between different PH professionals, also following collaborative agreement between the main scientific societies, may prove more effective than separate efforts in order to protect and promote health among workers:³⁸ to meet this goal, both organizational and environ-

Results, impact and outcomes				Factors that drive program and process		
Community health	Legal	Workplace Physical - Psychosocial - Organizational			Leadership	
Organizational performance		Work-Family-Community Interface	WORKER HEALTH AND WELL-BEING	Worker Health behaviour, health resource, care management	Strategic	
Human performance					Economic	Integrated
Worker health						Coordinated
Family health						Systematic
Efficiency/Effectiveness						Incentivized
Synergy	Political					Employment Global economy - Health benefits
Engagement		Social	Multi-level			
Participation			Multi-component			
Integration			Data-driven			
Collaboration			Prioritization			
Communication			Decision-making			

Table 2. Summary of the principal key words and strings on current knowledge in integrated worker health protection and promotion (IWHPP) programs (adapted from Pronk NP. *J Occup Environ Med* 2013⁴⁰).

Tabella 2. Riassunto delle principali parole chiave e stringhe di ricerca di attuale conoscenza all'interno del programma integrato di protezione e promozione della salute dei lavoratori (adattata da Pronk NP. *J Occup Environ Med* 2013⁴⁰).

mental levels, as well as individual and community levels, need to be properly addressed.

In this scenario, several frameworks and multidisciplinary programs have been described in the literature. For example, in the US, the proceedings of the National Institutes of Health and Centers for Disease Control and Prevention (NIH-CDC) chronic disease prevention workshop described an integrated model, the Integrated Worker Health Protection and Promotion (IWHPP) program, including intervention targets of work environment (physical, organizational, and psychological), individual health-related behaviours, and work-family-community interface, in the context of legal, social, political, and economic factors, facilitating collaboration, synergy, and integration. The framework considered the worksite as a primary setting for the protection and promotion of health among workers, but also for their families and the community at large.³⁹ It presented an integrated approach for the delivery and evaluation of programs organized around principles of business ethics, even taking into account legal and corporate factors (table 2).

Another experience is represented by the NIOSH Total Worker Health (TWH) as «a strategy integrating occupational safety and health protection with health promotion to prevent worker injury and illness and to advance health and well-being».³⁸ This program also explicitly recognizes that health and well-being of workers is an objective shared by workers, their families, and employers, conditioned by the work environment and extra-work activities.

A systematic review by the Task Force on Community Preventive Services in the US showed effectiveness for health risk assessment with feedback plus follow-up interventions.⁴⁰

Thus, an integrated approach is supported by existing evidence in terms of health outcomes, but will benefit significantly from high-quality research designed to strengthen the business case for employers.

Similar concepts have recently been shared in an official document by the main Italian PH scientific societies (the Italian Society of Occupational Medicine and Industrial Hygiene – SIMLII, the Italian Society of Hygiene, Preventive Medicine and Public Health – SItI, and the Italian Association of Industrial Hygiene – AIDII) in order to improve safety, OH, and health promotion alongside with the quality of applied research both in the workplace and the community.⁴¹

Furthermore, integrating EBOH interventions within the context of global PH policies may benefit the larger organization through cost reductions or cost savings: there is a general consensus that positive economic outcomes in society cannot be generated without effective interventions.

Promoting good health is a fundamental part of the smart, inclusive European Commission objectives of «Europe 2020 – Europe’s growth strategy». Keeping people healthy and active for longer has a positive impact on productivity and competitiveness:⁴² health quality and safety at all workplaces have a key-role to play in delivering smart, sustainable, and inclusive growth in Western countries.

Conflicts of interest: none declared

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Thursday 15 October
h. 11.30-13.00
Plenary Room

Monitoring the web to support vaccine coverage: results of two years of the portal VaccinarSi

Presidiare il web per sostenere le coperture vaccinali: risultati di due anni di attività del portale vaccinarSi

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Riassunto

Objectives. The increasingly widespread use of the Internet by the population to collect information regarding health and medical treatments and the circulation of many non-scientific documents on the effectiveness and safety of vaccines has led the Italian Society of Hygiene (SItI), in 2013, to promote a portal to provide scientific information that is verified and easily understood to counteract the rampant misinformation on health treatments and combat the phenomenon of vaccine hesitancy.

Methods. The project was launched in May 2013 and provides a portal with six main sections (vaccine preventable diseases, registered vaccines, benefits and risks of vaccination, against misinformation, pros & cons and travel immunizations) and other headings that relate to scientific events, comics and news coverage concerning vaccines. The contents are validated and evaluated by a scientific committee of high profile scientists and experts in computer-mediated communication.

Results. In the first two years of activity, the portal has published more than 250 web pages on all aspects related to vaccinations. The number of individual users was 860,411, with a constant increase over time. Of these, about 21.7% returned to the website at least once. The total visits in 24 months were 1,099,670, with a total page count of 2,530,416. The frequency of contact was almost exclusively Italian (95.6%), with a higher proportion of males (54.1%) and younger age groups (25-34 years, 33.5%, and 18-24 years, 27.5%). The data also show a significant position of the website in the major web search engines. The website has been certified by the Health On the Net Foundation. It is connected with the main social networks and it has recently opened its first regional section (Veneto).

Conclusions. The strong, progressive increase in web contacts, the involvement of several institutional bodies, and the appreciation of various stakeholders give an absolutely positive assessment of the first two years of the VaccinarSi project. The success of the website suggests future developments, with updates, sections devoted to regional problems, in-depth news analysis, and international expansion. The authors conclude that initiatives like this are to be implemented and constitute an effective way to counteract vaccine hesitancy.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 88-93)

Key words: immunization, vaccine hesitancy, communication, online portal, new media

Abstract

Obiettivi. Il sempre più diffuso utilizzo di Internet da parte della popolazione per attingere informazioni su salute e terapie e la circolazione di molti documenti non scientifici sull'efficacia e la sicurezza dei vaccini ha indotto la Società Italiana di Igiene (SItI), nel 2013, a promuovere un portale per fornire informazioni scientifiche verificabili e comprensibili per contrastare la dilagante disinformazione sanitaria e combattere le esitazioni all'utilizzo delle offerte vaccinali.

Metodi. Il progetto VaccinarSi ha preso avvio nel maggio del 2013 e prevede un portale con sei sezioni principali (malattie prevenibili da vaccino, vaccini disponibili, vantaggi e rischi delle vaccinazioni, contro la disinformazione, pro & contro, viaggi e vaccinazioni) e altre rubriche che riguardano eventi scientifici, fumetti illustrati e commenti alle principali notizie di cronaca sui vaccini. I contenuti sono validati e valutati da un Comitato scientifico di alto profilo scientifico e mediato da esperti di comunicazione informatica.

Risultati. Nei primi due anni di attività il portale ha pubblicato oltre 250 pagine web su tutti gli aspetti legati alle vaccinazioni.

Il numero di utenti singoli è stato di 860.411, con un incremento costante nel tempo. Di questi, circa il 21,7% è ritornato almeno una volta sul sito. Le visite complessive in 24 mesi sono state 1.099.670 con la visualizzazione di 2.530.416 pagine. La frequenza dei contatti è stata quasi esclusivamente italiana (95,6%) con una maggiore proporzione di maschi (54,1%) e di classi d'età inferiori (25-34, 33,5% e 18-24, 27,5%). I dati mostrano anche un posizionamento rilevante di VaccinarSi nei principali motori di ricerca web. Il portale ha ottenuto la certificazione dalla Health On the Net Foundation, è connesso con i principali *social network* e ha recentemente aperto la prima sezione regionale (Veneto).

Conclusioni. Il crescente e progressivo aumento di contatti, l'interessamento di diversi organi istituzionali e l'apprezzamento di molti *stakeholder* fanno ritenere assolutamente positivo il bilancio dei primi due anni del progetto vaccinarSi e meritevole di sviluppi futuri con aggiornamenti, sezioni dedicate alle problematiche regionali, approfondimenti di cronaca ed espansioni internazionali. Iniziative come questa devono, per gli autori, essere implementate e rappresentano un metodo efficace per contrastare il dilagante fenomeno di scetticismo verso le vaccinazioni.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 88-93)

Parole chiave: immunizzazione, *vaccine hesitancy*, comunicazione, piattaforma online, *new media*

BACKGROUND

Immunization is one of the most successful and cost-effective primary prevention tools; it is estimated that, globally, immunizations prevent between 2 and 3 million deaths every year.¹ CDC data show that vaccine introduction is responsible for an over 90% reduction in the number of cases for eleven vaccine-preventable diseases (VPDs) and a 100% reduction for two VPDs worldwide, this having largely contributed to the increase in life expectancy over the last decades.²

However, nowadays immunizations are victims of their own success and as the burden of VPDs has decreased, the risk of the vaccine is perceived to be greater than the risk of the disease.³ As a consequence, immunization is losing public confidence, a growing phenomenon known as «vaccine hesitancy»,⁴⁻⁷ ultimately leading to decreased coverage rates.

With the field of information and communication technologies flourishing in recent years, the way health information is gathered has been revolutionized and parental decision-making about vaccination is often negatively influenced by anti-vaccination movement arguments, which are widely available online.⁸⁻¹²

In Italy, it is estimated that 64% of families has an Internet connection at home, a percentage that rises to almost 90% when only considering families with at least one child aged <18 years.¹³ As Internet penetration increases, the web becomes a virtual place where health-related information is not only gathered but also actively expressed and shared. However, web-based content is not regulated and the spread of erroneous and misleading information cannot be monitored or limited.¹⁴

A large survey conducted in Italy reported that the Internet is the most used non-institutional source of information consulted by parents that decided not to vaccinate their children.¹⁵ In addition, a recent systematic review reported that in Italy 67% of vaccine-related websites have an anti-vaccination approach and that institutional websites providing information on vaccines have a low ranking in the Internet search engines and often contain data that is not easy to access or is not updated.¹⁶

These figures are alarming when considering that anti-vaccination movements are very active online on dedicated websites, blogs, forums, and social network accounts that are of-

ten used to disseminate wrong or unreliable data that ultimately have a negative impact on vaccine uptake at the population level.

In this context, the Italian Society of Hygiene and Preventive Medicine (SIIt) considering the idea of promoting “good” and “science-based” communication around vaccines to be not only in line with its institutional mission, but also a social priority, endorsed the VaccinarSi project. General aim of the project is to exploit the great potential offered by new media to communicate and educate the general population, as well as the healthcare community at large, about vaccines. In particular, specific objectives are:

- to produce and disseminate evidence-based, solid, comprehensive, understandable, and updated information about vaccines, counterbalancing the misleading and erroneous information circulating on the web on the topic;
- to raise awareness among health authorities and institutions on the use of new media to disseminate health-related information;
- to promote immunization programs.

METHODS

The VaccinarSi project components and target population

For the VaccinarSi Project a number of components that apply new media to educate the general population as well as the healthcare community at large on the benefits of immunization were designed, produced, and are constantly monitored and updated. They are:

- a web portal (www.vaccinarsi.org);
- dedicated accounts on social networks, specifically Facebook and Twitter;
- printed material (leaflets and brochure).

The VaccinarSi Project targets the general population, with particular reference to parents as well as healthcare professionals involved at different levels in immunization programs and campaigns.

Guiding principles

For the design, production, and update of the VaccinarSi con-

tents, strict ethical, deontological guiding principles as well as methodological rules are applied:

- all information published on the online portal and on the social networks is derived from solid scientific evidence (original studies, systematic reviews, official institutional and scientific reports) to which references are accurately made available;
- information is presented in a clear, transparent way, to be easily understood by the general population;
- conflicts of interest, if present, are always disclosed;¹⁷
- privacy and data protection laws are applied in line with legal and ethical standards.

Organizational structure

The VaccinarSi Project's organizational structure includes a coordinator, a steering committee, a scientific committee, an operational board, and a communication task force.

The steering committee comprises five members, including the coordinator, who is in charge of defining the guiding strategies of the VaccinarSi project.

The scientific committee includes 20 experts in the field of immunization from the academia and the national health service who are responsible for selecting the sources of data reported and validate the portal's scientific content.

The operational board is in charge of maintaining, updating, and monitoring the portal and the social network accounts; it comprises 36 members including a large share of medical residents in Hygiene and Preventive Medicine and IT technicians. The communication task force comprises 4 residents in Hygiene and Preventive Medicine from the University of Padova. They are in charge of monitoring the portal's content and publishing the VaccinarSi portal news.

Funding

Members of the steering committee, the scientific committee, the operational board, and the communication task force work at the VaccinarSi project on a voluntary basis.

The project is financed through unconditional support by Farmindustria, the Italian association of 174 pharmaceutical companies and member of Confindustria.

Analysis

In this paper we present and discuss the outcome of the two-year activity of the VaccinarSi project in terms of: content and structure of the portal and other components, dissemination and visibility, initiated collaborations and side projects.

The website traffic data we report are derived from Google Analytics (study period: 8th May 2013 – 8th May 2015). We also report on the comparison between 2012 and 2015 of web browser (google.it) search results for the key word queries (Italian for) «vaccine/s», «vaccination» and «immunization». As done elsewhere, we analyzed the first page^{18,19} search results categorizing websites into: i) negative, ii) positive (including institutional websites), and iii) neutral/descriptive approach towards vaccines.²⁰

RESULTS

Institutional patronage and other collaborations

The VaccinarSi project was launched in May 2013. It received the institutional patronage of the Italian Ministry of Health and the Italian Institute of Health, as well as that of more than 70 local health units and hospitals. In addition, it has been certified by the Health On the Net Foundation (HON), a non-profit, non-governmental organization, accredited to the Economic and Social Council of the United Nations, which promotes and guides the deployment of useful and reliable online health information, and its appropriate and efficient use. In the context of the VaccinarSi Project the Italian Society of Hygiene and Preventive Medicine (SIIt) has initiated collaborations with a number of Italian scientific societies involved in immunization programmes and policies, including the Italian Federation of Family Pediatricians (FIMP), the Italian Society of Paediatrics (SIP), and the Italian Federation of General Practitioners (FIMMG).

The VaccinarSi web portal

The VaccinarSi project's web portal was launched on 8th May 2013; in the last two years it has enlarged its content and now counts more than 250 different web pages.

Structure and content

The content of the portal is structured in three different levels so that readers can approach a single topic choosing between three different levels of details:

- first level: titles and abstract are presented to offer a clear overview of the topic;
- second level: topics are presented in a concise but comprehensive way (short essays) and references are made available;
- third level: links to external sources, original articles and data are made available for readers who wish to gain a deeper understanding of the topic.

All levels are coupled with selected pictures, tables, and illustrations. Before being published on the portal, all content is reviewed, in a two-step process, by the scientific and steering committees.

The portal is organized in six main sections:

- **Vaccine-preventable diseases (VPDs):** all VPDs are described in terms of transmission, signs and symptoms, national and global burden, with epidemiological morbidity and mortality data. Selected case reports are also reported. For each VPD links are made to sections on available vaccines.
- **Available vaccines:** for each vaccine, data on efficacy and safety are presented, as well as vaccine recommendations, schedules, and doses. As per editorial policy, no reference is made to commercial names of vaccines or pharmaceutical companies.
- **Vaccine benefits and risks:** benefits and risks of vaccines – as they are perceived by the general population – are listed and discussed in detail.
- **Against misinformation:** in this section the arguments and theories of anti-vaccination movements are presented with constructive criticism based on referenced, solid arguments.

■ **Pros&Cons:** this section presents recent news items that have appeared in the popular press on vaccine-related topics, put into scientific context and constructively commented with referenced, solid arguments.

■ **Travel immunization:** this section focuses on vaccine recommendations for international travellers. In addition, general recommendations are provided on prevention of food-borne infections.

The six sections are linked through key-word tags. In addition, all key words are compiled into a Glossary section with a list of key terms in the field of immunization and their definitions. In the context of the VaccinarSi project, a number of innovative communication formats are applied, including:

- training videos, multimedia presentations, and tutorials targeting both healthcare workers and the general public;
- stories: these are brief essays with a storytelling approach – similar to the one widely used by anti-vaccination movements – that describe case reports of diseases that could have been prevented with vaccination and which are aimed at motivating hesitant parents to vaccinate their children;
- cartoons (included in the dedicated section «ComXtrue»), used as an effective communication tool to communicate and educate about the benefits of vaccines; as an example, comics on vaccines by the famous cartoonist Maki Naro, previously published in the *New York Times*, have been translated and published on the portal.

Constant monitoring of the portal's content is carried out by the scientific committee and the communication task force. In particular, two sections are constantly monitored and updated:

- the News section: the communication task force is responsible for writing the portal News: brief texts reporting on recent published scientific studies, guidelines, immunization schedules, recently released epidemiological data, outbreaks, and infectious disease epidemics of national and international relevance. In the last two years, 280 News items have been published, with an average of three per week. Addressed topics include seasonal influenza surveillance,^{21,22} the «Fluad episode»,²³ MMR vaccine safety news, adult immunization, health education and communication issues, etc. Once published on the portal each News item is automatically forwarded via email to all VaccinarSi subscribers;
- the Events section, which lists relevant Italian and international conferences, congresses, and seminars in the field of immunization and infectious diseases.

Dissemination and visibility

The VaccinarSi portal has achieved a high placement rank on Google's Search Engine Results. In fact, when entering the search term «vaccinarsi» in Google anonymous search, the VaccinarSi portal ranks first; when entering the search term «vaccino/i» (Italian for «vaccine»/«vaccines») or «vaccinazione/i» (Italian for «vaccination»/«vaccinations») the VaccinarSi portal ranks among the first five Google results.

In the two-year study period, 860,411 single users accessed the VaccinarSi portal, and nearly 22% of them accessed it more than once, for a total of over one million visits. Overall, 2.5

million single web pages were accessed, with 1.87 web pages visited on average for each access to the portal and an average session duration of 1 minute and 36 seconds. Average visitors per month increased exponentially from 10,000 to 60,000. With regard to socio-demographic characteristics, 54.2% of users were males and the 18-34 years age group accounted for more than 60%. Other age groups accounted for 15.5% (35-44 years), 12.5% (45-54), and 5.5% (both 55-64 and over 65 years). The vast majority of users were from Italy (95.6%). Accesses from Switzerland, the USA, and the UK were reported. Within Italy, Lombardia (26.9%) and Lazio (18.9%) were the regions with the highest number of reported accesses to the portal. Milano (19.5%) and Roma (17.7%) were the highest ranking cities. Relative user distribution by region weighted by number of residents is presented in **table 1**; the table shows that, when taking the background population into account, Lazio (3.70%), Lombardia (2.83%), and Toscana (2.32%) were the regions with the highest share of population visiting the VaccinarSi portal, a share greater than the national percentage (1.73%). Personal computers (PCs) were the most widely used devices to access the portal (46.4%). Smartphones and tablets accounted for, respectively, 41.8% and 11.8%.

The majority of visitors access the VaccinarSi portal through Google, but some were also referred by social networks, local health units and other health authorities websites, the «vaccinar...si» blog and the official SItI website, among others.

With regard to specific webpage visits, the most visited pages were those on the hexavalent and MMR vaccines. More in general, data show that visitors surfed several website pages of the portal per visit. The most frequently searched keywords were (Italian for) «vaccine», «vaccination», «hexavalent vaccine»,

Regions	Sessions (N)	Residents (%)
Lombardia	282,633	2.83%
Lazio	199,550	3.40%
Toscana	86,826	2.32%
Veneto	81,354	1.65%
Emilia-Romagna	61,578	1.38%
Campania	58,786	1.00%
Piemonte	46,675	1.05%
Sicilia	43,959	0.86%
Puglia	39,541	0.97%
Liguria	21,600	1.36%
Friuli-Venezia Giulia	20,488	1.67%
Marche	18,495	1.19%
Sardegna	17,958	1.08%
Abruzzo	14,108	1.06%
Trentino Alto Adige (South Tyrol)	9,953	0.95%
Calabria	9,857	0.50%
Umbria	7,371	0.82%
Basilicata	1,963	0.34%
Molise	1,232	0.39%
Aosta	657	0.51%

Table 1. Vaccinarsi.org visits by region (2013-2015).

Tabella 1. Accessi al portale Vaccinarsi.org per regione (2013-2015).

«www.vaccinari.org», «MMR vaccine», «chickenpox vaccine», «vaccines and autism», «polio vaccine».

According to Webstatsdomain, a free online service that collects and analyzes data about domains and key words, the VaccinarSi portal ranks 920,253th among the 30 million most visited websites worldwide and has an estimated site value of 3.911 euros. In addition, it is considered to have 100% reputation in terms of web security and a total of 17,603 external backlinks. According to Alexa – a company which provides commercial web traffic data – VaccinarSi ranks 29,698th in Italy; it must be considered that there are over 28 million websites in Italy and one of the major anti-vaccination movement websites, comilva.org, is ranked number 42,386.

As the 2012-2015 websites search comparison showed, distribution of Italian websites with regard to approach to immunization has changed over time. The first 10 websites resulting from browser search for 4 key words related to immunization (40 websites in total) had a negative approach to immunization in 39% of cases in 2012 (google.it search carried out on 1st June 2012) but only 12.5% of cases in 2015 (google.it search carried out on 1st June 2015). The share of websites with positive/institutional/scientific approach to vaccination resulting from web searches increased from 40% in 2012 to 60% in 2015, the rest having a descriptive/neutral approach. Although we cannot assume this positive trend to be directly associated with the launch of the VaccinarSi project, we are pleased to see that a cultural shift is taking place in Italy towards fighting the growing phenomenon of vaccine hesitancy and disseminating of evidence-based health education messages on immunization to the general population.

The VaccinarSi social network accounts

VaccinarSi's official Facebook account was launched on 17th April 2014, the Twitter account was launched on 8th May 2013.

Structure and content

The VaccinarSi social network account content in the first two months after its launch was almost entirely based on the portal's content, with links to the portal's updates. After that, specific Facebook and Twitter content was developed and shared, including iconographic material and Internet memes, pieces of media which spread, often as mimicry, from person to person via the Internet (http://en.wikipedia.org/wiki/Internet_meme). As reported in the results of a survey conducted among the VaccinarSi Facebook followers, vaccine memes were considered an effective communication tool.

Two specific awareness-raising campaigns on polio and influenza vaccines were launched and disseminated through the VaccinarSi Facebook and Twitter accounts. The polio campaign was carried out between May and October 2014 and aimed at raising awareness on a forgotten disease through a narrative-historical approach; the influenza campaign was carried out between October and December 2014 and aimed at promoting influenza vaccination among at-risk subgroups of the population. Both campaigns were successful and

showed that social networks are key communication tools to spread health education. To further advertise the VaccinarSi Facebook account, a promotional campaign was launched in February 2015. Another innovative initiative carried out in the context of the VaccinarSi social network accounts was the live online sharing of national conferences on immunization policy content, including sharing speakers' key quotes, videos, and slides.

Content on VaccinarSi social network accounts is usually posted on a daily basis in hours of high Internet access (11am-9pm). Strict community standards are in place to allow fruitful discussions and encourage respectful behaviour.

Dissemination and visibility

The VaccinarSi Facebook account reached 4,821 "likes" in the study period. The majority of followers are females (70%) and subjects in the 25-34 year age group (36% of females users). Females are also reported to be more active sharing information and commenting on posts. The number of "likes" almost doubled after the February 2015 Facebook promotional campaigns. The average number of users to visit the VaccinarSi Facebook account is 1,507 per day (range: 60-24,300).

The Twitter account published 544 tweets over the study period, followed 140 profiles and was followed by 337 other accounts. Contrary to Facebook, the majority of VaccinarSi Twitter followers are males (54%). Since the VaccinarSi twitter account was launched, average retweets are 1.29 per tweet (range: 0-13), average «add to favourites» are 1.01 per tweet (range: 0-6), average replies are 0.04 per tweet (range: 0-1). The highest engagement (retweet+favourite+reply) was 19 per tweet.

DISCUSSION

In this context, a number of new activities have recently been planned and implemented. First, a regional VaccinarSi chapter for the Veneto region was launched in August 2014 (www.vaccinarsinveneto.org). The initiative was included in a decision of the Veneto Regional Council on the «Regional communication plan on vaccine preventable diseases». The content of the Veneto VaccinarSi chapter targets region-specific issues, including the Veneto immunization schedule, information on the immunization programs, and services offered in the region. The Veneto VaccinarSi section also includes an area dedicated to healthcare providers with online training material, updated data, and other useful resources. The project is still at an early implementation phase and its efficacy as a powerful regional health policy instrument will be assessed in the near future. At the same time, thanks to a national grant awarded to the VaccinarSi project in 2014 by the National Centre for Disease Prevention and Control (CCM), six other regional VaccinarSi chapters are scheduled to open in the next two years (for the regions of Liguria, Marche, Puglia, Sardegna, Sicilia, and Toscana); this being a priority objective for VaccinarSi.

Thanks to the CCM grant, the national VaccinarSi portal will be further enlarged with an expanded section on «immunization and travels». In addition, a working group has been es-

tablished to build and launch the English version of the project, in order to increase its penetration and visibility in the larger European and international arena.

On a different note, the VaccinarSi project has sponsored an amateur sports association with a semi-professional cycling team that participate in national races with the aim of promoting a healthy lifestyle and a correct approach to immunization, in line with the VaccinarSi project's mission.

CONCLUSION

In the first two years since its launch, the VaccinarSi project has had an enormous success: the number of visitors to the portal has grown exponentially, reaching a total of one million, the VaccinarSi website ranks among the first websites on the main Internet search engines and the initiative has obtained the patronage of the Ministry of Health, the highest health authority in Italy.

In addition, the VaccinarSi project has engaged a number of

key stakeholders in fruitful collaborations at the institutional, scientific, academic, and civil society level; the reduction in the availability of Italian-language websites with an anti-vaccination approach underlines its impact on the web and, more in general, a recent cultural shift towards an enhanced trust in immunization.

Building on the success, the authority and visibility gained by the VaccinarSi project in its first two years of activity, the objective for the future is to have it grow further, to reach out to an even wider audience, to engage in more collaborations with national and international agencies and scientific associations, to further apply innovative communication media and skills,^{19,20} to increase VaccinarSi satellite projects and components, with the overall aim of further promoting the culture of immunization and counteracting the alarming phenomenon of vaccine hesitancy.

Conflicts of interest: none declared

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WORKSHOP 6
Thursday 15 October
h. 11.30-13.00
Brown Room 2

Antibiotic consumption and resistance: results of the SPIN-UTI project of the GISIO-SItI

Consumo di antibiotici e resistenze: i risultati del progetto SPIN-UTI del GISIO-SItI

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Abstract

Objective. To evaluate trends and association between antibiotic consumption and resistance during an eight-year period, from 2006 to 2013.

Design. Prospective multicenter study.

Setting and participants. Intensive Care Units (ICUs) participating in the four editions of the Italian nosocomial infections surveillance in the ICU Network (Sorveglianza Prospettica delle Infezioni Nosocomiali nelle Unità di Terapia Intensiva, SPIN-UTI project).

Main outcome measures. The isolation density of selected species of microorganisms, antibiotic resistance rates (RRs), incidence density of resistant isolates and antimicrobial usage density were calculated.

Results. RRs of carbapenem-resistant *Acinetobacter baumannii*, of carbapenem-resistant *Klebsiella pneumoniae*, of third-generation cephalosporin (3GC)-resistant *K. pneumoniae* and of 3GC-resistant *Escherichia coli* showed significant increasing trends ($p \leq 0.001$). The consumption of each antibiotic class varied with years, although not significantly. Significant strongly positive correlations were detected between RRs and antibiotic consumption.

Conclusions. The present study describes high RRs and increasing trends of resistant microorganisms and highlights the need for continuous comprehensive strategies targeting not only the prudent use of antibiotics, but also infection control measures to limit the epidemic spread of resistant isolates.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 94-98)

Key words: antibiotic resistance, resistance rates, antimicrobial usage density, surveillance

Riassunto

Obiettivo. Valutare l'andamento e l'associazione tra consumo di antibiotici e resistenze durante un periodo di otto anni, dal 2006 al 2013.

Disegno. Studio prospettico multicentrico.

Setting e partecipanti. Unità di terapia intensiva che hanno partecipato alle quattro edizioni del progetto SPIN-UTI (Sorveglianza prospettica delle infezioni nosocomiali nelle unità di terapia intensiva).

Principali misure di outcome. Sono stati calcolati i seguenti indicatori: la densità di isolamento di specie di microrganismi selezionate, i tassi di resistenza agli antibiotici (RR), la densità di incidenza di isolati resistenti e la densità di utilizzo di antibiotici.

Risultati. I RR di *Acinetobacter baumannii* e *Klebsiella pneumoniae* resistenti ai carbapenemici, e di *K. pneumoniae* ed *Escherichia coli* resistenti alle cefalosporine di terza generazione, hanno mostrato significativi andamenti in aumento ($p \leq 0.001$). Il consumo di ciascuna classe di antibiotici varia con gli anni, sebbene non significativamente. Alcune significative correlazioni positive sono state evidenziate tra tassi di resistenza e consumi di specifici antibiotici.

Conclusioni. Il presente studio descrive elevati RR di microrganismi resistenti, in aumento nel tempo, ed evidenzia la necessità

di ampie e continue strategie indirizzate all'utilizzo prudente di antibiotici e a misure di controllo delle infezioni per limitare la diffusione epidemica di isolati resistenti.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 94-98)

Parole chiave: resistenza agli antibiotici, tassi di resistenza, densità di utilizzo di antibiotici, sorveglianza

INTRODUCTION

Italy is one of the European countries with high antibiotic consumption in the hospital setting,¹⁻³ especially in Intensive Care Units (ICUs) where the highest prevalence of patients on antibiotic treatment is observed.⁴ The intensive use and misuse of antibiotics have triggered the global spread of highly resistant pathogenic bacteria,⁵⁻⁷ a serious public health problem in Europe and worldwide affecting costs, treatment, and mortality rates.^{1,8} In particular, Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, and *Acinetobacter spp.*, are becoming resistant to all currently available antibiotics and in the near future no new antibiotic classes active against multi-resistant Gram-negative bacteria can be awaited.⁹ Surveillance of multidrug-resistant microorganisms and of the burden and trends of resistance are considered important components of an effective strategy against this problem.¹ High resistance rates (RRs) to antibiotics have been observed among pathogens that cause healthcare-associated infections (HAIs) worldwide and significant gaps in surveillance have been underlined,⁸ as well as the need of a prudent and rational use of antimicrobial agents.²

The objective of the present study is to evaluate trends and association between antibiotic consumption and resistance in the ICUs participating in the four editions of the Italian Nosocomial Infections Surveillance in the ICU Network (Sorveglianza prospettica delle infezioni nosocomiali nelle unità di terapia intensiva, SPIN-UTI project) during an eight-year period, from 2006 to 2013.

METHODS

Study design

The present study was conducted in the framework of the SPIN-UTI project, established in Italy in 2005 by the Italian Study Group of Hospital Hygiene (GISIO) of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI).¹⁰⁻¹² The SPIN-UTI project has adopted a protocol based on the HAIICU protocol of the European Centre for Disease Prevention and Control (ECDC).¹³

Each project survey included a six-months patient-based study conducted between the last quarter of one year and the first quarter of the following year. At present, since 2006, five editions have been conducted; in this study, the first four have been included.

Hospital participation was voluntary and results were handled confidentially. For the surveillance of HAIs, a web-based data collection procedure using four electronic data forms (for the collection of data regarding: i. characteristics of hospitals and ICUs, ii. patients, iii. HAIs, and iv. microorganisms) was used. Particularly, for each microorganism-associated HAI, an-

timicrobial resistance data were collected into the "microorganism" data form.

Microorganisms and antibiotic susceptibility tests

Data on microorganisms were obtained from clinical laboratories of the participating hospitals. Identification and routine antibiotic susceptibility testing were performed in each laboratory. Only susceptibility data for pathogens associated with HAIs were collected. Particularly, in the present study, resistance data for *A. baumannii*, *K. pneumoniae*, *E. coli* and *Staphylococcus aureus* were analyzed.

For each species, the isolation density was calculated as the number of isolates per 1,000 patient-days. Antibiotic RRs were calculated as the number of non-susceptible isolates (resistant or intermediate isolates) divided by the total number of isolates of the same species tested against the corresponding antibiotic, multiplied by 100. Furthermore, the incidence density of resistant isolates was calculated as the number of non-susceptible isolates per 1,000 patient-days.

Antibiotic consumption

Data on antibiotic consumption were obtained from the pharmacies of the participating hospitals. Consumption – that is, the Antimicrobial usage Density (AD) – was expressed as Defined Daily Dose (DDD) and was normalized per 1,000 patient-days. The DDD is the standard adult daily dose of an antimicrobial agent for a 1-day treatment defined by the World Health Organization.¹⁴ Particularly, data on consumption of aminoglycosides, carbapenems, fluoroquinolones, glycopeptides, penicillins, and third-generation cephalosporins (3GCs) were collected.

Statistical analyses

Statistical analyses were performed using the SPSS 22.0 statistical package (SPSS Inc., Chicago, IL, USA).

Trends over time of RRs were determined by the chi-square test (linear by linear association). Trends over time of incidence densities of resistant isolates and of ADs were analyzed by linear regression model. Pearson's correlation coefficient (r) was used to determine the relationship between ADs and RRs. A p value <0.05 was considered statistically significant.

RESULTS

Setting, microorganisms and antibiotic resistance

During the four editions of the SPIN-UTI project a total of 52 hospitals and 75 ICUs participated in at least one edition of the project. A total of 10,703 patients and 113,977 patient-days were included (table 1).

Data on 2,255 HAI-associated microorganisms were collected: 27.1% of microorganisms in the first, 20.7% in the second,

25.1% in the third, and 27.1% in the fourth edition. Overall, the most frequently isolated microorganisms were: *P. aeruginosa* (16.7% of isolates), *A. baumannii* (14.2% of isolates), *K. pneumoniae* (10.0% of isolates), *E. coli* (7.6% of isolates), and *S. aureus* (7.3% of isolates). Considering all four editions, isolation densities were: *P. aeruginosa* 3.3 per 1,000 patient-days; *A. baumannii* 2.8 per 1,000 patient-days; *K. pneumoniae* 2.0 per 1,000 patient-days; *E. coli* 1.5 per 1,000 patient-days; and *S. aureus* 1.4 per 1,000 patient-days. **Table 1** shows incidence densities of microorganisms isolated and of resistant isolates during the four editions of the project. Incidence density of carbapenem-resistant *K. pneumoniae* increased significantly from the first to the last edition of the project ($p=0.027$).

Considering all editions, the RR of carbapenem-resistant *A. baumannii* was 86.0%, of carbapenem-resistant *K. pneumoniae* 35.5%, of 3GC-resistant *K. pneumoniae* 68.1%, of carbapenem-resistant *E. coli* 4.9%, of 3GC-resistant *E. coli* 38.0%, and of methicillin-resistant *S. aureus* (MRSA) 45.2%.

Figure 1 reports RRs of the selected species during the four editions of the project. RRs of carbapenem-resistant *A. baumannii*, of carbapenem-resistant *K. pneumoniae*, and of 3GC-resistant *K. pneumoniae* showed significant increasing trends from the first to the last edition of the project ($p\leq 0.001$). Furthermore RRs of 3GC-resistant *E. coli* showed a significant increasing trend from the first to the third edition of the project and a decreasing trend in the last edition ($p=0.048$).

Antibiotic consumption

Antibiotic consumption over the eight-year period was 8,750 DDD per 1,000 patient-days (AD). Overall penicillins were the main antibiotic class consumed (32.1% of the total AD), followed by fluoroquinolones (19.7% of the total AD), glycopeptides (16.8% of the total AD), carbapenems (11.9% of the total AD), aminoglycosides (17.3% of the total AD), and 3GCs (6.0% of the total AD). The consumption of each antibiotic class (i.e., ADs) varied with editions, although not significantly (**table 1**).

Correlation between antibiotics consumption and resistance rates

Significant strongly positive correlations were detected between RRs of carbapenem-resistant *E. coli* and 3GC consumption ($r=0.953$; $p=0.047$) and penicillin consumption ($r=0.983$; $p=0.017$), and between RRs of MRSA and aminoglycosides consumption ($r=0.965$; $p=0.035$).

No correlations between the usage of other antimicrobial agents and resistance data were found.

DISCUSSION AND CONCLUSIONS

Antibiotic consumption contributes to the prevalence of resistant pathogens in the hospital setting, together with their clonal spread,^{15,16} especially in Italian ICUs where the highest prevalence of patients on antibiotic treatment⁴ has been

	SPIN-UTI PROJECT				p-value*
	2006-2007	2008-2009	2010-2011	2012-2013	
number of hospitals	32	22	22	22	-
number of ICUs	49	28	27	26	-
number of patients	3,053	2,163	2,478	3,009	-
patient-days	35,498	22,683	24,724	31,072	
incidence density (per 1,000 patient-days)					
<i>Klebsiella pneumoniae</i>	0.9	2.1	2.0	3.1	0.067
<i>Acinetobacter baumannii</i>	1.4	3.0	4.1	3.2	0.253
<i>Escherichia coli</i>	1.1	1.3	2.3	1.5	0.460
<i>Staphylococcus aureus</i>	1.5	1.2	1.2	1.7	0.684
incidence density of resistant isolates (per 1,000 patient-days)					
3GC-resistant <i>K. pneumoniae</i>	0.4	1.3	1.1	2.3	0.095
carbapenem-resistant <i>K. pneumoniae</i>	0.1	0.3	0.8	1.5	0.027
carbapenem-resistant <i>A. baumannii</i>	1.1	2.3	3.8	3.0	0.188
carbapenem-resistant <i>E. coli</i>	0.1	0.04	0.1	0.03	0.487
3GC-resistant <i>E. coli</i>	0.3	0.3	1.1	0.5	0.523
methicillin-resistant <i>S. aureus</i>	0.7	0.5	0.3	0.3	0.056
antimicrobial densities (ADs: DDD per 1,000 patient-days)					
aminoglycosides	384	441	124	237	0.318
carbapenems	345	189	222	283	0.713
3GCs	227	137	83	80	0.070
fluoroquinolones	469	338	531	387	0.920
glycopeptides	418	363	280	406	0.754
penicillins	1,101	541	646	516	0.218

*linear regression
 ICU: Intensive Care Unit; 3GC: third-generation cephalosporin; DDD: defined daily dose
 Significant values are indicated in colour

Table 1. Incidence density of microorganisms and of resistant isolates and Antimicrobial usage Densities (ADs) during the four editions of the SPIN-UTI project.

Tabella 1. Densità di incidenza dei microrganismi e degli isolati resistenti e densità di utilizzo di antibiotici durante le quattro edizioni del progetto SPIN-UTI.

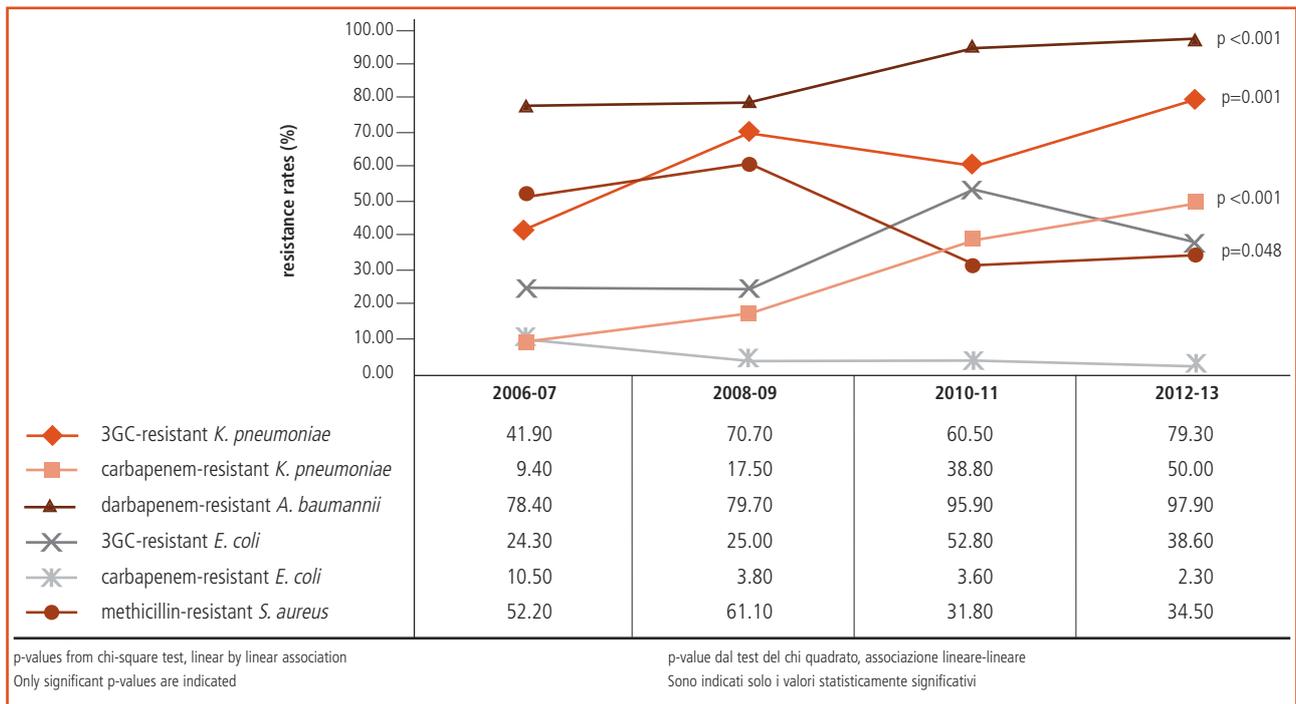


Figure 1. Resistance rates of selected species during the four editions of the SPIN-UTI project.

Figura 1. Tassi di resistenza delle specie selezionate durante le quattro edizioni del progetto SPIN-UTI.

observed and outbreaks due to multidrug-resistant pathogens are frequently reported.¹⁷⁻¹⁹

The European Antimicrobial Surveillance Network (EARS-Net) published resistance data from European countries based only on invasive isolates from hospitals (not only from ICUs), not representative of isolates from other sites, and thus, comparison should be undertaken with caution.¹ In any case, the present study confirms higher RRs of carbapenem-resistant *A. baumannii* than those in the other European countries¹ and an increasing trend, indicating seriously limited options for the treatment of patients infected with this microorganism. In 2013, the Italian Ministry of Health established a national surveillance of carbapenemase-producing *Enterobacteriaceae* (particularly, *K. pneumoniae* and *E. coli*) in order to monitor the frequency and geographical distribution of these microorganisms.²⁰ In the SPIN-UTI project a significant increasing trend was observed for carbapenem-resistant *K. pneumoniae*, confirming high RRs among the European countries.¹ Conversely, carbapenem-resistant *E. coli* remain generally rare as in the other European countries.¹ The spread of clonally related multidrug-resistant *A. baumannii* and *K. pneumoniae* isolates have been described in Italy¹⁷⁻¹⁹ contributing to the increasing trend of carbapenem resistance of such microorganisms. Thus, specific control measures should be implemented in order to limit the dissemination of extensively drug- or pandrug-resistant isolates.²¹⁻²³

In the SPIN-UTI project the percentage of 3GC-resistant *K. pneumoniae* isolates was higher than that reported for Italy in the European report¹ and an increasing trend was observed.

RRs of 3GC-resistant *E. coli* showed an increasing trend from 2006 to 2011 time frame of the project and a decreasing trend in 2012-2013.

MRSA is one of the most frequent resistant microorganisms associated to HAIs worldwide and even though a decreasing trend was observed in the last years, in Europe MRSA remains a significant public health problem.¹ In the SPIN-UTI project a decreasing trend of RRs was observed in the last years, although not significant. Notably, RRs of MRSA were higher than European data and prevention measures to control the spread should be improved.²⁴

Significant strongly positive correlations were detected between RRs of carbapenem-resistant *E. coli* and 3GC and penicillin consumption and between RRs of MRSA and aminoglycoside consumption. No correlations between the use of other antimicrobial agents and resistance data were found. The complex nature of the spread and emergence of antibiotic resistance can, at least partly, explain this result. Furthermore, as previously reported, DDD measurements are useful for benchmarking but may not fully correlate with antibiotic resistance due to the intrinsic biases.²⁵

One of the strengths of this study is that it was conducted in the framework of a prospective multicentre patient-based project. One limitation is the ecological study design that cannot fully prove a causative relationship between antibiotic consumption and resistance. In fact, other factors, including the volume of antibiotics prescribed in the outpatient setting, antimicrobial stewardship interventions implemented in participating ICUs, and the occurrence of outbreaks due to multidrug-resistant organism, already reported in a sample of

ICUs participating in the SPIN-UTI network,¹⁷⁻¹⁹ should be taken into account to explain this complex issue.

In conclusion, the present study describes high RRs and increasing trends of resistant microorganisms and highlights the need for continuous comprehensive strategies targeting not only the prudent use of antibiotics, but also infection control measures to limit the epidemic spread of resistant isolates.

Conflicts of interest: none declared

Acknowledgements

O.C. Grillo, L. Fabiani, M.D. Masia, V. Torregrossa, E. Righi

Acknowledgements

The Authors wish to thank all colleagues, physicians, and nurses in the participating hospitals and ICUs for providing surveillance data.

Funding: Project realized with partial financial support by the Ministry of Health – CCM 2012.

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WORKSHOP 7
Thursday 15 October
h. 14.00-15.30
Brown Room 1

Management of women at high risk of hereditary breast cancer in the Veneto Regional Program for Prevention

La gestione delle donne ad alto rischio di tumore mammario ereditario nel Piano regionale della Regione Veneto

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Abstract

Introduction. Today it is well-known that high risk of genetic breast cancer concerns a very limited part of the population: no more than 2-3 women are affected every thousand and this condition as a whole accounts for no more than 3%-5% of all breast cancers.

Objectives and methods. Following the directions contained in the 2014-2018 National Prevention Plan, Veneto's 2014-2018 Regional Program of Prevention (PRP), approved by Regional Council Resolution (DGR) No. 749 of 14.5.2015, consolidation of a pathway of diagnosis, observation, and prophylaxis for women at high risk of hereditary breast carcinoma is thus proposed. The principal activities of this policy will be the following: creation of a regional working group, survey of currently existing pathways for the identification of women at risk of hereditary breast cancer and adoption of the same, approval and consolidation of a structured regional pathway for women at high risk of hereditary breast and/or ovarian cancer, from paths of oncogenetic consultation and genetic testing to management of disease risk. Subsequent to the recognition of the pathway of diagnosis, observation, and prophylaxis for women at high risk of hereditary breast carcinoma, the Veneto region undertakes to develop a co-ordinated program of information and training on this pathway directed at the population and healthcare workers.

Conclusions. It is firmly hoped that with the inclusion of a program for the management of women at high risk of hereditary breast cancer within the Veneto PRP this topic may become more defined and structured in terms of sustainability, integration with the existing regional networks (mammography network, Breast Unit), contrasting inequality, monitoring and evaluation, in this way pursuing the objectives of a reduction of cause-specific mortality and improvement of quality of life.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 99-101)

Key words: hereditary breast cancer, cancer screening, public health

Riassunto

Introduzione. A oggi è noto che l'alto rischio mammario di origine genetica riguarda una quota molto limitata della popolazione: ne sono affette non più di 2-3 donne ogni mille, e questa condizione spiega complessivamente non più del 3-5% di tutti i tumori della mammella.

Obiettivi e metodi. Su indicazione del PNP 2014-2018, il Piano Regionale della Prevenzione (PRP) 2014-2018 della Regione Veneto, approvato con DGR N° 749 del 14.5.2015, si propone di consolidare un percorso di diagnosi, sorveglianza e profilassi per le donne con rischio elevato per carcinoma mammario ereditario. Le attività principali di tale linea progettuale saranno le seguenti: creazione di un tavolo di lavoro istituzionale regionale, censimento dei percorsi attuali esistenti per l'identificazione delle donne con rischio di tumore mammario ereditario e sulla presa in carico delle stesse, approvazione e consolidamento di un percorso regionale strutturato per le donne ad alto rischio di tumore mammario e/o ovarico ereditario, dai percorsi di consulenza oncogenetica e test genetico alla gestione del rischio di malattia. Successivamente al riconoscimento del percorso di diagnosi, sorveglianza e profilassi per le donne ad alto rischio di carcinoma mammario ereditario, la Regione Veneto si impegna a sviluppare un piano coordinato di informazione e formazione su tutto il territorio.

Conclusioni. Si auspica che con l'inserimento di un programma all'interno del PRP della Regione Veneto per la gestione delle

donne ad alto rischio di tumore mammario ereditario tale tema possa diventare maggiormente definito e strutturato in termini di sostenibilità, integrazione con le reti regionali esistenti (rete mammografica, Breast Unit), contrasto alle disuguaglianze, monitoraggio e valutazione perseguendo, in tal maniera, per tali categorie di donne gli obiettivi di riduzione di mortalità causa-specifica e miglioramento della qualità di vita.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 99-101)

Parole chiave: tumore mammario ereditario, screening oncologici, sanità pubblica

INTRODUCTION

It is well-known today that the high risk of genetic breast cancer concerns a very limited part of the population. In fact, no more than 2-3 women are affected every thousand and this condition as a whole accounts for no more than 3%-5% of all breast cancers. A particular feature of this condition, which differentiates it from other high-risk conditions, is that it derives from mutations with dominant-type transmission, thus all knowledge has direct implications on the family the patient belongs to, foremost the patient's progeny.^{1,2}

Despite its limited epidemiological significance, this condition represents a serious problem for women who are carriers of the mutation, or fear they are, and for their families, so the National Screening Observatory (ONS) considers it must be approached from a public health perspective.³

In Italy, the region Emilia-Romagna's program of active intervention on research into female carriers of hereditary risk currently stands out (Decree no. 2202011, Applicatory Circular no. 21, 2011 in www.saluter.it/screening_femminili and Diagnostic, Therapeutic and Care Paths PDTA 2014).⁴ This is a free program managed through a network-based model, based on a genetics Hub Centre and a breast pathology Spoke Centre, using as a primary filter to verify the family health history a questionnaire which is offered to women undergoing mammography in the breast cancer screening program. Furthermore, the family history risk can be evaluated through the same questionnaire by GPs and specialists in this area (radiologists/breast pathology specialists, gynaecologists, surgeons, etc.) on request of the female patient. This experience, certainly the most interesting from the point of view of public health, is currently under evaluation both in terms of effectiveness and efficiency.

The Health Minister, in line with the 2010-2012 National Program for Prevention (PNP), entrusted the Università Cattolica del Sacro Cuore with a policy to help make the use of genomic tests predicting complex diseases more suitable and rational, acting, among various strategies, by training those who could potentially prescribe genomic tests. Specifically, training has been implemented in Veneto, among other regions, both through distance learning and on-site courses at all provincial medical associations. In these courses the need emerged for GPs and prescribing doctors in general to know the potential of predictive medicine, in order to avoid creating false expectations and contribute in an interdisciplinary way to the implementation of this new dimension of medicine.

Hereditary breast cancer is also mentioned in the 2014-2018 National Prevention Plan in connection with the most recent

knowledge and in line with the previous PNP and the guidelines on «Genomics in Public Health»⁵ as per the agreement dating 13.3.2013.⁶ One of the strategic lines to adopt for cancer prevention is the development of an organized pathway for the prevention of breast cancer on the basis of genes (*BRCA1* and *BRCA2* mutations), with features integrating and complementing the already existing breast cancer screening program.

OBJECTIVES AND METHODS

Following the directions contained in the 2014-2018 National Prevention Plan, the 2014-2018 Veneto Regional Program of Prevention (PRP), approved by Regional Council Resolution (DGR) no. 749 of 14.05.2015,⁷ consolidation of a pathway of diagnosis, observation, and prophylaxis for women with a high risk of hereditary breast carcinoma is thus proposed. The principal activities of this policy will be the following:

- creation of a regional institutional working group which will involve experts on the topic in various capacities (personnel coordinating regional cancer screening, personnel from the Veneto Institute of Oncology-IOV, personnel from the regional Public Health Genomics Group, etc);
- survey of currently existing pathways for the identification of women at risk of hereditary breast cancer and adoption of the same.

On this subject, the multi-disciplinary working group of the Veneto Institute of Oncology, co-ordinated by the Hereditary-Family Breast/Ovarian Cancer Service has perfected a clinical/diagnostic course devoted to patients and healthy subjects belonging to families at high risk of breast and/or ovarian cancer. The activity of this group has permitted integration of the multi-disciplinary competences of the Institute connected to the genetic test, from genetic counselling to diagnosis, from prevention to therapy, including psychological aspects.

Co-ordination of a territorial network linking most of the Health Districts in Veneto and the autonomous provinces of Trento and Bolzano makes it possible to provide continuity of care to subjects at risk of hereditary cancer through structured multi-disciplinary coordination, according to the level of specialization, between the centres within the network. In particular, level II centres carry out the activity of cancer counselling, risk estimate, and referral to genetic testing, in line with what is indicated by the central specialized medical facility. The level II centres are also responsible for communication of the result of the test through post-test counselling, as well as extension of the genetic study to family members and activities

of prevention/observation of the subjects at risk of hereditary breast and ovarian cancer. Level I centres (primary care) carry out an initial evaluation of family history of cancer and select the patient to refer to the central specialized medical facility or the level II centre for genetic-cancer counselling.

Thanks to collaborative projects pooling national and international data, the most recent scientific acquisitions for the definition and management of «hereditary risk» are integrated in an operative model which has been the subject of verification and approval by international bodies for external quality control and has been subjected to the attention of the institutions acting as reference in Veneto. The database managed by the central specialized medical facility (IOV) contains the case history and genealogical as well as molecular data of 2,500 families for a total of 3,419 genetic tests (blood relations included). The individuals with a positive test result number 762. There are 429 individuals belonging to high-risk families but with a negative result for the family's mutation and therefore excluded from the intensive programs of prevention/observation. The current critical points of this pathway are:

- access to genetic tests for women (and family members) who, on the advice of a medical expert, wish to learn more about their own hereditary-family risk is linked to criteria based on recommendations and national and international guidelines which should be updated in the light of new scientific acquisitions and subjected to the region's approval;
- despite the high risk of disease (breast cancer and ovarian cancer) of female carriers of the *BRCA1/2* mutation, exemption from payment of the charge ("ticket") for pathways of

- observation/prevention does not currently exist in Veneto;
- incomplete training and information provided to personnel in the level I structures (primary care) on the criteria of selection and protocols of observation/prevention for high-risk subjects;
- approval and consolidation of a structured regional pathway for women at high risk of hereditary breast and/or ovarian cancer, from oncogenetic consultation and genetic testing to management of disease risk.

Subsequent to the recognition of the pathway of diagnosis, observation and prophylaxis for women at high risk of hereditary breast carcinoma, Veneto undertakes to develop a co-ordinated program of information and training on this pathway directed to the population and healthcare workers, and plan how to disseminate it to all Local Health Service Agencies.

CONCLUSIONS

It is firmly hoped that with the inclusion of a program for the management of women at high risk of hereditary breast cancer within the PRP of the Veneto Region, this topic may become more defined and structured in terms of sustainability, integration with the existing regional networks (mammography network, Breast Unit), the fight against inequality (exemption from payment), monitoring and evaluation, even taking as a reference model certain aspects of the organization of cancer screening programs, thus pursuing the objectives of reduction of cause-specific mortality and improvement of quality of life for women with high hereditary risk.

Conflicts of interest: none declared

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COMMUNICATIONS C14
Thursday 15 October
h. 8.30
Amber Room 4

Increased incidence of childhood leukemia in urban areas: a population-based case-control study

Il rischio di leucemia infantile è maggiore nelle aree urbane: uno studio caso-controllo di popolazione

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Abstract

Objective. We carried out a population-based case-control study to assess the possibility of an excess risk of childhood leukemia in urban areas, independently from road traffic pollution.

Methods. Study subjects were the 111 cases of childhood leukemia diagnosed from 1998 to 2011 among residents of two provinces of the northern Italian Emilia-Romagna region, and 444 controls matched by age and sex. Through mapping of the region carried out by remote sensing, we examined the percentage of urban or rural area in the 100-meter circular buffer around each child's house. We also modeled annual average exposure to benzene and PM10 from vehicular traffic at each residence.

Results. In a multivariate model adjusting for benzene and PM10, the odds ratio of leukemia associated with residence in a highly urbanized area and residential area ($\geq 95\%$ land use of this type near the child's home) was 1.4 (95% confidence intervals 0.8-2.4) and 1.3 (0.8-2.2), respectively. An increased risk was also found in association with the proximity to «dumps, scrap yards, and building sites». No association emerged with residence in rural areas or near industrial plants.

Conclusions. These results indicate that children living in urban areas experience an excess leukemia risk, independently from exposure to pollutants from vehicles.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 102-107)

Key words: childhood leukemia, urban area, benzene, PM10

Riassunto

Obiettivo. Abbiamo condotto uno studio caso-controllo di popolazione per valutare la possibile associazione tra incidenza di leucemia infantile e residenza in aree urbanizzate, indipendentemente dall'esposizione a inquinanti da traffico autoveicolare.

Metodi. Abbiamo individuato i 111 casi di leucemia infantile diagnosticati nel periodo 1998-2011 nelle province di Modena e Reggio Emilia e una popolazione di controllo, costituita da quattro bambini appaiati per sesso, anno di nascita e provincia di residenza a ciascun caso. Di tali bambini abbiamo georeferenziato l'indirizzo di residenza e determinato l'uso del suolo nelle immediate vicinanze (100 m), basandoci sulla mappatura del territorio regionale effettuata mediante telerilevamento.

Risultati. Il rischio relativo di leucemia nei bambini residenti in aree urbane o più strettamente residenziali (uso del suolo di tali tipologie $\geq 95\%$) è risultato rispettivamente pari a 1.4 (intervalli di confidenza al 95%: 0.8-2.4) e 1.3 (0.8-2.2), dopo aggiustamento per benzene e PM10. Un incremento del rischio è risultato associato anche alla prossimità ad aree estrattive, discariche e cantieri, mentre nessuna associazione è emersa con la residenza in aree rurali o industrializzate.

Conclusioni. Questi risultati suggeriscono come la residenza in aree altamente urbanizzate sia associata a un incremento del rischio di leucemia infantile, indipendentemente dall'inquinamento autoveicolare.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 102-107)

Parole chiave: leucemia infantile, area urbana, benzene, PM10

BACKGROUND

Childhood cancer is a primary cause of death in children and adolescents in the industrialized world, the most common form (around 30%) being leukaemia. The causes of childhood leukaemia, unfortunately, still remain largely unknown.¹ About 5%-10% of childhood leukaemia is ascribed to ionizing radiation, congenital genetic anomalies,² and inherited conditions such as ataxia telangiectasia.³ For the remaining cases, suspected risk factors are parental occupational exposures,⁴ magnetic fields from high-voltage lines,⁵ dietary factors,⁶ exposure to chemicals (pesticides, paints, and household solvents),⁷ and parental smoking.⁸ Residential proximity to industries has been associated with an increased risk of childhood leukaemia.⁹ An excess risk of childhood leukaemia has also been observed in urban areas of several countries in some⁹⁻¹¹ though not all studies,¹² and it has been ascribed to exposure to benzene and other traffic-related toxins,¹³ or to the nearby presence of industrial plants and waste incinerators.⁹ However, infectious agents spread through interpersonal contact, which is more likely in urban areas where population density is very high, might also be involved in the excess disease incidence seen in urban sites. Therefore, it has been proposed that infections and immunologic mechanisms may play a role in leukaemia aetiology, particularly for the acute lymphoblastic subtype, and this hypothesis is supported by some epidemiological features of the disease, such as age distribution, with its peak at 3-4 years, the greater incidence in developed countries, and a history of clustering.¹⁴ Leukaemia might be caused by an abnormal immune response to common infection during early life.^{15,16} The existence of a specific leukaemia-causing agent, causing epidemic episodes in particular population mixing, has also been proposed.^{17,18} We carried out a case-control study in a northern Italian population to ascertain the possible effect of residence in urban areas on childhood leukaemia risk, taking into account exposure to traffic-related atmospheric pollutants.

METHODS

Study population

We identified all cases of childhood leukaemia newly diagnosed from 1998 to 2011 in children aged 0-14 while residing in Modena and Reggio Emilia, two provinces (total population about 1,200,000) of the Emilia-Romagna region in northern Italy. Cases, along with their leukaemia subtype, were identified through the nation-wide hospital-based registry of childhood malignancies managed by the Associazione italiana ematologia oncologia pediatrica (AIEOP),¹⁹ which also made it possible to retrieve the children's residence at diagnosis. For each case, we randomly selected four population controls among all residents with the same year of birth, sex, and province of residence, using the historical population databases of the National Health Service to match them by calendar year of case diagnosis, as well. We also collected information about paternal annual income for the index year from the Revenue Agency of the Ministry of Finance database, as an indication of family socio-economic status.

Exposure assessment

We georeferenced the residential houses of patients at diagnosis and of the matched controls in the corresponding year in a Geographical Information System (GIS) using Arc-GIS software (version 9.2, ESRI, Redlands, CA 2006). The satellite coordinates of the residences were retrieved from a database available from the Modena and Reggio Emilia Provinces Service or, for addresses not included in the database, through Google Earth or a direct in loco measure using a portable GPS device (GPSmap 60CSx, Garmin Int. Corp., Olathe, KS).

We assessed the types of land use near each geocoded home according to GIS-based information collected by the Emilia-Romagna region by remote sensing in the year 2003 (the best one available for the study period). The Land Use Map 2003 for the Modena and Reggio Emilia provinces is available from the «Emilia-Romagna Geoportal»;²⁰ it contains a detailed description of land use with the specifications of Corine Land Cover.²¹ Roads, including names, technical and administrative classification were also obtained from the cartographic archive of Emilia-Romagna region. We defined a circular buffer with a 100-meter radius around each child's home, and we selected for the study analysis two major predefined subtypes of land use: «urban area» and «rural area». «Urban area» included anthropic structured spaces and surfaces with residential buildings, roads, railways, production/commercial plants, public/private services, networks for water distribution and for production/transportation of energy. «Rural area» comprised territories allocated to agriculture with crop fields dedicated to different cultivations. «Urban area» was further detailed in three specific subtypes: «residential», «industrial plants», and «dumps, scrap yards, and building sites». «Residential» area refers to surfaces covered by over 50% by buildings intended for exclusive residential use. «Industrial plants» included industrial manufacturing facilities, factories, waste incinerators, water treatment plants, hospitals. «Dumps, scrap yards, and building sites» comprised the mining and quarrying of sand, gravel, stone, or other material, industrial scrap yards or repository, waste landfills, and construction sites. Finally, we calculated the percentages of rural and urban area, with their specific subcategories, within each circular buffer, using Python programming language, directly related to the GIS environment. For patients diagnosed with leukaemia before 2010 and their controls, we also had the modeled exposure at the home of residence to benzene and particulate matter $\leq 10 \mu\text{m}$ (PM10) from motorized traffic available from a previous study.²² Briefly, the California Line Source Dispersion Model, version 4 (CALINE4),²³ a line source air quality model, had been used to model the dispersion of emissions from vehicular traffic, considering specific vehicular emission factors for pollutants, vehicular traffic flow parameters for the main roads of both provinces and meteorological data. Such information could not be computed for the few subjects residing in sparsely populated mountain municipalities, for methodological reasons.²²

Data analysis

We estimated the relative risk of childhood leukaemia associated with the intensity of urbanization by calculating the disease odds ratios (ORs) and their 95% confidence intervals (CI) in crude and multivariate conditional logistic regression models, according to percentage of land use within a 100-meter circular buffer around the child's home. The multivariate model was adjusted for exposure to benzene and PM10, two pollutants from vehicular traffic, and also for paternal income when available. The linearity of the associations between land use and disease risk was tested by computing a P value for trend based on percentage of area subtype as a continuous variable in the conditional logistic regression model. We also modeled the relationship between percentage of urbanized area and risk of leukaemia using restricted cubic splines, using the "mkspline" and "xblc" commands in Stata 13.²⁴ The optimal number of knots was selected using Akaike's information criterion (AIC), with knot placement as recommended by Harrell.²⁵ Based on the lowest AIC, we selected a model with three knots, placed at the 10th, 50th, and 90th percentiles.

RESULTS

We identified 111 newly-diagnosed cases of childhood leukaemia during the study period, including 86 (77.5%) of acute lymphoblastic subtype (ALL) (average age at diagnosis 6.1, standard deviation 3.8 years), 22 (19.8%) of acute myeloid subtype (AML) (5.3±4.9) and 3 cases included in the chronic myeloid category. Four hundred and forty four controls were also included in the study. Sixty five (58.5%) cases and 235 (52.9%) controls lived in highly-urbanized areas having ≥95% of «urban area» land use within the 100-meter circular buffer

around the home building. Most of them were also living in areas defined as «residential» (38 [34.2%] cases and 133 [29.9%] controls), while a few of them lived in areas characterized as «industries» or «dumps, scrap yards, and building sites». Only four (3.6%) cases and 24 (5.4%) controls lived in areas defined as «rural», i.e., having ≥95% of «rural» land use. Benzene concentration was higher for children living in intensely urbanized districts (0.5 µg/m³) than for those living in a «rural» area (0.1 µg/m³), while concentrations of PM10 were substantially similar in both environments (6.6 and 6.5 µg/m³, respectively).

Table 1 reports the OR of childhood leukaemia subtypes associated with a 10% increase in specific land uses within the 100-meter circular buffer around the child's home building. The urban area was further split into «residential» area, «industrial plants», and «dumps, scrap yards, and building sites». Adjusted analyses for annual average benzene and PM10 exposure showed an increased risk related to each 10% increase in residence in an «urban area» for all leukaemia (OR 1.05; 95%CI 0.95-1.16) and for single-disease subtype with an OR of 1.06 (0.95-1.19) and 1.02 (0.81-1.29) for ALL and AML, respectively. Analysis for specific subcategories of urban area showed an increased risk for «residential» areas (1.04; 0.97-1.12), no association with «industrial plants», and an excess incidence in relation with residence near «dumps, scrap yards, and building sites» (1.36; 0.75-2.49), especially for AML (11.15; 0.39-322.6). No association with «rural area» was identified.

Table 2 shows the OR of childhood leukaemia related to high intensity of urban or residential land use (≥95% around the child's home), according to child age and leukaemia subtype. The relative risk of leukaemia in children living in such a

	All leukemia (cases/controls 111/444)		ALL ¹ (cases/controls 86/344)		AML ¹ (cases/controls 22/88)	
	OR (95%CI)	P-trend ²	OR (95%CI)	P-trend ²	OR (95%CI)	P-trend ²
urban area						
crude ³	1.02 (0.94-1.10)	0.667	1.00 (0.92-1.09)	0.975	1.07 (0.88-1.31)	0.489
adjusted ⁴	1.05 (0.95-1.16)	0.321	1.06 (0.95-1.19)	0.293	1.02 (0.81-1.29)	0.879
residential area						
crude ³	1.03 (0.97-1.09)	0.350	1.03 (0.96-1.10)	0.441	1.05 (0.91-1.21)	0.484
adjusted ⁴	1.04 (0.97-1.12)	0.292	1.04 (0.96-1.14)	0.309	1.04 (0.88-1.24)	0.622
industrial plants						
crude ³	1.01 (0.91-1.13)	0.826	1.01 (0.91-1.13)	0.826	1.03 (0.81-1.31)	0.787
adjusted ⁴	0.99 (0.87-1.12)	0.876	1.02 (0.89-1.18)	0.744	0.93 (0.69-1.26)	0.643
dumps, scrap yards, building sites						
crude ³	0.92 (0.60-1.39)	0.680	0.79 (0.45-1.38)	0.405	9.92 (0.35-279.6)	0.178
adjusted ⁴	1.36 (0.75-2.49)	0.312	1.06 (0.51-2.22)	0.868	11.15 (0.39-322.6)	0.160
rural area						
crude ³	0.96 (0.89-1.05)	0.382	0.98 (0.89-1.07)	0.581	0.94 (0.77-1.15)	0.534
adjusted ⁴	0.94 (0.84-1.04)	0.218	0.92 (0.42-1.75)	0.181	0.99 (0.78-1.24)	0.909

¹ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia

²P for linear trend based on continuous values

³crude analysis

⁴analysis adjusted for annual average atmospheric concentration (µg/m³) of benzene and PM10; estimates not possible for subjects diagnosed after 2009 or residing in mountain municipalities

Table 1. Odds ratios (OR) with 95% confidence intervals (95%CI) of overall and subtype-specific childhood leukaemia associated with a 10% increase in specific land uses within the 100-meter circular buffer around the child's home building.

Tabella 1. Odds ratios (OR) e intervalli di confidenza al 95% (IC 95%) di leucemia infantile associati a incremento del 10% di differenti tipologie di uso del suolo presenti nell'area circolare di 100 metri di raggio definita intorno alla abitazione di ogni bambino.

	Urban area					Residential area				
	<95% ¹		≥95%			<95% ¹		≥95%		
	cases/ controls	OR	cases/ controls	OR (95%CI)	P-trend ²	cases/ controls	OR	cases/ controls	OR (95%CI)	P-trend ²
all leukemia										
crude	46/191	1.00	65/235	1.07 (0.69-1.66)	0.667	73/311	1.00	38/133	1.22 (0.78-1.89)	0.350
adjusted ³	28/138	1.00	55/194	1.36 (0.78-2.37)	0.321	51/227	1.00	32/105	1.33 (0.81-2.20)	0.292
age <5 years										
crude	22/97	1.00	34/127	1.19 (0.64-2.21)	0.811	38/157	1.00	18/67	1.11 (0.59-2.07)	0.999
adjusted ³	10/61	1.00	28/91	1.32 (0.54-3.24)	0.968	23/102	1.00	15/50	1.21 (0.57-2.59)	0.374
age ≥5 years										
crude	24/94	1.00	31/126	0.96 (0.52-1.79)	0.711	35/154	1.00	20/66	1.34 (0.72-2.49)	0.188
adjusted ³	18/77	1.00	27/103	1.32 (0.54-3.24)	0.279	28/125	1.00	17/55	1.38 (0.69-2.76)	0.097
ALL										
crude	38/144	1.00	48/200	0.90 (0.55-1.48)	0.975	58/241	1.00	28/103	1.23 (0.69-2.19)	0.441
adjusted ³	22/105	1.00	42/151	1.33 (0.70-2.49)	0.293	40/173	1.00	24/83	0.97 (0.49-1.92)	0.309
age <5 years										
crude	18/66	1.00	24/102	0.86 (0.42-1.72)	0.674	31/113	1.00	11/55	0.74 (0.35-1.56)	0.542
adjusted ³	7/40	1.00	20/68	1.38 (0.49-3.87)	0.851	18/68	1.00	9/40	0.85 (0.35-2.09)	0.382
age ≥5 years										
crude	20/78	1.00	24/98	0.95 (0.47-1.92)	0.666	27/128	1.00	17/48	1.71 (0.84-3.49)	0.098
adjusted ³	15/65	1.00	22/83	1.24 (0.54-2.81)	0.267	22/105	1.00	15/43	1.68 (0.77-3.67)	0.071
AML										
crude	7/42	1.00	15/46	2.03 (0.73-5.72)	0.489	12/61	1.00	10/27	1.87 (0.72-4.86)	0.484
adjusted ³	5/33	1.00	13/39	1.96 (0.55-6.96)	0.879	10/51	1.00	8/21	1.71 (0.57-5.12)	0.622
age <5 years										
crude	3/28	1.00	9/20	5.00 (1.00-24.90)	0.315	5/38	1.00	7/10	7.04 (1.38-35.8)	0.225
adjusted ³	2/21	1.00	8/19	2.05 (0.26-16.37)	0.692	4/31	1.00	6/9	4.12 (0.67-25.2)	0.966
age ≥5 years										
crude	4/14	1.00	6/26	0.81 (0.20-3.25)	0.749	7/23	1.00	3/17	0.61 (0.14-2.53)	0.775
adjusted ³	3/12	1.00	5/20	1.25 (0.24-6.41)	0.970	6/20	1.00	2/12	0.65 (0.12-3.42)	0.979

¹urban and residential use <95% used as reference category

²P for linear trend based on continuous values of land use

³adjusted for annual average atmospheric concentration (µg/m³) of benzene and PM10; estimates not possible for subjects diagnosed after 2009 or residing in mountain municipalities

Table 2. Crude and adjusted odds ratios (OR) with 95% confidence intervals (95%CI) of childhood leukaemia in highly urbanized areas (≥95% of urban or residential use in the 100-meter circular buffer around the child's home building), according to age group and leukemia subtype (ALL, acute lymphoblastic leukaemia, and AML, acute myeloid leukaemia).

Tabella 2. Odds ratios (OR) e intervalli di confidenza al 95% (95%CI) di leucemia infantile associati alla residenza in aree altamente urbanizzate (>95% di area residenziale nel buffer circolare di 100 metri di raggio definito intorno alla abitazione), per fasce di età e sottotipo di leucemia (ALL, leucemia linfatica acuta e AML, leucemia mieloide acuta).

highly urbanized area, after adjustment for atmospheric concentrations of benzene and PM10, was 1.36 (0.78-2.37). Considering only «residential» land use and investigating the two different subtypes of leukaemia, we found that the increased risk for ALL was confined exclusively to children ≥5 years, while for AML the opposite was true.

Spline regression analysis with adjustment for the matching variables, benzene and PM10 exposure also suggested a positive association between percentage of urbanized area and leukaemia risk (figure 1).

When we also adjusted the analysis for paternal income, the OR did not change (data not shown), but estimates were more unstable, as data were only available for 77% of the study subjects.

CONCLUSIONS

A greater incidence of childhood leukaemia in urban than rural areas has already been noted for several countries.⁹ This increased risk was often attributed to high exposure to at-

mospheric benzene and other pollutants from motor vehicular traffic, or to the nearby presence of industrial plants, waste incinerators, or other sources releasing potentially carcinogenic chemicals.^{9-11,13} Other authors suggested that the excess risk found in urban areas was due to the spread of infectious agents through interpersonal contact, which is clearly more intense in urban areas where population density is higher and the proportion of commuters or immigrant residents is higher, with an increased degree of population mixing,²⁶ though some evidence is inconsistent with this hypothesis.²⁷

Findings of our study indicate that children living in highly urbanized areas have an increased risk of leukaemia compared to those living in rural areas, and that such excess risk is present regardless of exposure to benzene and PM10 from vehicular traffic, likely risk factors for this disease.^{13,22} Our analysis also shows that childhood leukaemia risk is higher near «dumps, scrap yards, and building sites» or in areas generally defined as «residential».

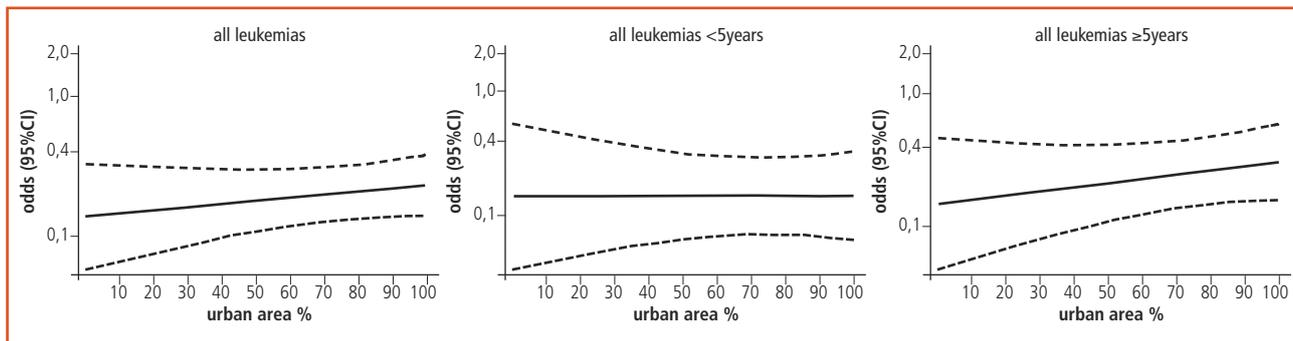


Figure 1. Natural cubic spline models from a generalized additive model for the relation between odds of case status and percentage of urban use controlling for benzene and PM10 exposure.

Figura 1. Rappresentazione grafica della relazione tra rischio di leucemia e uso del suolo presso l'abitazione di residenza.

Overall, these findings are consistent with the hypothesis of an infectious and immunological etiology of the disease, taking into account that our urban and particularly residential areas are characterized by the highest population density and strongly promote social interpersonal contacts. A role for infectious and immunologic mechanisms in the aetiology of childhood leukaemia, particularly of ALL, is supported by some epidemiological features of the disease, such as age distribution, with its peak at 3-4 years, greater incidence in developed countries, and history of clustering. It is possible that, particularly in genetically susceptible children, the immune system may suffer from lack of sufficient microbial challenges during early life due to extremely high hygienic conditions, thus developing an altered response to infections later encountered in childhood (the so-called «hygiene» or «delayed infection» hypothesis).^{15,16,28} Alternatively, a specific leukaemia-causing agent may exist,¹⁷ promoting the onset of the disease in densely-populated areas, and this might be due to viruses such as human herpesvirus and polyomavirus.¹⁴

The lower risk experienced in our study population by children living in rural areas might be hypothetically explained by adequate stimulation of the immune system in early life, as they are more subject to exposure to microbiological agents owing to their different lifestyle (more time spent outdoors, homes on the ground floor, windows open longer, larger families, more children per family) and less careful and sophisticated hygienic conditions compared with children living in cities and more generally in urban areas. In addition, this lower risk observed in rural areas does not appear to support a role of environmental pesticide exposure in leukaemia aetiology.

Of interest is the excess ALL risk that we found in children

aged ≥ 5 years living in residential areas, after adjustment for vehicular traffic. This may support the hypothesis of a second mutation occurring at around 3-5 years of age, shortly before the occurrence of the typical peak of this specific leukaemia subtype.¹⁶ We also saw an excess risk for AML < 5 years, and this observation agrees with what has already been noted for this disease subtype, which showed a typical peak in the neonatal period and in adolescence.

The increased risk associated with residing near «dumps, scrap yards, and building sites» might be attributed to the presence of toxic substances in the nearby environment. However, lack of measured or modeled data on the amount and type of chemical pollution present in such study areas, including the possible release of benzene and PM10 from other sources than vehicular traffic, and the very low number of exposed children on which these statistically unstable risk estimates were based greatly hamper the evaluation of this finding.

In conclusion, our study indicates that an excess risk of childhood leukaemia exists in urban areas, particularly residential ones, and that such excess may not entirely be ascribed to pollution from motorized traffic. These results are consistent with the hypothesis of a role of infectious agents and insufficient stimulation of the immune system in early life in the etiology of childhood leukaemia.

Conflicts of interest: none declared

Funding: financial support was provided by the Associazione Sostegno Oncologia Ematologia Pediatrica - ASEOP, «Fondazione Pietro Manodori» of Reggio Emilia and the Italian Ministry of Education, University, and Research (Project PRIN2010-11, 2010WLNIFY2).

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COMMUNICATIONS C15
Thursday 15 October
h. 10.00
Brown Room 1

Malnutrition decreases the odds of attaining motor milestones in HIV exposed children: results from a paediatric DREAM cohort

La malnutrizione infantile ritarda lo sviluppo motorio nei bambini esposti a HIV: risultati dalla coorte pediatrica del programma DREAM

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Abstract

Objective. HIV and malnutrition are the two major causes of infant mortality in Sub-Saharan Africa. The study describes the impact of malnutrition on motor milestone development in HIV-exposed children.

Design. Randomized community intervention trial (SMAC, Safe Milk for African Children).

Setting and participants. Growth, motor development, and malnutrition were assessed in a sample of 76 HIV-exposed children, aged 0-24 months, at the Blantyre Dream Centre in Malawi.

Main outcome measures. We assessed growth and selected motor milestone achievement in agreement with WHO/UNICEF criteria. Odds ratios and 95% confidence intervals were calculated according to motor milestones and malnutrition indices. Multivariable logistic regression was performed with 18 months data.

Results. High rates of malnutrition were observed. Underweight increased by 6.7/9.2 and 3.2/5.5 the odds of not standing alone and not walking alone at 15 and 18 months. Stunting increased by 9.7 the odds of not standing alone at 11 months and by 6.1 the odds of not walking alone at 18 months. Wasting increased by 5.5/10.3 the odds for not walking with assistance at 12 and 18 months. Low weight for age was associated with delay in walking at 18 months (HR=2.9).

Conclusion. Malnutrition in HIV-exposed children decreases the likelihood of adequate development.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 108-112)

Key words: malnutrition, motor milestones, HIV-exposed, DREAM program

Riassunto

Obiettivi. HIV e malnutrizione sono le principali cause di mortalità infantile nell'Africa sub-sahariana. Lo studio descrive l'impatto della malnutrizione sul raggiungimento delle *motor milestones* in bambini esposti a HIV.

Disegno. Trial clinico randomizzato (SMAC, Safe Milk for African Children).

Setting e partecipanti. Crescita, sviluppo motorio e malnutrizione sono stati valutati in un campione di 76 bambini HIV esposti (0-24 mesi), del Centro DREAM di Blantyre in Malawi.

Principali misure di outcome. La crescita e lo sviluppo motorio sono stati valutati in accordo con i criteri WHO/UNICEF. Sono state calcolate mensilmente le odds ratio (IC95%) per malnutrizione e "motor milestones". Una regressione logistica multivariata è stata realizzata a 18 mesi.

Risultati. Sono stati osservati alti tassi di malnutrizione. Il sottopeso aumenta il rischio di non stare in piedi da solo e di non camminare da solo a 15 (6.7/9.2) e a 18 mesi (3.2/5.5). Lo «stunting» aumenta il rischio di non stare in piedi da solo a 11 mesi (9.7) e di non camminare da solo a 18 mesi (6.1). Il «wasting» aumenta il rischio di non camminare con assistenza a 12 e 18 mesi (5.5/10.3). Il basso peso per età era associato al ritardo nel camminare da solo a 18 mesi (HR=2.9).

Conclusioni. La malnutrizione in bambini HIV-esposti diminuisce la probabilità di un adeguato sviluppo neuromotorio.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 108-112)

Parole chiave: malnutrizione, *motor milestones*, HIV-esposti, programma DREAM

INTRODUCTION

Childhood malnutrition is a critical issue in Africa and elsewhere.¹ Prior research studies have shown an association between malnutrition and delayed motor and cognitive development.^{2,3} Early childhood malnutrition and HIV have been associated with delayed development. Limited data exist, however, about the timing of developmental delay early in life, particularly for HIV-exposed children.

In Malawi, HIV and malnutrition are the two major causes of infant morbidity and mortality.^{4,5} Children born to HIV-positive women are particularly susceptible to malnutrition. Following review of recent HIV perinatal guidelines, the World Health Organization proposed the administration of antiretroviral therapy to mothers during the lactation period. Malnutrition nevertheless remains a challenge to the health of HIV-exposed children.^{6,7} There is very limited data on motor milestone achievement in these children. The DREAM Program (Drug Resource Enhancement Against AIDS and Malnutrition), sponsored by the Community of Sant'Egidio, an Italian faith-based non-governmental organization, has been a pioneer in the prevention of mother-to-child transmission of HIV/AIDS in Sub-Saharan Africa.^{8,9} The present study describes the assessment of growth and four motor milestones (standing with assistance, walking with assistance, standing alone, walking alone) in a sample of 76 HIV-exposed children originally randomized to an interventional study at the Blantyre DREAM Centre in Malawi.

MATERIALS AND METHODS

The study was approved by the National Health Sciences Research Committee of Malawi (approval number 486), with a separate informed consent signed by the mothers/guardians of participants.

Study population included HIV-exposed children born to pregnant women attending the DREAM program antenatal clinic in Blantyre. DREAM is a public health program aimed at the prevention and treatment of HIV/AIDS with multiple centres in 10 African countries. The DREAM program's approach to the diagnosis, treatment, and prevention of HIV/AIDS in Africa has been described in prior studies.⁸⁻¹⁰

Subjects in this analysis were a subpopulation of 76 children followed in the interventional SMAC study (Safe Milk for African Children)¹¹ from April 2008 to August 2009. The current analysis encompasses 35 males (46.1%) and 41 females (53.9%), all HIV-exposed, followed from the time they were born up to 24 months of age. Motor milestone assessment was initiated prospectively at 9 months of age. Infants were exposed to ARTs in utero and were given prophylactic AZT after birth. Their primary exposure was ART prophylaxis. HIV-exposed children were breastfed up to 6 months of age (the recommended duration of breastfeeding at the time of the study). All women received antiretroviral therapy and monthly nutritional supplementation as part of program guidelines. All mothers came from low socioeconomic households. At baseline all children were HIV-uninfected based on viral load testing.

Anthropometric and clinical exams of HIV-exposed chil-

dren were performed monthly and measures were registered through a software package obtained in collaboration with the Department of Nutrition of the World Health Organization. Motor development assessed in terms of age of achievement of motor milestones was included as part of the DREAM software.¹²⁻¹⁴

Following WHO criteria, malnutrition indices were defined as stunting (length for age < -2 SD), wasting (weight for length < -2 SD), and underweight (weight for age < -2 SD).

Malnutrition was assessed and managed in accordance with the Malawian guidelines for the management of malnutrition.¹⁵ The assessment of motor behaviour, which is an essential aspect of child development, includes six specific milestones: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone. Evaluation of motor milestone performance consists in observing whether a child can perform a milestone independently or after being placed into position. In this study, all milestones were assessed by a dietician using standardized testing procedures of the WHO Multicentre Growth Reference Study Group.¹⁴ Details on our nutritional rehabilitation program have been previously described.^{16,17}

Only HIV-exposed children 9-24 months were included (N=76). WHO Anthro Software (Version 3.2.2, January 2011) was used to compute children's weight-for-age (WAZ), weight-for-length (WLZ), and length-for-age (LAZ) z-scores per WHO standards. Further analysis of the data was completed using SPSS software system 20.0 (IBM Somers, NY, USA). Median age of the highest observed milestone was calculated (age of MM achievement) and compared with the WHO reported median for the following selected motor milestones: standing with assistance, walking with assistance, standing alone, walking alone.

From 9 to 24 months the odds ratios (95%CI) between malnutrition indices (underweight, wasting, stunting) and motor milestone achievements were estimated. At 18 months, the odds ratio (95%CI) was calculated through a multivariate logistic regression analysis in order to assess the associations between growth parameters and walking alone.

RESULTS

A total of 76 HIV-exposed children (53.9% females) born between April 2008 and August 2009 were enrolled. The characteristics of the children at birth and at 18 months of age and maternal data are reported in **table 1**. The mean weight for age z-score at birth was -0.8 SD with 20.8% of the sample having a low birth weight (< 2.5 kg). Mean duration of breastfeeding was 24.7 weeks. At baseline, mothers had a mean CD4 cell count of $390/\text{mm}^3$. At 18 months, all children were tested for HIV for the last time before being discharged from the DREAM prevention mother-to-child transmission program. Final HIV status was available for all children. Among them one acquired HIV infection. No deaths occurred during the 24-month study period.

At 18 months, mean WAZ score was -1.5 , mean LAZ score was -2.4 and mean WLZ was -0.5 . Eight children (10.5%) were

Characteristics	Value
mothers*	
age in years, mean (SD)	28 ± 4.8
HIV WHO stage, N (%)	
I	55 (72.4%)
II	16 (21%)
III	4 (5.3%)
IV	1 (1.3%)
CD4+cell count/mm ³ , mean (SD)	390 ± 238
BMI in kg/m ² , mean (SD)	23.4 ± 2.9
duration of breastfeeding (weeks), mean (SD)	24.7 ± 4.5
children**	
girls: n (%)	41 (53.9%)
birth weight (kg), mean (SD)	2.9 ± 0.6
birth weight, weight for age z score, mean (SD)	-0.8 ± 1.1
low birth weight (<2.5 kg): N (%)	16 (20.8%)
HIV positive at 18 months: N (%)	1 (0.1%)
weight at 18 months (kg), (SD)	9 ± 1.3
WAZ at 18 months, mean (SD)	-1.5 ± 1.2
length at 18 months (cm), mean (SD)	75.2 ± 3.5
LAZ at 18 months mean (SD)	-2.4 ± 1.3
WLZ at 18 months mean, (SD)	-0.5 ± 1.1
WAZ <-2 at 18 months: N (%)	28 (36.8%)
LAZ <-2 at 18 months: N (%)	46 (60.5%)
WLZ <-2 at 18 months: N (%)	8 (10.5%)
walking alone at 18 months: N (%)	60 (78.9%)

*at first visit during pregnancy, **at birth and at 18 months

Table 1. Characteristics of HIV-exposed children and their mothers.

Tabella 1. Caratteristiche dei bambini HIV-esposti e delle loro madri.

wasted and 16 (21%) were not able to walk alone. The t-test did not show any statistically significant associations between maternal characteristics (age, CD4 count, BMI, duration of breastfeeding) and the ability of a child to walk alone at 18 months.

The median ages (in months) at achievement of the four specific motor milestones are illustrated in **table 2** and compared with results from other studies. In the present study, for the four milestones, the median age was 10 months for standing alone, 12 months for walking with assistance, 15 months for standing alone, and 15 months for walking alone.

Among the sample, 34 children were delayed in achieving motor milestones when evaluated based on the WHO window of achievement assessment: 2 children in standing with assistance (2.6%), 6 in walking with assistance (7.8%), 10 in stand-

ing alone (13.1%), and 16 in walking alone (21%). Among them, 24 children (70.5%) were underweight. This data confirms the role of malnutrition in the retardation of achievement of motor milestones.

Table 3 reports the odds ratios and 95%CI by month between malnutrition indices and motor milestone achievement. The risk of not being able to walk with assistance at 12 months increased 5.5 times (95%CI 1.3-23.6) in wasted children. A high risk for not standing alone at 18 months was also seen in wasted children (OR 10.3; 95%CI 2.0-52.1). Similar risks of not standing alone were seen in children who were stunted at 11 months (OR 9.7; 95%CI 1.1-83), underweight at 18 months (OR 9.2; 95%CI 1.7-47.2), and also underweight at 15 months (OR 6.6; 95%CI 2.2-19.3). At 18 months the risk of not walking alone increased 8.6 times (95%CI 1.8-41.5) in wasted children, 6.1 times in stunted children (95%CI 1.3-29.3) and 5.5 times in underweight children (95%CI 1.6-18.4).

In order to confirm these results, a multivariable logistic regression was performed with 18 months of age data, with anthropometric parameters: WAZ, LAZ, WLZ, weight assessed at 18 months of age versus the motor milestone «walking alone». The model verified an association between low values for WAZ and not walking alone at 18 months, with a hazard risk of 2.9 and 95%CI of 1.6-5.4 with a p-value of <0.001 (WLZ 0.25 p=0.61; LAZ 0.45 p=0.5; weight 1.09 p=0.29).

Table 4 shows the evolution of growth parameters, nutritional indices, and developmental milestones between ages 9 and 24 months.

DISCUSSION

The present data supports the conclusion that HIV-exposed children in Sub-Saharan Africa are a very vulnerable population who experience high rates of malnutrition. Prior studies have described delays in the age of achievement of specific motor milestones in malnourished children (14, 18-22) but few have investigated the relationship between malnutrition and motor development among HIV-exposed children. Our study demonstrates that during the first year of life, HIV-exposed children experienced significant growth and neuromotor development delays. Interestingly except for one child who acquired HIV-infection during the observation period via breastfeeding, 75 of 76 children in this analysis were uninfected. The findings of delayed motor development are tied to the effects of acute and chronic malnutrition which plague paediatric HIV-exposed and unexposed populations in many Sub-Saha-

Motor milestone	WHO median (ref. 14)	Vietnam median (ref. 21)	Zanzibar median (ref. 22)	Present study median	Indonesia median (ref. 20)	Malawi geometric mean (ref. 18)	Italy median (ref. 19)
study type	longitudinal	cross-sectional	cross-sectional	longitudinal	cross-sectional	randomized trial	longitudinal
standing with assistance	7.4	9.9	10	10	8	not assessed	not assessed
walking with assistance	9	12.2	12	12	11	10.6	not assessed
standing alone	10.8	13.2	12	15	13	11.3	11.2-11.4
walking alone	12	15.7	15	15	14	13.8	12.7-12.9

Table 2. Comparison of median age in months at motor milestone achievement between different studies of non-HIV-exposed children and the present study.

Tabella 2. Confronto dell'età media di raggiungimento (in mesi) delle *motor milestones* di bambini "non HIV-esposti" in differenti studi e nel presente studio.

	Hands-and-knees crawling	Standing with assistance	Walking with assistance	Standing alone	Walking alone
underweight 11 months	1.5 (0.3-5.7)	4.6 (0.4-46.8)	0.9 (0.3-2.4)	5.8 (0.7-49.7)	1.1 (1-1.2)*
wasting 11 months	4.7 (0.6-32.9)	5.2 (0.4-61.6)	1.7 (1.4-2.2)*	1.1 (1-1.2)*	1.1 (1-1.1)*
stunting 11 months	0.8 (0.2-3.3)	2.8 (0.3-28.6)	1.5 (0.6-4)	9.7 (1.1-83.6)*	1.1 (1.0-1.3)*
wasting 12 months	5.5 (1.1-23.6)*	0.8 (0.6-1.1)	5.5 (1.3-23.7)*	3.1 (0.4-26.1)	1.3 (0.1-11.8)
underweight 15 months	2.5 (0.5-12)	0.9 (0.9-1)	3.8 (0.6-22.4)	6.7 (2.2-19.3)*	3.2 (1.2-8.3)*
wasting 15 months	1.1 (1-1.2)*	1 (0.9-1)	1 (1-1.1)*	5 (0.8-29.5)	2.5 (0.4-14.6)
stunting 15 months	1 (0.2-4.9)	0.9 (0.9-1)	1.6 (0.3-9.2)	3.2 (1.1-9.4)*	3.1 (1.2-8.3)*
underweight 18 months	1.1 (0.1-7.3)	0.9 (0.9-1)	3.6 (0.3-41.8)	9.2 (1.7-47.2)*	5.5 (1.6-18.4)*
wasting 18 months	1 (1-1.1)*	1 (0.9-1)	4.7 (0.3-58.8)	10.3 (2.0-52.1)*	8.6 (1.8-41.5)*
stunting 18 months	2.7 (0.2-25.9)	0.9 (0.9-1)	0.9 (0.9-1)	7 (0.8-58.9)	6.1 (1.3-29.3)*
wasting 21 months	1.1 (1-1.1)*	1 (0.9-1)	1 (0.9-1)	1 (0.9-1)	2.6 (0.2-26.9)
wasting 24 months	1 (1-1.1)*	1 (0.9-1)	1 (0.9-1)	1 (0.9-1)	1 (0.9-1)

*statistical significance

Table 3. Odds ratios and 95%CI by age (in months) between malnutrition indices and achievement of specific motor milestone achievements.

Tabella 3. Odds ratios e limiti di confidenza al 95% per età (mesi) tra indici di malnutrizione e mesi di raggiungimento delle specifiche *motor milestones*.

ran African settings. The present study demonstrates that malnutrition as manifested by specific indices, such as underweight status, stunting, and wasting, decreased the odds of attaining motor milestones, particularly the four milestones assessed at 9 months of age, standing with assistance, walking with assistance, standing alone, and walking alone.

When we compared motor milestone achievements in our population with results from different studies of non-HIV-exposed children, we saw that the median age of achievement of specific motor milestones in our cohort was delayed as compared to the ages reported in the WHO multicenter study,¹⁴ as well as studies conducted in Malawi,¹⁸ Italy,¹⁹ and Indonesia.²⁰ Our study had similar findings to studies conducted in Vietnam²¹ and Zanzibar,²² where the median age of achievement for the four motor milestones was similar to that

observed in our cohort. It is important to note, however, that most studies in the literature to date evaluated motor development in malnourished non HIV-exposed children, who are distinct from our own population of HIV-exposed infants. A study in Brazil²³ described motor development in HIV-exposed children in Sao Paulo and demonstrated a 10% delay in the achievement of motor milestones, which was not related to environmental or maternal parameters using the Alberta Infant Motor Scale (AIMS). The study had a sample size of 30 subjects, less than half of the present analysis, and the population differed significantly from ours in the fact that HIV-exposed children in Brazil are not breastfed and use formula since infancy. In addition, our malnutrition indices were very high, with more than 60% of our cohort having evidence of stunting with LAZ of <-2 and nearly 40% having WAZ <-2 at 18

Parameters	Age (months)						
	9	11	12	15	18	21	24
mean weight (kg±SD)	7.56±1.08	7.8±1.2	8.0±1.2	8.5±1.3	9.0±1.3	9.6±1.3	10.3±1.4
mean length (cm±SD)	67.4±3.5	68.5±3.2	69.9±3.4	72.6±3.6	75.2±3.5	77.6±3.6	80.0±3.7
WAZ	-1.2±1.2	-1.5±1.3	-1.4±1.3	-1.5±1.3	-1.5±1.2	-1.4±1.1	-1.3±1.1
LAZ	-1.8±1.2	-2.2±1.4	-2.2±1.4	-2.3±1.4	-2.4±1.3	-2.4±1.3	-2.0±1.2
WLZ	-0.2±1.2	-0.3±1.2	-0.4±1.1	-0.5±1.1	-0.5±1.1	-0.3±1.1	-0.3±1.1
underweight [N (%)]	19 (33.3%)	31 (44.2%)	31 (40.7%)	28 (36.8%)	28 (36.8%)	25 (32.8%)	24 (32%)
wasted [N (%)]	2 (3.5%)	3(4.2%)	8 (10.5 %)	6 (7.9%)	8 (10.5%)	7 (9.2%)	3 (4%)
stunted [N (%)]	26 (45.6%)	39 (55.7%)	41 (53.9%)	43 (56.5%)	46 (60.5%)	46 (60.5%)	44 (58.6%)
sitting without support [N (%)]	57 (100%)	70 (100%)	76 (100%)	76 (100%)	76 (100%)	76 (100%)	76 (100%)
crawling [N (%)]	33 (57%)	60 (85%)	68 (89.5%)	69 (90.7%)*	71 (93.4%)*	70 (92.1%)*	71 (93.4%)*
standing with assistance [N (%)]	28 (49%)	66 (94%)	73 (96%)	75 (98.6%)	75 (98.7%)	75 (98.6%)	75 (98.6%)
walking with assistance [N (%)]	3 (5.2%)	28 (40%)*	49 (64.4%)*	70 (92.1%)*	73 (96.1%)	75 (98.6%)	75 (98.6%)
standing alone [N (%)]	1 (1.7%)	8 (11.4%) [§] *	18 (23.6%)	52 (68.4%) ^{#§}	66 (86.8%) ^{#*}	74 (97.3%)	75 (98.6%)
walking alone [N (%)]	0	4 (5.7%) ^{#§}	9 (11.8%)	41 (53.9%) ^{#§}	60 (78.9%) ^{#§*}	71 (93.4%)	75 (98.6%)

SD: standard deviation
 statistical significant association (p <0.05) between: *wasting, [§]stunting, [#]underweight, and developmental milestones

Table 4. Growth and developmental milestones in our cohort between 9 to 24 months of age.

Tabella 4. Crescita e raggiungimento delle *motor milestones* nella nostra coorte da 9 a 24 mesi di età.

months of age. Low birth weight was present in 21% of our cohort, which demonstrates that malnutrition is already present at birth and worsens over time, as reported in prior assessments of our paediatric cohorts.¹⁷

Our findings likely underestimate the degree of the problem in similar settings in Sub-Saharan Africa, as our patients received nutritional supplementation and were followed very closely in a study setting. Nevertheless, even in more optimal conditions the impact of food insecurity was still tangible in this cohort. One of the study limitations was that we were unable to assess earlier developmental milestones in many subjects and, for this reason, we focused our analysis on later periods which coincide with a time of higher food insecurity in an infant's life, after the introduction of solids, when breastfeeding is no longer a source of full sustenance. It is likely that delayed developmental milestones would have worsened over time, paralleling growth faltering, which is more prevalent in the second

semester of life, following the interruption of breastfeeding. Nevertheless, the ability to evaluate developmental milestones between 9 and 18 months of age allowed us to assess a critical window period of both growth and development.

In summary, in order for health care programs to address the negative impact of food insecurity, intrauterine retardation, and reduced exposure to breastfeeding, a holistic approach to management needs to be supported. Routine evaluation of gross motor milestones should be included in programs as a surrogate for nutritional assessment in order to optimize the care of malnourished HIV-exposed children.

Conflicts of interest: none declared

Acknowledgements

We acknowledge with gratitude the Community of Sant'Egidio, all the staff and the participating patients of the Blantyre DREAM centre for their contribution to this study.

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COMMUNICATIONS C4
Wednesday 14 October
h. 17.30
Brown Room 2

Reducing external drainage-related cerebrospinal fluid infections through implementation of a multidisciplinary protocol: experience in a paediatric hospital

Ridurre le infezioni correlate alle derivazioni liquorali esterne con l'applicazione di un protocollo condiviso: l'esperienza di in un ospedale pediatrico

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Abstract

Objective. To assess the frequency of external cerebrospinal fluid (CSF) drain-related CNS infections before and after implementation of a protocol for their prevention.

Design. Quasi-experimental study, with comparison of incidence before and after the implementation of the intervention.

Setting and participants. Bambino Gesù Children's Hospital in Rome, Italy. Children receiving an external cerebrospinal fluid drain from 1 January 2013 to 31 March 2015.

Main outcome measures. Drain-related infections.

Results. Fifty-two patients were included in the study. Before protocol implementation, cumulative incidence was 14 per 100 drains. Incidence rate was 8/1,000 catheter-days. After protocol implementation, cumulative incidence and incidence rate were 6.7 per 100 drains and 4.6 per 1,000 catheter-days ($p=0.61$ and $p=0.2$ versus the pre-intervention period, respectively). Infected patients were significantly younger (median age: 16.5 days vs 13.4 months; $p=0.026$), had a significantly higher number of procedures (5 vs 1 procedure per patient; $p<0.0001$) and were most frequently affected by post-haemorrhagic hydrocephalus of premature newborns (50% vs 16.7%; $p=0.039$), compared to non-infected patients.

Conclusions. After protocol implementation, we observed a reduction of incidence of CSF drain-related infections, though the short post-intervention period limited the power of the study to detect a significant difference. Patients <1 year of age, with multiple interventions and post-haemorrhagic hydrocephalus had higher risk of CSF drain-related infections.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 113-118)

Key words: external cerebrospinal fluid (CSF) drains, protocol, prevention

Riassunto

Obiettivo. Valutare la frequenza delle infezioni del sistema nervoso centrale correlate ai drenaggi liquorali esterni (DLE) prima e dopo l'applicazione di un protocollo per la loro prevenzione.

Disegno. Studio quasi-sperimentale, con comparazione dell'incidenza pre-post attuazione dell'intervento.

Setting e partecipanti. Bambini che hanno ricevuto un drenaggio liquorale esterno dal 1-1-2013 al 31-3-2015, nell'Ospedale Pediatrico Bambino Gesù, Roma.

Principali misure di outcome. Infezioni correlate a drenaggi liquorali.

Risultati. Sono stati valutati 52 pazienti, con 136 drenaggi totali. Nel periodo pre-intervento, l'incidenza cumulativa è stata 14 infezioni/100 drenaggi e il tasso di incidenza 8/1.000 giornate di derivazione. Nel periodo post-intervento, l'incidenza cumulativa e il tasso di incidenza sono state rispettivamente 6,7/100 e 4,6/1.000 ($p=0,61$ e $p=0,2$ rispetto al periodo pre-intervento). I pazienti con infezione erano più piccoli (età mediana: 16,5 giorni contro 13,4 mesi; $p=0,026$), con un maggior numero di procedure (5 contro 1; $p<0,0001$) e più frequentemente affetti da idrocefalo postemorragico del prematuro (50% rispetto al 16,7%; $p=0,0039$), rispetto ai pazienti non infetti.

Conclusioni. Dopo l'intervento abbiamo osservato una riduzione di incidenza di infezioni DLE correlate, sebbene il breve pe-

riodo post-intervento limiti la potenza dello studio. I pazienti di età <1 anno, con interventi multipli e idrocefalo post-emorragico hanno avuto un più alto rischio di infezioni correlate a drenaggi liquorali.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 113-118)

Parole chiave: drenaggi liquorali esterni, protocollo, prevenzione

INTRODUCTION

External cerebrospinal fluid (CSF) drains, including ventricular (EVD) and lumbar drains (ELD), are temporary devices used to perform CSF diversion in acute conditions, such as primary and secondary acute hydrocephalus, or for intracranial pressure monitoring.¹ Sometimes, clinical conditions cause patient dependence on CSF diversion and approximately one quarter requires conversion into permanent and implanted shunts.^{2,3} Conversely, temporary drains may be inserted because of shunt complications, especially to prevent recurrent shunt infections.⁴ Use of external CSF drains is associated with risk of central nervous system (CNS) infections, such as ventriculitis and meningitis, which cause increased patient morbidity and mortality, length of hospital stay and costs.⁵⁻⁷ These complications can also be associated with external subdural drains (ESD) employed to empty the subdural space of CSF pools, such as subdural hygroma or CSF layer.⁸

Predisposing factors for CSF drain-related ventriculitis or meningitis include intraventricular and subarachnoid haemorrhage, craniotomy, systemic infection, and underlying disease.⁹ Other risk factors are catheter duration, multiple catheter insertions and exchanges, surgical technique of insertion, and multiple infections in other anatomical sites.^{10,11} Coagulase-negative *Staphylococcus* and *Staphylococcus aureus* are the most common associated pathogens.^{9,12} In adults, reported incidence of CSF drain-related infections ranges from 2% up to 25% of cases per drain placed, with mortality rates as high as 22% for ventriculitis caused by Gram-negative bacteria. Incidence rates range from 7.2 to 32 per 1,000 catheter-days.¹²⁻¹⁴ In children, available data show that CNS infections occur in 9.4% of EVD insertions; reported incidence rate is 8.6 infections/1,000 catheter-days and mortality rate is 22.8%.¹⁵⁻¹⁷ Results reported from various studies are difficult to compare, because of differences in patient age, underlying diseases, case definition, and case ascertainment.^{18,19} In order to prevent external CSF drain-related infections, several healthcare organizations have adopted standardized protocols and bundle approaches.^{5,6,10,20} Despite possible severe consequences, there is little ongoing surveillance of external CSF drain-related CNS infections. In children, there is scarce evidence about the impact of preventive strategies.^{16,21}

In this article, we present the results of surveillance targeting external CSF drain-related CNS infections in a tertiary care children's hospital in Italy, and we describe the impact of a multidisciplinary protocol for their prevention.

METHODS

Setting

The Bambino Gesù Children's Hospital (Ospedale Pediatrico

Bambino Gesù, OPBG) is a 607-bed tertiary care research hospital in Rome, Italy. The hospital's acute inpatient admissions were 26,164 in 2013 and 26,716 in 2014. Hospital patient population includes children at high risk of acquiring health-care-associated infections (HAIs), such as pre-term newborns and immunocompromised patients. In-hospital actions for prevention and control of HAIs have been implemented over time.²² A multidisciplinary committee for infection control annually prioritizes interventions and monitors results of actions taken. In 2014, prevention of surgical site infections was identified as a priority for improvement.

Study design, case definitions, and data collection

This was a quasi-experimental study, with a pre- and post-intervention analysis. Patients with EVD, ELD, externalized catheter shunt, or ESD were identified through retrospective analysis of electronic records of surgical procedures, by extracting all procedures coded as ICD9-CM 01.26, 01.28, 01.31, 02.2, 02.31, 02.32, 02.39, 02.41, 02.42, 03.71-03.79, from January 2013 to March 2015.

Patients' clinical records were then reviewed to verify consistency of coding with description of the procedure and to collect the following information: age, gestational age for pre-term newborns, sex, first external drainage indication, catheter duration in days and removal causes, clinical symptoms compatible with diagnosis of ventriculitis or meningitis, CSF characteristics, and results of microbiological investigations.

Ventriculitis and meningitis were defined by the detection of a microorganism in the CSF, associated with compatible clinical signs (including fever >38°C, headache, stiff neck, meningeal signs, cranial nerve signs, and irritability, hypothermia <36.0°C, apnoea, bradycardia in patients ≤1 year) and at least one pathologic CSF finding (i.e., elevated cell count and/or decreased glucose level).

Infections were considered drain-related if at the time of microbiological confirmation the drain had been in place for at least 48 hours or had been removed within 48 hours prior to the diagnosis. CSF infections already present at drainage insertion were excluded from count of drain-related infections.

Preventive strategies

In 2014, a multidisciplinary group (neurosurgeons, neonatologists, clinical epidemiologist, microbiologists, pharmacist, infection control professionals, infectious disease physician) revised the recommendations for prevention of external CSF drain-related CNS infections and defined a specific protocol.^{6,9,23} The protocol provides recommendations on patient preoperative preparation, surgical antibiotic prophylaxis, surgical technique, catheter type to be used, and postoperative

Steps	Actions
preoperative patient preparation	<ul style="list-style-type: none"> ■ body showering or sponging with antiseptic soap (chlorhexidine or povidone iodine) the evening before and the morning of surgery ■ hair washing with cleaning soap or with a waterless shampoo cap ■ trichotomy with clipper the day of surgery, within 2 hours before surgery ■ head washing after trichotomy
antibiotic prophylaxis	<ul style="list-style-type: none"> ■ single dose of antibiotic (cefazolin or vancomycin in MRSA carrier) within 60 minutes before incision ■ intraoperative antibiotic dose repeated if the operation duration exceeds antibiotic hemi-life ■ antibiotic prophylaxis continued for 24 hours after surgery
EVD insertion	<ul style="list-style-type: none"> ■ physicians scrub up and wear cap, mask, sterile gown, and sterile gloves ■ all members of the staff wash their hands and wear cap, mask, and sterile gowns ■ head washing with antiseptic soap (chlorhexidine or povidone iodine) ■ full sterile draping of patient's head and body ■ skin preparation with gauzes soaked in 2% chlorhexidine and followed by gauzes soaked with povidone iodine ■ unsterile staff keeps at least 50 cm away from the surgical field. ■ rifampin/clindamycin-coated ventricular catheter in post-hemorrhagic hydrocephalus and in the absence of infection ■ non impregnated catheter in case of infection ■ catheter is tunneled approximately 3 cm (patients weighing less than 1,500 g) to 5 cm from insertion site ■ collection of two CSF samples of 1 ml for chemical and microbiological analysis
dressing	<ul style="list-style-type: none"> ■ catheter is secured using surgical staples ■ two patches are applied at 1 and 3 cm over catheter exit site and a three-way valve at the distal end of the catheter ■ a transparent patch is applied on the surgical scar ■ dressing should be kept intact for 72 hours, unless it is wet, dirty, or saturated with either blood or secretions
EVD manipulation	<ul style="list-style-type: none"> ■ nurse checks dressing daily ■ all healthcare professionals involved in manipulation practice hand hygiene and wear cap, mask, sterile gown, and sterile gloves ■ every 72 hours, neurosurgeon checks dressing, replaces necessary parts, and collects a CSF sample of 1 ml for chemical analysis ■ before and after collection, access port and surrounding tubing are cleaned with 0.5% chlorhexidine in alcohol solution ■ height of the collection system is regulated by the neurosurgeon with the pressure level of "0" cm H₂O corresponding to the external acoustic meatus of the patient
EVD failure	<ul style="list-style-type: none"> ■ in case of diastasis of the surgical incision, CSF leak, or accidental removal, neurosurgeon puts reinforcement stitches
EVD infection	<ul style="list-style-type: none"> ■ in the presence of at least one sign or symptom of ventriculitis/meningitis and in the absence of other known causes, chemical and microbiological analysis, CSF Real-Time PCR, and blood cultures are performed ■ in the absence of signs and symptoms but with chemical or physical alterations of CSF found during routine testing, it is recommended to repeat CSF analysis with calculation of cell index, CSF culture, and Real-Time PCR

Table 1. Protocol for the prevention of EVD-related infections. / **Tabella 1.** Protocollo per la prevenzione delle infezioni DVE-correlate.

management, including infection and failure management (table 1). It was published on the Hospital intranet in September 2014.

Data analysis

We describe characteristics of CSF drain-related CNS infections by type and time period, before (January 2013-September 2014) and after (October 2014-March 2015) the implementation of preventive strategies.

Continue variables were described as median and range interval, and compared using the Mann-Whitney *U* Test. Categorical variables were described as proportions and compared using the Chi-square test or the Fisher exact test, as appropriate. Cumulative incidence of CSF drain-related infections was estimated as number of cases per 100 CSF drains (cumulative incidence) and as number of cases per 1,000 catheter-days (incidence rate). Estimates of cumulative incidence and incidence rate were compared using the Chi-square test or the Fisher exact test, as appropriate. Statistical analysis was performed with SPSS version 22.0 (SPSS Software, IBM, NY).

RESULTS

Over the study period, 52 patients (31 males and 21 females)

had at least one procedure related to CSF drain placement. Patients' characteristics and type of inserted drain are reported in table 2. Five patients underwent placement of different types of drains. The vast majority of patients (46/52; 89%) had an EVD, mostly due to post-haemorrhagic hydrocephalus, or meningitis. Patients with EVD were younger than patients who had other types of drains (median age at first drain placement: 5.6 months versus 4.6 years for ELD and 10 months for ESD; $p=0.004$). The total number of drains was 136, with 2 drains per patient as median value. Median length of stay of catheter per patient was 28 days.

Patients' characteristics were similar in the two study periods, i.e., prior and after the implementation of the protocol with recommended interventions. No statistically significant differences were noted regarding sex, median age at first drain placement, or median duration of catheter either in the entire patient sample or in the EVD group.

Table 3 shows cumulative incidence and incidence rate of CSF drain-related infections by type of drain and study period. Before protocol implementation, there were 9 patients who had at least one CNS infection related to external CSF drains (19.1%) and 17 total infections, all in the EVD group. Cumulative incidence was 14 per 100 drains overall, and 15 per 100 EVDs.

	EVD	ELD	ESD	Total
number of patients	46	3	8	52 ^a
number of males (%)	26 (56.5%)	3 (100%)	2 (25%)	31 (59.6%)
median age at first drain placement (range)	5.6 months (24 gestational week- 13.3 years)	4.6 years (4.4-11.4 years)	10 months (4.9 months-7 years)	6.6 months (24 gestational week- 13.3 years)
indication for first drain placement (%)				
post-haemorrhagic hydrocephalus of premature newborns	12 (26.1%)	0	0	12 (23.1%)
meningitis	9 (19.6%)	0	1 (12.5%)	10 (19.2%)
shunt infection	6 (13%)	0	0	6 (11.5%)
mechanical shunt complications	4 (8.7%)	0	0	4 (7.7%)
tumour	6 (13%)	3	1(12.5%)	10 (19.2%)
primary hydrocephalus	3 (6.5%)	0	0	3 (5.8%)
secondary hydrocephalus (other causes)	2 (4.3%)	0	0	2 (3.9%)
intraventricular haemorrhage	3 (6.5%)	0	0	3 (5.8%)
subdural hygroma or CSF layer	0	0	1 (12.5%)	1 (1.9%)
injury	1(2.2%)	0	0	1 (1.9%)
total number of drains	121	3	12	136
median number of drains per patient (range)	2 (1-13)	1 (1-2)	1 (1-1)	2 (1-13)
median duration of catheters in days per intervention (range)	17 (1-61)	7 (3-76)	8 (3-29)	16 (1-76)
median duration of catheters in days per patient (range)	28 (1-251)	5 (3-76)	8 (3-67)	28 (1-251)

^a five patients inserted more than one type of drain / ^a cinque pazienti hanno inserito più di un drenaggio

Table 2. Characteristics of patients with external CSF drain, by type of drain.

Tabella 2. Caratteristiche dei pazienti con drenaggi liquorali esterni per tipo di drenaggio.

	EVD		ELD		ESD		Total	
	pre	post	pre	post	pre	post	pre	post
patients	42	6	2	1	6	2	47 ^a	7 ^a
drains	113	8	2	1	6	6	121	15
catheter-days	2012	115	79	5	45	96	2136	216
patients with at least one infection (%)	9 (21.4%)	0	0	0	0	1 (50%)	9 (19.1%)	1 (14.3%)
infections	17	0	0	0	0	1	17	1
infections/100 patients	40.5	0	0	0	0	50	36.2	14.3
infections/100 drains	15	0	0	0	0	16.7	14	6.7
infections/1,000 catheter-days	8.4	0	0	0	0	10.4	8	4.6

^a five patients inserted more than one type of drain; two patients were involved in both study periods / ^a cinque pazienti hanno inserito più di un tipo di drenaggio; due pazienti sono stati coinvolti in entrambi i periodi di studio

Table 3. Cumulative incidence and incidence rate of CSF drain-related infections by type of drain and study period.

Tabella 3. Incidenza cumulativa e tasso d'incidenza per le infezioni correlate alle derivazioni liquorali, per tipo e periodo di studio.

Incidence rates in all drains and in EVDs were 8 and 8.4 per 1,000 catheter-days, respectively. After protocol implementation, one patient had an infection (14.3%); the patient was in the ESD group. Cumulative incidence and incidence rate were 6.7 per 100 drains and 4.6 per 1,000 catheter-days ($p=0.61$ and $p=0.2$ vs the pre-intervention period, respectively).

As shown in **table 4**, patients who developed at least one infection were significantly younger compared to non-infected patients (16.5 days vs 13.4 months; $p=0.026$). Median number of procedures and median duration of catheters per patient were significantly higher in infected patients than in non-infected patients (5 vs 1 procedure/patient $p<0.0001$ and 85.5 vs 23.5 catheter-days/patient, $p<0.0001$ respectively). Indeed, the 10 infected patients underwent 44.1% of all interventions. Indication for first drain placement also significantly differed between infected and non-infected patients, as post-haemorrhagic hydrocephalus of premature newborns was the

indication in 50% of patients with infections vs 16.7% of patients with no infections ($p=0.039$).

CSF infections occurred after a median duration of 11 catheter-days. The majority of infections were sustained by Gram-positive bacteria (12/18; 72.2%), with Coagulase-negative staphylococci detected in 9 cases (50%), and *Enterococcus* species in 3 (16.7%). One positive CSF culture was observed for each of the following organisms: methicillin-resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Candida albicans*, *Escherichia coli*, and *Serratia marcescens*.

CONCLUSIONS

In our experience, the implementation of a multidisciplinary protocol for prevention of CNS infections in children with CSF drains was followed by a reduction of approximately 25% of infected patients and of 42% of the incidence rate per 1,000 catheter-days. Compared to the pre-intervention period,

	Patients with infections	Patients with no infections	Total
number of patients	10	42	52
number of males (%)	8 (80%)	23 (54.8%)	31 (59.6%)
median age at first drain placement (range)	16.5 days (24 gestational week-6.5 years)	13.4 months (31 gestational week-13.3 years)	7.5 months (24 gestational week-13.3 years)
Type of drain			
EVD	57 (95%)	64 (84.2%)	121 (89%)
ELD	0	3 (4%)	3 (2.2%)
ESD	3 (5%)	9 (11.8%)	12 (8.8%)
Indication for first drain placement (%)			
post-haemorrhagic hydrocephalus of premature newborns	5 (50%)	7 (16.7%)	12 (23.1%)
meningitis	1 (10%)	9 (21.4%)	10 (19.2%)
shunt infection	2 (20%)	4 (9.5%)	6 (11.5%)
mechanical shunt complications	1 (10%)	3 (7.1%)	4 (7.7%)
tumour	1 (10%)	9 (21.4%)	10 (19.2%)
primary hydrocephalus	0	3 (7.1%)	3 (5.8%)
secondary hydrocephalus (other causes)	0	2 (4.8%)	2 (3.8%)
intraventricular haemorrhage	0	3 (7.1%)	3 (5.8%)
subdural hygroma or CSF layer	0	1 (2.4%)	1 (1.9%)
injury	0	1 (2.4%)	1 (1.9%)
Indication for drain removal (%)			
death	0	3 (3.9%)	3 (2.2%)
persistent CSF infection	18 (30%)	8 (10.5%)	26 (19.1%)
drain failure	6 (10%)	6 (7.9%)	12 (8.8%)
no further clinical indication	7 (11.7%)	23 (30.3%)	30 (22.1%)
internalization operation	19 (31.7%)	33 (43.4%)	52 (38.2%)
replaced during other procedure	6 (10%)	2 (2.6%)	8 (5.9%)
accidental removal	4 (6.6%)	1 (1.3%)	5 (3.7%)
total number of drains	60	76	136
median number of drains per patient (range)	5 (2-13)	1 (1-6)	2 (1-13)
median duration of catheter in days per patient (range)	85.5 (17-251)	23.5 (1-127)	28.5 (1-251)
median duration of catheter in days per insertion (range)	17 (2-61)	14.8 (1-76)	16 (1-76)

Table 4. Characteristics of patients with external CSF drain, by CNS infection presence.

Tabella 4. Caratteristiche dei pazienti con drenaggi liquorali esterni, per presenza di infezione del SNC.

when we observed 17 CNS infections, only one infection occurred in the post-intervention period.

Our study focused on a paediatric population with a younger age and with different clinical indications than reported by other studies:^{15,16} we observed mostly infants in the first year of life who had EVD for hydrocephalus, while other case series involve older children with tumours and trauma as prevalent clinical indications. In addition, the median catheter length of stay in our study (16 days) was more than twice that found in others (7 days).^{3,15,16} These differences in patient population make comparison among studies difficult. In the pre-intervention period, our proportion of infected patients was higher than reported by other authors (19.1% *vs* 6%) however, due to longer duration of catheter use, EVD-related infection incidence rate per 1,000 catheter-days was similar (8.4/1,000 *vs* 8.6/1,000).

First EVD infections occurred at 11 catheter-days of median duration, confirming increased risk of EVD infection related to placement length beyond 10 days, reported by Kim et al., although a paediatric study and review recorded an increased risk during the first 10 catheter-days.^{16,19} This apparent discrepancy may be due to the paucity of studies describing patients with drain duration longer than 10 days.¹⁹ In our experience, the number of procedures per patient were

significantly higher in patients infected. These results are compatible with those reported in other studies, where drainage contamination during placement is a recognized risk factor for infection.^{17,24}

Our study also confirms that Coagulase-negative staphylococci are most frequently responsible for EVD-related infections.^{15,21} Moreover, it seems to confirm the increased infection risk in cases of intraventricular haemorrhage, especially in post-haemorrhagic hydrocephalus of premature newborns, which represents the most frequent condition in our infected patients and may be due to their major clinical susceptibility.²⁵

Our study is limited by the shortness of the post-intervention period, with a low number of patients who underwent external CSF drains, and by lack of other information that could influence infection risk, such as use of antibiotic-impregnated or standard catheters, surgical antibiotic prophylaxis, and antibiotic use in the postoperative period. An extended period of observation, along with collection of these data, could allow to better evaluate the impact of protocol implementation on prevention of external CSF drain-related infections.

Conflicts of interest: none declared

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COMMUNICATIONS C9
Thursday 15 October
h. 8.30
Brown Room 1

Assessment of the effectiveness of the universal varicella vaccination program in Toscana (Italy), in the period 2010-2013

Valutazione dell'efficacia del programma di vaccinazione universale antivaricella in Toscana (Italia), nel periodo 2010-2013

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Abstract

Objective. To assess the effectiveness of the varicella vaccination program in Toscana after one dose of vaccine, in the birth cohorts 2008-2011.

Design. Varicella vaccine effectiveness (VE) was calculated using the "screening method", based on vaccine coverage (VC) at 24 months and proportion of vaccinated subjects among varicella notified cases (PVC), verified through the Local Health Units' (LHUs) immunization registries. Breakthrough varicella (BV) was defined as a case of varicella occurring in a child vaccinated ≥ 42 days before the date of disease onset.

Setting and participants. The study was conducted in the 12 Tuscan LHUs and included all varicella cases notified in 2010-2013 in children of the birth cohorts 2008-2011.

Main outcome measures. BV cases; VE after one dose of varicella vaccine; time interval between varicella vaccination and symptom onset.

Results. VC was 79.8%, VE reached 90.8% (95%CI 89.5%-92.0%) and the proportion of BV among notified cases was 26.6%. The median time interval between vaccination and symptom onset was 25 months.

Conclusions. The very low rate of BV cases among vaccinated children confirms the high effectiveness even of a single dose of varicella vaccine and does not support a change of the current immunization schedule.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 119-123)

Key words: varicella, vaccine effectiveness, screening method, breakthrough varicella, Toscana

Riassunto

Obiettivo. Valutare l'efficacia del programma di vaccinazione antivaricella in Toscana, dopo una singola dose di vaccino, per le coorti di nascita 2008-2011.

Disegno. Per calcolare l'efficacia vaccinale (EV) è stato applicato il "metodo di screening" utilizzando i dati di copertura vaccinale a 24 mesi e la proporzione dei casi vaccinati (*varicella breakthrough*, VB), verificati attraverso le anagrafi vaccinali delle ASL. Sono stati classificati come VB i casi con sintomi insorti dopo almeno 42 giorni dalla prima dose di vaccino.

Setting e partecipanti. Lo studio include i casi di varicella notificati nel periodo 2010-2013, per le coorti di nascita 2008-2011, nelle 12 ASL della Toscana.

Principali misure di outcome. Casi VB; EV dopo singola dose di vaccino; intervallo di tempo tra vaccinazione e inizio sintomi.

Risultati. La CV è stata del 79,8%, l'EV è risultata pari al 90,8% (IC95% 89,5%-92,0%) e la percentuale dei casi VB sul totale delle notifiche è stata del 26,6%. L'intervallo mediano tra la vaccinazione e la comparsa dei sintomi è stato di 25 mesi.

Conclusioni. La bassissima percentuale di casi VB sul totale dei vaccinati conferma l'elevata efficacia sul campo anche di una sola dose di vaccino anti-varicella e non depone per una modifica della attuale schedula vaccinale.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 119-123)

Parole chiave: varicella, efficacia vaccinale, metodo di screening, fallimenti vaccinali, Toscana.

INTRODUCTION

Varicella is an acute contagious viral disease, caused by the varicella zoster virus (VZV), which is spread by air droplets or by contact with vesicle liquid. Varicella has a worldwide distribution, affects mostly children and, despite being generally a mild disease, may be fatal, especially in neonates and immunocompromised people.¹

A live attenuated varicella vaccine has been available since 1974, and in 1996 universal one-dose routine vaccination was introduced in United States.^{2,3} This led to a drastic reduction of varicella incidence. Nevertheless, the observation of “breakthrough” varicella (BV) cases (cases of varicella occurring 42 days or more after vaccination following exposure to wild-type virus), even in communities with a high vaccination coverage, with a relative shift of the disease onset towards older ages, led the Advisory Committee on Immunization Practices (ACIP) to recommend a second dose of the vaccine for children aged 4-6 years in 2007.⁴

In Europe, six countries endorsed Universal Varicella Vaccination (UVV) for children at the national level (Cyprus, Germany, Greece, Latvia, Luxemburg and Austria) and two countries at the regional level (Spain, Italy).⁵ A two-dose schedule, with an interval of 1 to 6 years, is used for administration of Measles-Mumps-Rubella (MMR) vaccines in most countries in Europe.⁶

In Italy, UVV was introduced in 2003 and has been limited to those regions able to guarantee high level (over 80%) of vaccination coverage (VC), in order to avoid a possible shift of infection towards adulthood.⁷

A two-dose regimen for varicella vaccination is recommended and has been now implemented for at least 2 years in eight Italian regions (Puglia, Basilicata, Calabria, Friuli-Venezia Giulia, Sardegna, Sicilia, Veneto, and Toscana) with different schedules. A general reduction of incidence and hospitalization rates for varicella was observed between 2003-2012. Moreover, immunization coverage with first dose at 24 months of age was high in the eight regions (84%–95%) in 2012.⁷ Since 2015, other regions have included UVV in their immunization program. Toscana had 3,750,511 inhabitants in 2014, of whom 191,356 (5,1%) were under 5 years.⁸ The Tuscan health system is organized in 12 LHUs (Local Health Units). Each LHU ensures the essential levels of assistance, including routine vaccination programs; all vaccine doses administered are registered in a computerized vaccination registry.

Tuscany was one of the first Italian regions to introduce a program of universal vaccination against varicella with a combined measles, mumps, rubella, and varicella (MMRV) vaccine, in July 2008. The schedule calls for the first dose of vaccine at the age of 13-15 months and a second dose at the age of 5-6 years.⁹ The aim of this study is to assess the effectiveness of the varicella vaccination program in Toscana in preventing varicella cases, in subjects belonging to the birth cohorts 2008–2011.

MATERIALS AND METHODS

Varicella is subject to mandatory notification in Italy. All notifications are routinely collected at the regional level and repor-

ted in the Italian Computerized Surveillance System for Communicable Diseases (SIMI). In SIMI, patient information such as date of birth, gender, date of symptom onset, date of notification, place of residence, and vaccination status are available.¹⁰ In order to assess whether surveillance data collected in Toscana permitted a rapid “screening” analysis, a pilot study was performed in 2014 in two Tuscan LHU (Firenze and Prato),¹¹ and subsequently extended to all LHUs during 2015.

Immunization coverage at 24 months of age for varicella-containing vaccines in the years 2010-2013 were obtained from official regional data. Notification data were retrieved from SIMI and the vaccination status was double checked into each LHU immunization registry.

The current study was conducted in the 12 Tuscan LHUs and included all varicella cases notified between 1 January 2010 and 31 December 2013 in children born between 1 January 2008 and 31 December 2011. In the current analysis, only birth cohorts for whom vaccination coverage data at 24 months were available (2008-2011) were included.

Varicella vaccine effectiveness for at least one dose of vaccine was calculated using the screening method proposed by Farrington.¹² Such method is based on the known relationship between the proportion of vaccinated population (PPV=vaccination coverage), vaccine effectiveness (VE) and proportion of vaccinated subjects among disease cases (PCV); identifying two of those parameters it is possible to calculate the third. Therefore, reliable values of VC and PCV are essential in order to obtain a good estimate of vaccine effectiveness.¹³

VE is then given by the following formula:

$$VE = 1 - [(PCV / 1-PCV) (1-PPV / PPV)]$$

Moreover, 95% confidence intervals were calculated by birth cohort, expressing VE with the following equation:¹⁴

$$VE = 1 - (\text{incidence rate}_{\text{vaccinated}} / \text{incidence rate}_{\text{unvaccinated}})$$

The ratio between the incidence rates among vaccinated and unvaccinated individuals corresponds to a relative risk.

Data collection was performed from February 2015 to May 2015 and consisted of three phases:

- extraction of all varicella notifications collected in SIMI between 2010 and 2013;
- selection of cases that occurred in children born in the birth cohorts 2008-2011;
- assessment of their vaccination status using the LHU immunization registries.

Exclusion criteria were: place of residence outside Toscana, wrong date of birth, data missing in the immunization registry. The case definition for breakthrough varicella (BV) adopted in this study was a case of varicella occurring in a child vaccinated ≥ 42 days before the date of disease onset.

The time interval between date of vaccination and date of symptom onset was calculated for all BV cases and expressed in months of 30 days. The median of the time interval, the 25th, and the 75th percentiles were also calculated.

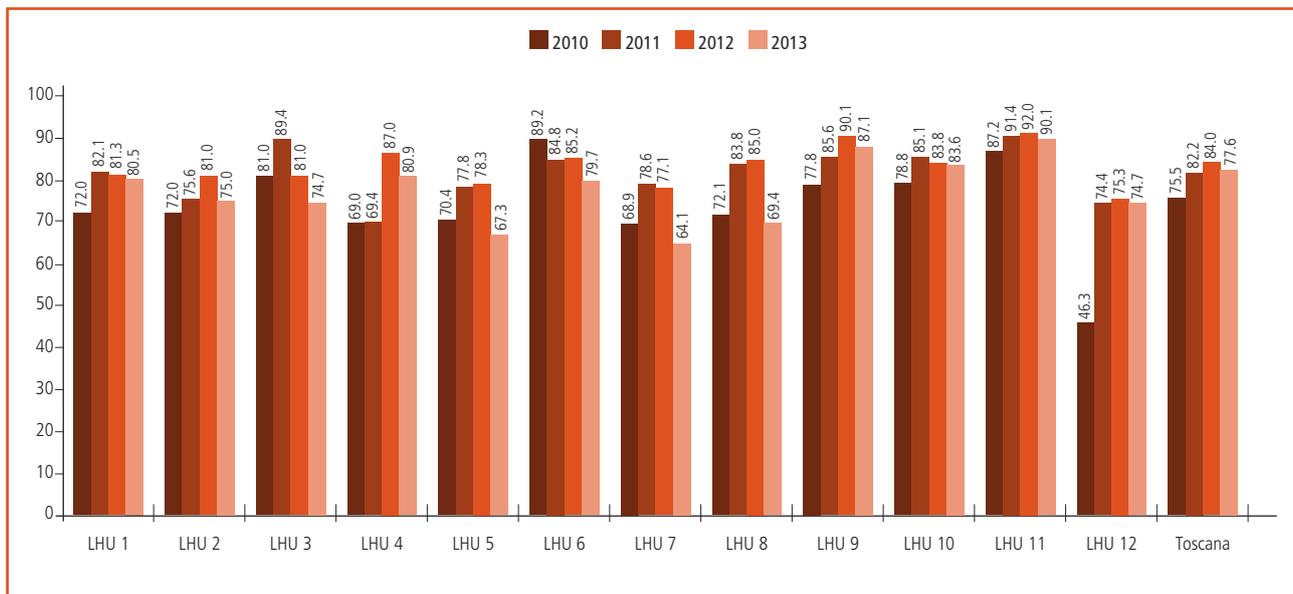


Figure 1. Varicella vaccination coverage (%) at 24 months of age in Toscana and in the 12 LHUs, in the period 2010-2013.

Figura 1. Copertura vaccinale (%) a 24 mesi in Toscana e nelle 12 ASL, nel periodo 2010-2013.

RESULTS

In Toscana, immunization coverage at 24 months of age for varicella vaccination in the years 2010-2012 (birth cohorts 2008-2010) rose from 75.4% to 84%, while in the 2011 birth cohort, recorded in 2013, it decreased to 77.6%.

Vaccination coverage data show a wide variability among all LHUs, with a range from 46.3% (LHU 12) to 89.2% (LHU 6) in the 2008 birth cohort, and from 64.1% (LHU 7) to 90.1% (LHU 11) in the 2011 birth cohort. In 2013, a lower level of VC was observed in all LHUs compared to 2012 (figure 1).

The proportion of BV among notified cases showed a wide variability in the 12 LHUs. In LHU 2, no BV case was registered, while in two LHUs (LHU 1 and LHU 6) the percentage reached 40% (table 1). Overall, the percentage of vaccinated subjects experiencing BV in the birth cohorts 2008-2011 was only 0.3% at the regional level (table 1).

Between 2010 and 2013, 103,738 out of 130,012 children born between 2008 and 2011 and resident in Toscana had received at least one dose of varicella vaccine (average VC of 79.8%). In the same period 1,080 cases of varicella were diagnosed in chil-

dren of the same birth cohorts, 287 (26.6%) of these cases had previously been vaccinated (varicella breakthrough cases). Therefore, effectiveness after one dose of varicella vaccine, calculated with the screening method, was 90.8% (95%CI 89.5-92.0) with a range from 77.8% to 98.6% (table 2).

In breakthrough varicella cases, analyzing the time interval between vaccination and symptom onset, a median value of 25 months was calculated for the whole population. In particular, 64 BV cases occurred 15 months after vaccination (25th percentile) and 246 cases after 35 months (75th percentile).

DISCUSSION

The present study was performed to assess the effectiveness of the varicella vaccination program in Toscana using the screening method, as already done in Navarre (Spain) and Puglia (Italy). Both studies reported a high VE value of 96.8% and 98.8% respectively.^{15,16}

The effectiveness of a single dose of vaccine against the disease of any severity reported by varicella surveillance in the United States and international case-control studies outside of outbreak

	VC (%)	Vaccinated	Notified cases	BV cases	PCV (%)	BV/vaccinated (%)
LHU 1	78.7	4,880	15	6	40.0	0.1
LHU 2	75.8	5,966	13	0	0.0	0.0
LHU 3	83.6	8,667	52	12	23.1	0.1
LHU 4	76.2	7,481	40	4	10.0	0.1
LHU 5	73.5	9,211	226	58	25.7	0.6
LHU 6	84.8	9,548	120	48	40.0	0.5
LHU 7	72.3	6,892	89	27	30.3	0.4
LHU 8	77.6	9,277	98	25	25.5	0.3
LHU 9	85.0	6,036	94	28	29.8	0.5
LHU 10	82.8	23,832	191	51	26.7	0.2
LHU 11	90.2	8,409	114	26	22.8	0.3
LHU 12	67.2	3,539	28	2	7.1	0.1

Table 1. Vaccination coverage at 24 months of age for varicella in the birth cohorts 2008-2011, breakthrough varicella (BV) cases and proportion of cases notified in vaccinated subjects (PCV), rate of BV cases among all vaccinated subjects, by LHU in Toscana (Italy), 2010-2013.

Tabella 1. Copertura vaccinale per varicella nelle coorti di nascita 2008-2011, casi di "varicella breakthrough" (BV) e proporzione di casi notificati in vaccinati (PCV), proporzione di casi BV sul totale dei vaccinati (BV/vaccinated), per ASL in Toscana (Italia), 2010-2013.

Birth year	Population			Varicella cases			Vaccine effectiveness (%) (95%CI)	
	N	vaccinated		N	vaccinated			
		n	%		n	%		
2008	33,541	25,310	75.5	459	186	40.5	77.8	(73.3 - 81.6)
2009	32,797	26,964	82.2	292	63	21.6	94.0	(92.1 - 95.5)
2010	32,464	27,259	84.0	218	33	15.1	96.6	(95.1 - 97.6)
2011	31,210	24,205	77.6	111	5	4.5	98.6	(96.7 - 99.4)
2008-2011	130,012	103,738	79.8	1,080	287	26.6	90.8	(89.5 - 92.0)

Table 2. Estimated vaccine effectiveness (%) of varicella vaccination program by birth cohort (2008-2011), in Toscana (Italy), 2010-2013.

Tabella 2. Stima dell'efficacia vaccinale (%) del programma di vaccinazione antivariella per coorte di nascita (2008-2011), in Toscana (Italia), 2010-2013.

periods falls in the range between 71% and 87%.¹⁷ Results of the current study show a cumulative VE of 90.8% in the birth cohorts targeted by the UVV, in line with other studies. Vaccine effectiveness registered a progressive increase from the 2008 to the 2011 birth cohort. This result could be explained by the herd immunity effect and the reduced probability to become infected with VZV, even in case of primary vaccination failure. As a matter of fact, our data do not allow us to establish whether possible changes in accuracy occurred in the assessment of the vaccination status among the birth cohorts, in order to justify the lower value of VE registered in the 2008 birth cohort compared to the other cohorts.

In Toscana, VC at 24 months was high since the first years of UVV introduction; in fact in the 2008 birth cohort, the oldest one considered in our study, VC was over 75%, a successful result for the regional health services. This result is explained by the use of the combined MMRV vaccine, taking advantage of high vaccination coverage for MMR in Toscana after the implementation of the Regional Plan for measles and congenital rubella elimination (i.e., 92% of VC in 2010).¹⁸

Although there is no doubt in adopting a two-dose schedule for varicella vaccination, as recommended by all international societies (AAP, ACIP, STIKO), on the basis of the US experience,^{4,19,20} a lively debate is still undergoing about the best distance between the two doses.

Our findings on the median time interval between vaccination and symptom onset (25 months) suggest that a shorter interval between the two doses of varicella vaccine might be preferable to reduce breakthrough varicella cases. According to our results, a second dose of varicella vaccine given at 3 years of age would have prevented about half of BV cases in our birth cohorts. Nevertheless, in the Tuscan context, considering the low proportion of BV cases among all vaccinated children of the analyzed cohorts and the high varicella VC obtained up to now, shortening the time interval between the two doses of vaccine would not be convenient and should be carefully considered to avoid any potential disruption to a well-established vaccination schedule.¹⁷ Moreover, further studies on primary and secondary vaccine failure should be wisely evaluated prior to suggesting a possible change in the regional recommended schedule. Finally, no consistent trend between breakthrough varicella rate and time since vaccination resulted from our findings.

A limitation of the present study may be related to the reliability

of the input data used to calculate VE. In particular, during our data collection, mismatches between the official regional data system (SIMI) and the vaccination registries of the LHUs were found.

Regarding SIMI, a certain proportion of notified cases in the regional database recorded uncertain or missing fields in reporting vaccination status and date of birth. In order to attain reliable surveillance data, a better implementation of the infectious disease information system would be advisable. For instance, an alert system to avoid empty and misreported fields should be provided.

Moreover, in view of further studies on the impact of the Tuscan vaccination program, it might be useful to adopt a unique regional vaccination registry to reduce the current heterogeneity of local vaccination registries. As a matter of fact, currently the 12 LHUs of Toscana have different computerized vaccination registries available.

Another critical issue was the unavailability of data related to VC at 24 months of age for the first birth cohort target of the UVV (children born in 2007) and consequently the need to exclude it from this study. This was due to the fact that in 2009 VC data for varicella were collected together with those for MMR. The regional data collection form for varicella VC data was implemented in 2010, and varicella vaccination coverage data have therefore been available since that year.

Moreover, at the time of data collection, the unavailability of notification data for the year 2014 and the consequent choice to limit the study period to 2013 could have resulted in an overestimate of VE, mostly for the youngest birth cohort of 2011. The strengths of the study consisted in the voluntary contribution of all 12 Tuscan LHUs to provide data required for the analysis. In particular, this allowed us to obtain results which are representative of the whole regional population. Furthermore, the collaboration between the University of Florence, the healthcare personnel of the 12 LHUs and the regional public health sector contributed to providing a good opportunity to perform supplementary studies on the same topic.

Further development of this study is needed to extend the observation period including 2014 data and to assess the effectiveness of the varicella vaccination program in Tuscany in preventing severe varicella cases, in particular those requiring hospitalization.

Conflicts of interest: none declared

Acknowledgements

The authors would like to thank Michela Baccini, Department of Statistics (University of Florence), for her assistance in the analysis of data, and Emanuela Balocchini, Lucia Pecori, and Sara Gallicchio, Sector of Prevention and Safety in Living and Working Environments, Food and Veterinary - General Direction Rights of citizenship and social cohesion (Toscana Region), for their support in the realization of the study.

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COMMUNICATIONS C1
Wednesday 14 October
h. 16.00
Brown Room 1

The first Italian validation of the most widespread health literacy assessment tool: the Newest Vital Sign

La prima validazione in Italia dello strumento per valutare la *health literacy* più usato al mondo: il Newest Vital Sign

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Abstract

Objective. This work represents the first attempt to validate, for the Italian population, the most widespread health literacy assessment tool: the Newest Vital Sign (NVS).

Design. The UK version of this tool was adapted for Italy using a translation/back-translation process. A web-based survey was then administered to a multidisciplinary panel of experts to assess its face validity. Finally, a preliminary study of construct validity was conducted, focusing on efficiency, comprehensibility, reliability, and sensitivity of the items of the test. For the evaluation of these dimensions we adopted Pearson's *r* correlation and calculated the average scores obtained for the subscales.

Results. Data analysis shows that the NVS-IT can be considered, under every aspect, an adequate tool for the assessment of individual health literacy grade level, given the optimal correlation among the experts' judgments and the average scores above the acceptability threshold.

Conclusion. Our study aims to encourage use of the NVS for the Italian population and, furthermore, introduce a scientific approach to health literacy, an issue that is gaining interest even in our country, though, to date, this has mainly resulted in the production of theoretical works.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 124-128)

Key words: validation, NVS, health literacy

Riassunto

Obiettivi. Scopo del lavoro è stato validare, per la popolazione italiana, lo strumento più utilizzato a livello mondiale per la misurazione dell'alfabetizzazione sanitaria: il Newest Vital Sign (NVS).

Disegno. Lo strumento oggetto dello studio (NVS-UK) è stato adattato alla popolazione italiana attraverso una procedura di "translation-back translation". Successivamente è stata valutata la validità di facciata attraverso una survey informatizzata somministrata a un panel bilanciato di esperti indipendenti. Inoltre, sono stati prodotti i primi dati per la validazione del costrutto di *health literacy* relativi alla sensibilità, accuratezza e appropriatezza degli *item* proposti. Per valutare le proprietà psicometriche di interesse è stato adottato il coefficiente di correlazione *r* di Pearson, e calcolate le medie dei punteggi ottenuti nelle sottoscale.

Risultati. Dall'analisi statistica dei risultati del sondaggio si evince che l'NVS in lingua italiana può essere considerato uno strumento valido per misurare il livello di alfabetizzazione sanitaria, ottenendo correlazioni tra i giudici adeguate e punteggi medi sempre superiori alla soglia di adeguatezza.

Conclusioni. Questo lavoro apre la strada all'utilizzo nella realtà italiana del test NVS e, più in generale, a un approccio di tipo scientifico in un ambito, quale quello della *health literacy*, che sta suscitando crescente interesse in Italia, seppur oggetto finora soprattutto di studi di tipo teorico.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 124-128)

Parole chiave: validazione, NVS, *health literacy*, alfabetizzazione sanitaria

INTRODUCTION

The concept of health literacy (HL) has been discussed in the literature since the 1980s.¹ The most recent, and probably ultimate, definition of health literacy was proposed by Sorensen in 2012: «Health literacy is linked to literacy and entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course».² Therefore, HL should be considered to promote patient empowerment and population health. The importance of this issue has been increasingly recognized in European health policies, such as «Health 2020».³ Hence, HL measurement is a critical component of the process of identifying topics and populations that are most in need of support.⁴ There are many tools available to measure HL: the measurements vary from basic screening items to more comprehensive assessments, based on how the concept of health literacy has been operationalized into a measurable construct – i.e., the measurable dimensions of HL, and specific skills and competencies.⁵ The Newest Vital Sign (NVS) is a survey tool based on information presented on a nutritional label, which measures literacy, comprehension, numeracy, application/function, and evaluation skills. It originally consists of six questions regarding the nutritional label; the questions have to be administered to the subject through an interview. Through an objective evaluation, which is expressed with a final score ranging from 0 to 6, this tool helps to classify the subject into one out of three categories:

- high likelihood of limited literacy (score: 0-1);
- possibility of limited literacy (score: 2-3);
- adequate literacy (score: 4-6).

It is quick to administer (taking approximately five minutes) and was developed in the USA in English and Spanish,⁶ and then validated and adapted in many other countries, for example, in the UK,⁷ the Netherlands,⁸ Turkey,⁹ and Japan.¹⁰ Moreover, the NVS has been included in the «European Health Literacy survey».¹¹ To the best of our knowledge, no Italian validation studies relating to the NVS are described in the literature nor in any other health literacy assessment tool, with the exception of the s-TOFHLA for Italian-speaking Swiss.¹² Therefore, the aim of this study is to undertake a process of testing with health practitioners and academics to adapt and validate the NVS for the Italian population.

METHODS

For the Italian validation, the NVS-UK was used. The validation steps followed a standard procedure: translation and back translation; drafting of the final Italian version, which was then shared by the research group; creation of the structured survey to be administered to the group of experts (judges) to test the face and preliminary construct validity of the draft; and administration and data analysis.¹³

NVS-UK

For our work, we used the UK version of the NVS, which had been adapted and validated by Rowlands⁷ from the USA ver-

sion.⁶ The NVS-UK was chosen because it contains a nutritional label that is consistent with European regulations. This tool comprises an instruction page to be read by the interviewers, which aims at standardizing the administration procedure, a typical nutritional label that can be found on a container of ice cream, seven questions related to the nutritional label, the sheet where the score of each question should be reported (1 for correct answers and 0 for wrong ones), as well as the total score.

The NVS-UK differs from the USA version for the presence of an additional question, which specifically investigates the comprehension of the item related to allergic reactions.

Forward-translation and back-translation of the NVS-UK

In order to strengthen the translation process, we selected two independent pairs of translators (i.e., two native English speakers and two native Italian speakers) who autonomously translated and later proofread the result of the back-translation process. Finally, a focus group out of the research groups was formed to assess and verify any discrepancies emerging from the process, while the output was the ultimate version of the NVS translated into Italian (NVS-IT, see [Supplementary file 1](#), available online).

Creation and administration of the structured validation survey

In order to test the face and construct validity of the NVS-IT, we developed a web-based survey that was distributed to a selected panel of experts who could complete the self-administered test by themselves (see [Supplementary file 2](#), available online).¹⁴ The protocol for the self-administered survey was divided into two steps: first, a standardized set of instructions was administered by the researchers of our group; second, the experts were asked to complete the survey directly on the web. Data was automatically stored online at the end of the collection so that participants could no longer access them. Filling in the questionnaire required around 25 minutes and none of the experts reported any trouble regarding the procedure.

At the beginning of the survey, the socio-demographic dimensions of interest (i.e., age, gender, education, and employment) were collected in order to evaluate possible interactions with the ratings of the experts. Then the questionnaire was structured into 10 sections, one for each original section of the tool, with five different dimensions for each section (i.e., aesthetic validity, efficiency, comprehensibility, reliability, and sensitivity)¹³ collected using Likert scale scores – ranging from 1 (not sufficient) to 5 (optimal), with a threshold of 3 which represented an adequate level.

Aesthetic validity was assessed to reflect how the items of each section are properly perceived by the subjects as adequate to measure their specific targets. Efficiency, reliability, and sensitivity were introduced to estimate the experts' judgements regarding these important features of the different sections of the NVS. Finally, the comprehensibility score was used to estimate the general population's degree of accessibility to the items of the instrument (i.e., disregarding their specific expertise or education). Data collection took place between September and October 2014.

Panel selection criteria

Given the multidisciplinary nature of the topic and the different settings suitable for the adoption of the tool (e.g., general practitioner clinics, hospitals, and schools), a balanced panel of experts was assembled by selecting clusters of healthcare professionals (both from academia and the National Health System) – on a voluntary basis – in order to investigate their different perceptions of the NVS-IT. A convenience sample was chosen, as suggested by other authors, in order to involve the most accessible participants with knowledge on health and health literacy.^{15,16} Each cluster was adequately numerous, and the panel was sufficiently balanced regarding genders, in spite of the prevalence of women among healthcare professionals. During data analysis we merged different types of expertise by assembling three different groups: physicians and biologists, considering their common background and activity related with organic aspects; psychologists and dieticians, who usually cover behavioural and counselling aspects; and nurses, given their peculiar role in direct care of patients.

Data analysis

The data analysis was conducted by using IBM® SPSS v.22©.17 The procedures required two stages. During the first stage, data pre-processing involved descriptive statistics dealing with the socio-demographic data and the score of each item for each section. Then the preconditions required by the subsequent inferential analysis were verified. At this stage, the sample number, the balance of subsamples, and the normal distribution of continuous variables (i.e., skewness and kurtosis ranging from -1 to +1) were assessed. In order to verify the im-

port of discrete socio-demographic factors on the instrument perception, the validity criteria were discretized at two levels by using the median. Then the validity criteria taken into account were computed for each subsection of the NVS-IT, as well as for the instrument as a whole, thereby producing 15 different scores. At the second stage, an inferential analysis was conducted to assess the relations between the socio-demographic factors and the final scores obtained for the NVS-IT validation procedure, and the relations within the validity criteria, respectively. We used Pearson's *r* to evaluate the effects of age, the chi-square test to assess the relation between the discrete unbalanced socio-demographic factors (i.e., education and gender) on the discretized validity criteria, and, finally, the ANOVA test to assess the effects of expertise.

The average values and standard deviations for each section, as well as for the aggregated total scores of the instrument as a whole, were then produced and evaluated with respect to the adopted thresholds.

RESULTS

In order to validate the NVS-IT as regards the dimensions considered, we split the procedure into two phases. Initially, the average scores and the degree of agreement between the experts were assessed, and the effects of the socio-demographic variables were then evaluated. Accordingly, the diversity of the expert sample was the first dimension to be taken into account, and the factors characterizing it were explicitly considered in terms of effects and relation with subscale perception and comprehension.

Table 1 reports the distribution of the socio-demographic vari-

	Sample as a whole	Physicians and biologists	Dieticians and psychologists	Nurses
number	60	24	21	15
age (years; mean ± DS)	41.1 ± 9.9	35.9 ± 8.2	44.1 ± 11.7	45.3 ± 5.6
gender (female)	42 (70%)	17 (70.8%)	16 (76.2%)	9 (60%)
education				
Bachelor's degree	11 (18.3%)	0	8 (38.1%)	3 (20%)
Master's degree	27 (45%)	11 (45.8%)	8 (38.1%)	8 (53.3%)
spec./Ph.D.	22 (36.7%)	13 (54.2%)	5 (23.8%)	4 (26.7%)
sections (mean±SD)				
instructions	4.1 ± 0.7	4.3 ± 0.5	3.7 ± 0.7	3.9 ± 0.8
show card	4.2 ± 0.6	4.4 ± 0.4	3.9 ± 0.8	4.3 ± 0.5
question #1	4.0 ± 0.7	4.2 ± 0.5	3.7 ± 0.9	3.9 ± 0.7
question #2	4.0 ± 0.8	4.2 ± 0.6	3.7 ± 1.0	3.9 ± 0.6
question #3	3.8 ± 0.8	4.0 ± 0.6	3.6 ± 0.9	3.8 ± 0.6
question #4	3.9 ± 0.8	4.2 ± 0.5	3.5 ± 0.9	3.9 ± 0.7
question #5	3.9 ± 0.9	4.2 ± 0.8	3.5 ± 1.1	3.9 ± 0.7
question #6	3.9 ± 1.0	4.3 ± 0.7	3.5 ± 1.2	3.8 ± 0.8
question #7	3.9 ± 0.9	4.3 ± 0.7	3.7 ± 1.1	3.7 ± 0.9
score sheet	4.2 ± 1.1	4.6 ± 0.8	4.1 ± 1.1	3.8 ± 1.2
general dimensions (mean±SD)				
aesthetic validity	4.0 ± 0.7	4.3 ± 0.5	3.7 ± 0.8	3.5 ± 1.0
efficiency	4.0 ± 0.8	4.3 ± 0.6	3.7 ± 0.9	3.8 ± 0.7
comprehensibility	3.8 ± 0.7	4.2 ± 0.5	3.5 ± 0.7	3.7 ± 0.5
reliability	4.1 ± 0.8	4.5 ± 0.7	3.7 ± 0.9	4.1 ± 0.6
sensitivity	3.7 ± 0.9	3.9 ± 0.7	3.5 ± 1.0	3.7 ± 0.8

Table 1. Socio-demographic characteristics of the expert sample and descriptive statistics of scores.

Tabella 1. Caratteristiche sociodemografiche del campione di esperti e statistiche descrittive dei punteggi.

ables, showing the balance between the expert subsample. In the same table, the average scores obtained for each section of the tool (i.e., average score considering the five dimensions for all experts) and for the five general dimensions are reported. In particular, a score higher or equal to 3 indicates an adequate result. The data shows the good representativeness of the expertise involved in the health literacy assessment. Moreover, good results for each assessed section and dimension, with average scores always greater than the acceptability threshold (3), is demonstrated by the data, even when we take into account the potential ranges.

Table 2 reports the average scores obtained for each item of the tool. Once again, all sections have good scores for each dimension, even taking into account the potential ranges. The second part of the inferential analysis considered the relations between the socio-demographic factors and validity criteria (**table 3**).

As shown in **table 3**, no significant statistical differences emerged with regard to gender and education, while age weakly correlates only with comprehensibility, thereby explaining less than 7% of the variance of this criterion and suggesting, as expected, that the higher the age, the lower the comprehensibility score. Despite the good scores obtained by all the expert clusters for each dimension (**table 1**), significant differences emerged in four dimensions (with the only exception of sensitivity) between the physician and biologist clusters, compared with the clusters of dieticians and psychologists. In particular, the first always has a higher score in comparison with the second.

DISCUSSION

In this study, we developed an Italian version of the NVS, and tested its face and preliminary construct validity. Our results show that the NVS-IT presents a good level of adequacy for each investigated dimension (aesthetic validity, efficiency, comprehensibility, reliability, and sensitivity), both for each section/question and for the tool as a whole.

Face validity is a technical description of the belief that a scale looks reasonable. In particular, face validity indicates whether, on the face of it, the instrument appears to be assessing the desired qualities.¹³ Construct validity, on the other hand, deals with the capability of a tool to assess a dimension (e.g., functional literacy) in accordance with the theory that defines it (e.g., Nutbeam's health literacy classification).¹

Despite the importance of these aspects, face and construct validities are infrequently assessed in validation studies of health literacy assessment tools, as well as in other psychometric properties.^{18,19}

Good face validity of the NVS-IT is a fundamental aspect for future use of this tool at the population or patient levels: face validity increases motivation and cooperation among respondents; it may attract candidates and reduce dissatisfaction among users: this means policy-makers and others are more likely to accept the results.¹³ A good level of construct validity demonstrates the accuracy of our tool, which is an essential requirement for acceptance among the scientific community pending the results of future assessment works based on the NVS-IT.

Even though the analysis of the scores of each dimension bro-

	Aesthetic validity	Efficiency	Comprehensibility	Reliability	Sensitivity
sections (mean \pm SD)					
instructions	3.9 \pm 1.0	4.1 \pm 1.0	4.1 \pm 0.8	4.4 \pm 0.8	3.6 \pm 1.0
show card	n/a	4.4 \pm 0.8	4.0 \pm 0.7	4.4 \pm 0.7	n/a
question #1	4.1 \pm 0.9	4.1 \pm 0.8	3.9 \pm 0.8	4.1 \pm 0.8	3.6 \pm 1.0
question #2	4.1 \pm 0.8	4.1 \pm 0.8	3.6 \pm 0.9	4.2 \pm 0.9	3.9 \pm 0.9
question #3	4.0 \pm 1.0	3.9 \pm 0.9	3.5 \pm 0.9	4.1 \pm 1.0	3.7 \pm 1.0
question #4	4.1 \pm 0.9	4.0 \pm 0.9	3.5 \pm 0.9	4.1 \pm 0.9	3.7 \pm 1.0
question #5	4.0 \pm 1.0	4.0 \pm 1.0	3.9 \pm 1.0	3.9 \pm 1.1	3.8 \pm 1.1
question #6	4.0 \pm 1.0	4.0 \pm 1.0	3.9 \pm 1.0	3.9 \pm 1.1	3.7 \pm 1.1
question #7	4.0 \pm 1.0	4.0 \pm 1.0	4.0 \pm 1.0	4.0 \pm 1.1	3.7 \pm 1.1
score sheet	n/a	4.2 \pm 1.1	4.2 \pm 1.1	n/a	n/a

n/a: not applicable

Table 2. Scores and validity measures. / **Tabella 2.** Punteggi e misure di validità.

	Aesthetic validity	Efficiency	Comprehensibility	Reliability	Sensitivity
age	ns	ns	r. = -0.26*	ns	ns
gender	ns	ns	ns	ns	ns
education	ns	ns	ns	ns	ns
job#	F = 3.85*	F = 3.95*	F = 7.60**	F = 5.47**	F = 1.10
A vs B	14.8*	4.9*	6.9*	13.0**	ns
A vs C	ns	ns	ns	ns	ns
B vs C	ns	ns	ns	ns	ns

*p < 0.05; **p < 0.01 ns: not significant;
#job clusters: A=physicians and biologists, B=diicians and psychologists, C=nurses. The difference value is reported and the Scheffe test was performed in order to estimate the statistical significance. If the value is positive, it means that the score reported by the first group is higher than the second.

Table 3. Scores and validity measures. / **Tabella 3.** Punteggi e misure di validità.

ken down by expert profession shows a statistically significant association (the scores assigned by physicians and biologists are generally higher than those assigned by dieticians and psychologists), the NVS-IT presents an adequate or good level of adequacy for all clusters of healthcare professionals. Considering this, we can say that there is a general consensus among the included clusters of experts in judging the adequacy of the NVS-IT in resembling what it intends to measure. This result is particularly important if we consider that there is no need to check the degree, specialization, or professional skills of the operators for the NVS as well as for other health literacy

tools, but only minimal training on how to administer the tool is required.⁵

In conclusion, the results of our survey indicate that the NVS-IT can be used in pre-testing and field-testing surveys to complete its validation process. Our study aims to introduce a scientific approach to health literacy, an issue which is gaining interest in our country, to enable the scientific community to measure aspects of functional literacy in individuals, groups, or communities.

Conflicts of interest: none declared

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Molecular typing of XDR *Acinetobacter baumannii* strains in an Italian ICU

Caratterizzazione molecolare di *Acinetobacter baumannii* isolati da pazienti ricoverati in un reparto di terapia intensiva

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Abstract

Objective. To investigate the antimicrobial susceptibility and clonal relationship of *Acinetobacter baumannii* strains isolated in an Italian ICU.

Design. Epidemiological, observational, retrospective, longitudinal study.

Setting and participants. The ICU of the University Hospital of Sassari, Italy.

Main outcome measures. Pulsed Field Gel Electrophoresis (PFGE) and Multi Locus Sequence Typing (MLST) were used to evaluate the genomic features of the isolated strains.

Results. Drug susceptibility testing for all isolated strains showed the same resistance pattern, characterized by resistance to the most important antibiotics, with the only exception of colistin. PFGE showed a very poor between-strain variability; three distinct clusters, 11, 4, and 1 isolates in size, were identified (Dice's coefficient: 92.11%). MLST showed that all isolated strains belonged to sequence type 2 (ST2). All isolates collected from the environment and the human samples were positive for the following genes: blaOXA-23, blaOXA-51-like, blaVIM-like, blaIMP-like, and ISAb₁; however, blaOXA-24-like, blaOXA-58-like, and blaNDM-like were not detected.

Conclusions. The survey identified XDR strains belonging to the same cell clone, confirming the wide circulation and environmental persistence of this microorganism.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 129-133)

Key words: *Acinetobacter baumannii*, outbreak, PFGE, MLST

Riassunto

Obiettivo. Descrivere le caratteristiche fenotipiche e genotipiche dei microrganismi di più frequente isolamento nei reparti dell'Azienda Ospedaliero-Universitaria di Sassari.

Disegno. Studio epidemiologico osservazionale, retrospettivo.

Setting e partecipanti. Unità di rianimazione e terapia intensiva, Ospedale universitario di Sassari, Italia.

Principali misure di outcome. Profilo fenotipico e genotipico dei ceppi di *Acinetobacter baumannii* isolati.

Risultati. I microrganismi isolati hanno evidenziato un profilo XDR con resistenza ai carbapenemi, ma sensibilità alla colistina. L'analisi di macrorestrizione ha evidenziato minime differenze tra i ceppi (coefficiente di Dice: 97,15%), facendo supporre una possibile discendenza clonale tra essi. I templati allelici ottenuti dall'analisi di sequenza hanno evidenziato l'appartenenza all'allele 2 per tutti i geni considerati. La combinazione allelica ottenuta corrisponde al ST2. Tutti gli stiptipi hanno mostrato positività per i geni blaOXA23-like, blaVIM-like e blaIMP-like, ISAb₁, mentre sono risultati negativi i test per la ricerca dei geni blaOXA24-like, blaOXA58-like e blaNDM-like.

Conclusioni. L'indagine condotta sugli stiptipi isolati dai pazienti ricoverati nel reparto ha permesso di identificare ceppi MDR appartenenti allo stesso clone cellulare confermando l'ampia circolazione e la particolare persistenza ambientale di tale microrganismo.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 129-133)

Parole chiave: *Acinetobacter baumannii*, outbreak, PFGE, MLST

INTRODUCTION

Acinetobacter baumannii is one of the most frequent opportunistic microorganisms detected in healthcare settings.¹ Clinical care of infections caused by *Acinetobacter baumannii* has been complicated by the emergence and spread of multi-drug resistant strains.² Morbidity and mortality can be relevant in some settings, particularly in intensive care units (ICUs), as a consequence of life-threatening infections, including ventilator-related pneumonia, sepsis, urinary tract infections, and skin and soft tissue disorders.^{1,3-5}

Complicated drug resistance patterns have been recently described in nosocomial outbreaks where the isolates were resistant to all antibiotics with the only exception of polymyxins.⁶ Extensively drug-resistant (XDR) *Acinetobacter baumannii* infections, implying resistance to three or more antibiotic classes, can be deemed a serious public health issue worldwide because of the few current therapeutic options, high infection rates, and poor patient outcomes.⁷

Several Authors highlighted the crucial role of the *Acinetobacter baumannii* resistance to carbapenems, mediated by oxacillinases (OXA-class D) and, less frequently, by metallo- β -lactamases (MBL-class B).^{8,9} In particular, five OXA subgroups are associated with *Acinetobacter baumannii* resistance: blaOXA-51-like, blaOXA-23-like, blaOXA-40-like, blaOXA-58-like, and blaOXA-143-like.¹⁰ It was found that the insertion sequence IS-Aba1 can activate blaOXA-23-like and blaOXA-51-like genes.^{11,12}

blaOXA-58-like, blaOXA-23-like, and blaOXA-24-like are the most frequent genes detected in European isolates.¹³

The aim of this study was to investigate the antimicrobial susceptibility and clonal relationship of *Acinetobacter baumannii* strains isolated from human and environmental samples collected during a potential nosocomial outbreak in 2012-2013 in an Italian ICU, located in the University Hospital of Sassari, Italy.

MATERIAL AND METHODS

Setting

The study was carried out in an ICU located in a 500-bed tertiary university hospital in Italy. An epidemiological investigation was performed by the public health specialists of the same hospital after the collection of four multi-drug resistant *Acinetobacter baumannii* strains in a time-period of 10 days (November-December, 2012).

The total duration of the epidemiological surveillance was 10 months (November, 2012-August, 2013).

Biological samples were collected from the environment and several anatomical sites of the patients admitted during the above-mentioned period. The ICU included 10 beds, divided into two different types of room (i.e., single and triple bed). Environmental sampling was performed on circulating air, surfaces, and devices located in the rooms.

We carried out an epidemiological, observational, retrospective, longitudinal study in order to assess the epidemiological characteristics of a potential nosocomial outbreak.

Pulsed Field Gel Electrophoresis (PFGE) and Multi Locus

Sequence Typing (MLST) were used to evaluate the genomic features of the isolated strains.

Conventional microbiology

Nasal and broncho-alveolar lavage (BAL) samples were collected from the patients after notification of a potential outbreak. Drug susceptibility testing was carried out on the isolates obtained from solid culture media using the following antibiotics: aminoglycosides, carbapenems, fluoroquinolones, tetracyclines, penicillins, cephalosporins, and colistin (Vitek II, BioMerieux).

Pulsed field gel electrophoresis

PFGE was carried out according to the method recommended by ARPAC (Antibiotic Resistance Prevention and Control).¹⁴ Bacteria were suspended in low melting point agarose disks; then, their DNA was extracted and purified. The agarose disks were cut using the *ApaI* restriction enzyme. DNA fragments were separated by agarose PFGE using a Clamped Homogeneous Electric Fields DRII SYSTEM (BIORAD). Gel images were analyzed by means of Image Master Program (Pharmacia). The identification of the position of the electrophoretic bands, as well as the definition of the phylogenetic dendrogram, was obtained with the GelCompar II software (Applied Maths).

Multi-locus sequence typing

MLST analysis was performed according to the Protocol of the Pasteur Institute.¹⁵ Fragments of seven internal housekeeping genes (i.e., *cpn60*, *fusA*, *gltA*, *pyrG*, *recA*, *rplB*, *rpoB*) were amplified and sequenced. Sequence analysis was performed with the Bioedit software. Each sequence was compared with sequences deposited in the website of the Pasteur Institute to evaluate the «percentage of identity» and compatibility.

The presence of *Acinetobacter baumannii* genes encoding carbapenemases (blaOXA-23, blaOXA-24-like, blaOXA-51-like, blaOXA-58-like) and metallo-beta-lactamases (blaVIM-like, blaIMP-like, blaNDM-like) was assessed for all the collected isolates using Multiplex and single PCR, respectively.^{16,17}

blaOXA51-like and OXA 23-like alleles were simultaneously genotyped together with the insertion sequence ISAbal in order to evaluate the resistance to carbapenemases.¹⁸⁻²⁰

Statistical analysis

An *ad hoc* electronic form was prepared to collect demographic, epidemiological, clinical, and microbiological variables. Frequencies (percentages) and medians and ranges were used to summarize qualitative and quantitative variables, respectively. Data were analyzed using STATA version 13 (StataCorp, College Station, Texas).

RESULTS

Nine patients (median [range] age: 72 [4-88] years; males [%]: 7/9 [77.8]) were admitted to the ICU of the university hospital of Sassari, Italy, between November 2012 and March 2013, and were found positive for *Acinetobacter baumannii*.

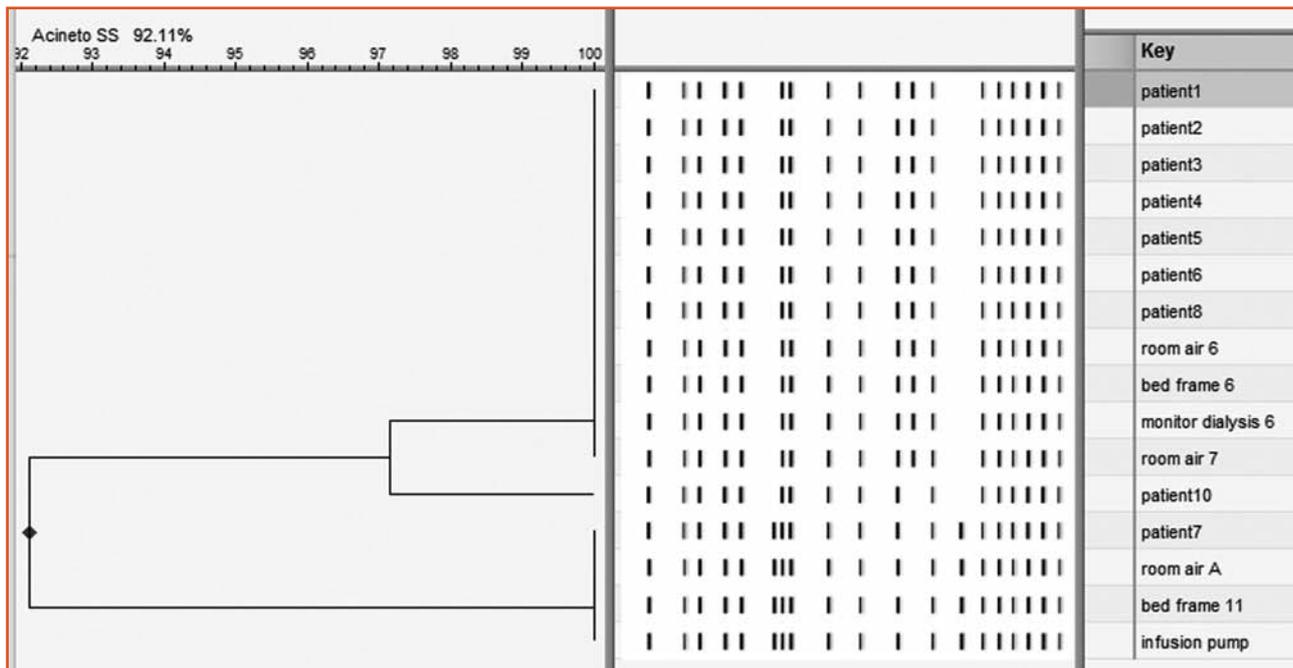


Figure 1. Dendrogram and electrophoretic bands of the isolated *Acinetobacter baumannii* strains.

Figura 1. Dendrogramma e profilo elettroforetico degli isolati di *Acinetobacter baumannii*.

In particular, drug susceptibility testing for all isolated strains showed the same resistance pattern, characterized by resistance to the most important antibiotics, with the only exception of colistin.

The median hospital stay was 58 days (range 20-163). Unfortunately, 4/9 (44.5%) died; 60-day mortality was 3/9 (33.3%). The majority of them (6/9, 66.7%) were admitted in a medical ward before their transfer to the ICU.

Furthermore, 7 XDR *Acinetobacter baumannii* were isolated from surfaces located in the patients' rooms (i.e., dialysis machine and parenteral administration monitors, and headboard of the beds), together with *Pseudomonadaceae*, *Enterobacteriaceae*, and fungi.

In total, 16 *Acinetobacter baumannii* strains sharing the same phenotypic profile were collected in a short time period (November 2012 – March 2013), suggesting a potential outbreak supported by environmental sources. PFGE showed a very poor between-strain variability, with a number of electrophoretic bands ranging from 18 to 22 and a molecular weight ranging from 100 Kb to >1,000 Kb.

Three distinct clusters (11, 4, and 1 isolates in size) were identified using the GelCompar II software, with a Dice's coefficient of 92.11%.

MLST showed that all isolated strains belonged to allele 2 following the sequence typing of the *fusA*, *pyrG*, *recA*, *rplB*, *cpn60*, *rpoB*, and *gltA* genes, corresponding to sequence type 2 (ST2).

All isolates collected from the environment and the human samples, were positive for the following genes: *blaOXA-23*, *blaOXA-51-like*, *blaVIM-like*, *blaIMP-like*, and *ISAba1*; however, *blaOXA-24-like*, *blaOXA-58-like*, and *blaNDM-like* were not detected.

After the last *Acinetobacter baumannii* collection, in August 2013 a new ST2 strain, showing the same phenotypic resistance profile, was isolated from a patient admitted to the same hospital, but the molecular profile showed differences (Dice's coefficient: 79.47%), highlighting a different clonal origin because of >3 different stripes, according to the classification obtained using the between-groups linkage method.²¹

DISCUSSION

The epidemiological investigation and molecular analysis carried out in an ICU of a tertiary university hospital showed that nine patients were infected by XDR *Acinetobacter baumannii* strains sharing the same clonal characteristics.

This report confirmed previous findings, which pointed out the important role played by the environment.²² It was not possible to assess the potential contamination/infection of the health-care providers who could have favoured the transmission of bacterial strains from the environment to the patients.²³ However, the environmental sampling of several devices and surfaces allowed the identification of the same genotypes in the ICU rooms.

On this basis, it is necessary to underline the importance of epidemiological investigation and implementation of immediate preventive measures to interrupt nosocomial transmission (i.e., isolation of infected patients, hand hygiene, turnover of personal protective equipment, and cleaning/disinfection of contaminated environmental areas). The effectiveness of the infection control interventions implemented in the Italian ICU was proved by the missing identification of *Acinetobacter baumannii* strains after March; the identification of a different strain in August showed the interruption of the epidemiological transmission.

Patient	Sex	Age (years)	PFGE type	ST	Clinical sample	Clinical wards	Date of admission	Date of discharge	Mode of dismissal
1	M	68	A	2	BAL	surgical	12/10/2012	21/11/2012	death
2	M	88	A	2	BAL	medical	01/10/2012	28/11/2012	death
3	F	79	A	2	BAL	medical	02/11/2012	05/03/2013	ordinary
4	M	67	A	2	BAL	medical	07/12/2012	16/01/2013	death
5	M	70	A	2	wound swab	surgical	03/09/2012	13/02/2013	death
6	F	4	A	2	BAL	medical	24/12/2012	01/03/2013	ordinary
7	M	72	A1	2	nasal swab	medical	10/02/2013	02/03/2013	ordinary
8	M	74	A	2	nasal swab	surgical	16/02/2013	13/04/2013	ordinary
10	M	83	A2	2	BAL	medical	23/02/2013	26/04/2013	ordinary

Table 1. Epidemiological, phenotypic and genotypic data of the *Acinetobacter baumannii* isolates and of the patients enrolled in the study.

Tabella 1. Dati epidemiologici, fenotipici e genotipici degli isolati di *Acinetobacter baumannii* e dei pazienti inclusi nello studio.

The epidemiological study we conducted raised two important clinical and public health issues: the isolation of XDR strains which did not allow the administration of important antibiotics, particularly in vulnerable patients affected by several co-morbidities (44.4% of the infected individuals died during the initial period of hospitalization) and the rapid transmission of *Acinetobacter baumannii* strains in a high-risk ward. The potential outbreaks caused by those XDR strains should be immediately detected, particularly with the support of advanced molecular techniques, which can assess the clonality of the isolated strains and the genotypic drug-resistance pattern.

PFGE and cluster analysis showed two different clusters with a Dice's coefficient of 97.2%; furthermore, the implementation of MLST confirmed the PFGE results.

Limitations of the present study are related to its retrospective nature and to the missing active surveillance in the hospital, which may have provided a partial evaluation of the epidemi-

ology of the potential outbreak. Furthermore, health-care workers were poorly involved in the bacteriological screening, hindering the possibility of better assessing the transmission chain. However, the use of several molecular techniques and the simultaneous evaluation of both the patients and the environment allowed targeted preventive interventions which stopped further contamination.

It was demonstrated that the knowledge and attitudes of the health-care workers towards this important clinical issue are poor in terms of diagnosis, treatment, and prevention.

Training sessions and microbiological surveillance focused on the admitted patients and the environment, as well as the evaluation of the effectiveness of the preventive measures, represent a priority in high-risk medical and surgical wards in order to reduce the clinical, public health, and economic burden associated with *Acinetobacter baumannii* infections.

Conflicts of interest: none declared

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COMMUNICATIONS C17
Thursday 15 October
h. 11.30
Amber Room 1

Invasive pneumococcal disease in children and adults in seven Italian regions after the introduction of the conjugate vaccine, 2008-2014

Infezioni invasive da *Streptococcus pneumoniae* nel bambino e nell'adulto in 7 Regioni italiane dopo l'introduzione del vaccino glicoconiugato, 2008-2014

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Abstract

Objective. To describe the trend of invasive pneumococcal disease in the years 2008-2014; to verify the impact of the conjugate vaccine and monitor the occurrence of serotype replacement.

Design. Prospective observational study based on data from the national surveillance for invasive bacterial diseases coordinated by the Istituto superiore di sanità.

Setting and participants. Seven Italian regions (A.P. Bolzano, A.P. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), accounting for 43% of the national population.

Main outcome measures. Number of cases and incidence of invasive pneumococcal diseases: global, stratified by age groups and by serotypes included or not in the PCV13.

Results. In 2008-2014, in the 0-4 age group IPD incidence for all serotypes decreased from 7.1 to 2.9/100,000; incidence for vaccine serotypes (VT) decreased from 5.5 to 1.1/100,000, while incidence for non-vaccine serotypes (NVT) increased from 1.6 to 2.0/100,000 (2.5 in 2013). In the >64 age group, IPD incidence increased from 5.3 to 7.5/100,000; VT incidence decreased from 3.9 to 3.2 (4.9 in 2010 and 4.3 in 2013), whereas NVT incidence increased from 1.4 to 4.4/100,000.

Conclusion. Use of the conjugate vaccine has reduced the number of cases of IPD by VT in children; the increase in IPD by NVT, above all in older age groups, suggests a serotype replacement.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 134-138)

Key words: invasive bacterial diseases, surveillance, *Streptococcus pneumoniae*, vaccination, serotype replacement, invasive pneumococcal diseases

Riassunto

Obiettivi. Descrivere l'andamento dei casi di malattia invasiva pneumococcica (IPD) negli anni 2008-2014 per verificare l'impatto del vaccino coniugato e monitorare l'insorgenza del rimpiazzo dei sierotipi.

Disegno. Studio prospettico osservazionale, basato sui dati della sorveglianza nazionale delle malattie batteriche invasive, coordinata dall'Istituto superiore di sanità.

Setting e partecipanti. Dati da 7 Regioni italiane (Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, P.A. di Bolzano, P.A. di Trento, Veneto), corrispondenti al 43% della popolazione nazionale.

Principali misure di outcome. Numero di casi e incidenza di malattia invasiva da pneumococco: globale, stratificata per fascia di età e per sierotipi inclusi e non inclusi nel vaccino PCV13.

Risultati. Nel periodo 2008-2014, in 0-4 anni l'incidenza delle IPD per tutti i sierotipi è diminuita da 7,1 a 2,9 casi/100.000, quella da sierotipi vaccinali (TV) è diminuita da 5,5 a 1,1/100.000, mentre quella da sierotipi non vaccinali (TNV) è aumentata da 1,6 a 2,0/100.000 (2,5/100.000 nel 2013). Nella fascia >64 l'incidenza delle IPD è passata da 5,3 a 7,5/100.000, quella da TV è passata da 3,9 a 3,2 (4,9 nel 2010 e 4,3 nel 2013), mentre quella da TNV è aumentata da 1,4 a 4,4 casi/100.000.

Conclusioni. L'uso del vaccino coniugato ha portato a un decremento dei casi di IPD da TV tra i bambini; l'aumento dell'incidenza delle IPD da TNV, soprattutto negli anziani, suggerisce un rimpiazzo dei sierotipi.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 134-138)

Parole chiave: malattie batteriche invasive, sorveglianza, *Streptococcus pneumoniae*, vaccinazione, rimpiazzo dei sierotipi

BACKGROUND

Streptococcus pneumoniae (*S. pneumoniae* or pneumococcus) is an important human pathogen causing upper and lower respiratory tract infections (otitis, sinusitis, and pneumonia) and invasive pneumococcal diseases (IPDs), such as meningitis and sepsis. Children under 5 years of age and elderly people are the population groups most affected by these diseases. The World Health Organization estimated that 476,000 deaths due to pneumococcal infections in HIV-negative children under five years of age occurred globally in 2008, representing 5% of all cause-child mortality under five in HIV-negative children.¹

In Italy, universal paediatric vaccination against *S. pneumoniae* was introduced at the national level with the 2012-2014 National Immunization Plan.² However, since the 21 Italian regions can decide autonomously about immunization programs and vaccination schedules, many regions recommended and offered this vaccination free of charge before the introduction of the national recommendation.³ In Italy, vaccination coverage for the pneumococcal conjugate vaccine (PCV) (7-valent PCV until mid-2010 and then 13-valent PCV) has progressively increased; in 2013, national coverage, assessed at 24 months (2011 birth cohort), was 88%.

The aim of this paper, mainly based on data from the national surveillance system for invasive bacterial diseases, is to report the incidence of IPD and time trends in the years 2008-2014, the frequency of isolated serotypes, and vaccination coverage, in order to describe the impact of vaccination programs against *Streptococcus pneumoniae* in Italy.

METHODS

Surveillance and laboratory data

In Italy, cases of IPD are reported through a national voluntary passive enhanced surveillance system of invasive bacterial diseases,⁴ the MIB, which is coordinated by the national Public Health Institute (Istituto superiore di sanità, ISS) with the financial support of the Ministry of Health (MoH). The system was implemented in 1994 as a surveillance system for all bacterial meningitis and in 2007 it was extended to all invasive diseases by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.⁵

A case of invasive pneumococcal disease is defined as a patient of any age with symptoms of invasive disease (e.g., sepsis, meningitis, bacteremic pneumonia, cellulitis, arthritis) diagnosed with one or more of the following positive tests: culture from blood or cerebrospinal fluid (CSF) or other sterile site; PCR from blood or CSF; antigen test from CSF. The only difference compared to the EU case definition is the presence of symptoms compatible with IPD. Hospitals report any confirmed case to local health units, generally using a paper form. The local health units start the investigation and upload the information about the case on the database of the invasive bacterial disease surveillance system (the MIB database) through a web form. Even the National Reference Laboratory (NRL), located at the ISS, can access the MIB database; the NRL adds the results of the laboratory tests and characterizations for the isolates that are sent from local or regional laboratories. All autho-

rized users (local/regional/national staff in charge of managing notifications or investigation of invasive bacterial diseases) can view and edit all notifications concerning the geographical area of their competence archived in the MIB database, including NRL results. The database includes demographic information, clinical picture (i.e., meningitis, sepsis, or other IPD), vaccination status, antimicrobial resistance, serotype, laboratory results, thus making it possible to share information among different levels.

For this analysis we included all reports with reporting date or date of positive test between 1st January 2008 and 31st December 2014. Serotyping data were provided by the local laboratories or the NRL; if results were provided both from the local laboratories and the NRL, priority was given to the latter.

At the NRL, isolates are serotyped by Quellung reaction using sera from the Staten Serum Institut of Copenhagen (Denmark) and tested for antimicrobial resistance using E-test with EUCAST breakpoint and ATCC 49619 as reference isolate.

Incidence was calculated using the estimated population at 1st January of each year, according to the National Institute for Statistics (Istat).⁶ Beside national incidence, we focused on incidence data of a sample of the seven Italian regions (Autonomous Province of Bolzano, Autonomous Province of Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto) that have a more solid regional surveillance system and are less prone to under-reporting or under-diagnosis. The population of these 7 regions accounts for 43% of the overall Italian population.

In order to estimate the quota of preventable cases with the use of the vaccine, we estimated a stratified incidence by serotype (i.e., serotype included in PCV13, VT; serotype not included in PCV13, NVT). As more than 50% of the confirmed cases were not serotyped, for each year of reporting the proportion of VT and NVT found in all serotyped confirmed cases was applied to those confirmed cases for which serotype was unknown.

Differences among the incidences were calculated as $(1-IRR)*100$, where IRR is Incidence Risk Ratio. Statistical analysis for the trends was performed using Student's t-test with $p < 0.05$ as the level of significance.

Vaccination coverage data

Vaccination coverage at 24 months for the 2005-2009 birth cohorts was collected through a dedicated survey conducted in 2013; representatives from the 21 Italian regions involved in vaccine-preventable diseases were invited to fill in a web form, powered by SurveyMonkey®.⁷

Provisional coverage of the 2010 and 2011 birth cohorts was provided by the MoH, which has routinely collected pneumococcal vaccination coverage since 2013. In Italy, vaccine coverage at 24 months is estimated by an administrative method, using the number of children of a specific birth cohort immunised with a complete series of a pneumococcal conjugate vaccine by 24 months as numerator and the total birth cohort population as denominator. Vaccination coverage stratified by 7-valent PCV and 13-valent PCV is not available at the national level.

RESULTS

Number of cases and incidence

A total of 5,694 cases of IPD (7 without information about age) were reported at the national level in the study period, with an incidence of 1.2/100,000 in 2008 (6.6/100,000 for children less than 1 year of age, 3.5/100,000 for children 0-4 years of age, 2.7/100,000 for the >64 age group) and 1.4/100,000 in 2014 (3.3/100,000 for children less than 1 year of age, 1.6/100,000 for children 0-4 years of age, 3.6/100,000 for the >64 age group).

In the seven regions selected, the number of cases during the study period was 4,975, 87% of the overall cases reported at the national level. The incidence calculated including only the seven regions was approximately double than the national incidence: in 2008 it was 2.3/100,000 (12.0/100,000 for children less than 1 year of age, 7.1/100,000 for children 0-4 years of age, 5.3/100,000 for the >64 age group), and in 2014 it was 2.9/100,000 (5.9/100,000 for children less than 1 year of age, 3.1/100,000 for children 0-4 years of age, 7.5/100,000 for the >64 age group).

As expected, children aged 0-4 years and adults >64 years had the highest incidence rate.

In the selected regions, incidence declined significantly (table 1) in the age group that is the target of vaccination (0-4 years; $p < 0.001$) and increased significantly in the >64 age group ($p < 0.01$). The decline for the 0-4 age group from 2008 to 2014 was 56%. This decline was mainly attributable to the decrease in cases in the first year of life (from 12.0/100,000 to 5.9/100,000).

In the >64 age group, incidence showed an increase of 30% from 2008 (5.3/100,000) to 2014 (7.5/100,000). Regarding clinical presentation, in 43% of cases of all ages presentation was meningitis or meningitis + sepsis in 2008, whereas in 2014 this percentage was 36%.

Diagnostic methods and serotypes

Information on the tests used to confirm IPD cases was available in 4,739 cases (95%). Culture was still reported as the main diagnostic method (81% alone; 93% together with one or more other tests). PCR was reported to be used only in 3% of cases, but there was an increasing trend (2% in 2008-2011;

4% in 2012-2014). PCR alone was reported to be used in 2% of cases.

The percentage of overall reported cases with a result of serotyping was 31% and 58% in 2008 and 2014, respectively. However, this percentage presented differences by age group: for the 0-4 age group it was 62% in 2008 and 70% in 2014; for the >64 age group it was 27% and 56% in 2008 and 2014, respectively. The estimated incidence by serotype group (VT or NVT) is reported in figure 1. A significant decline in incidence of VT ($p < 0.001$) was observed in the 0-4 age group from 2008 to 2014. In this class of age, the percentage of serotypes included in PCV13 was 77% in 2008, 64% in 2011, and 35% in 2014. A significant increase ($p < 0.001$) in the incidence of NVT cases was observed in the >64 age group. The VT incidence decrease, a sign of a possible herd immunity effect of the vaccinated children on the older population, was not significant ($p = 0.40$). The percentage of serotypes included in PCV13 for the >64 age group was 78% in 2008, 53% in 2011, and 42% in 2014.

Vaccine coverage

National VC for PCV7/PCV13 progressively increased from 46% in 2007 (2005 birth cohort) to 88% in 2013 (2011 birth cohort). Overall, VC is good, but it varies widely between regions and years; some regions, like Abruzzo, Calabria, and Sardegna, still reported a coverage lower than 65% in 2013 (table 1). As reported at the bottom of table 1, VC in the seven selected regions is similar or slightly lower compared to the national VC (table 2).

DISCUSSION AND CONCLUSION

In Italy IPDs still represent a public health problem as frequent, and often severe, vaccine-preventable diseases. Monitoring the number of cases, incidence, and serotypes causing the infections makes it possible to evaluate the impact of the vaccination programs and the serotyping replacement that is a concern for pneumococcal infections.⁸⁻¹⁰

The MIB surveillance system collects notifications from all 21 Italian regions, but many of them report a very low number of cases; since a large number of cases is expected even in regions with very high VC because around 50% of IPDs are curren-

	0 yy		1-4 yy		5-9 yy		10-14 yy		15-24 yy		25-64 yy		>64 yy		All ages	
	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc	N	Inc
2008	29	12.0	56	5.9	16	1.4	6	0.6	8	0.4	177	1.2	280	5.3	572	2.2
2009	26	10.5	46	4.7	14	1.2	6	0.5	10	0.4	252	1.7	327	6.1	683	2.7
2010	23	9.3	50	5.1	17	1.4	6	0.5	7	0.3	263	1.8	380	7.0	748	2.9
2011	21	8.6	51	5.1	18	1.5	1	0.1	5	0.2	185	1.3	354	6.5	636	2.4
2012	18	7.7	33	3.4	19	1.6	5	0.4	5	0.2	217	1.5	433	7.9	730	2.9
2013	12	5.2	32	3.3	30	2.5	7	0.6	9	0.4	294	2.1	479	8.5	863	3.4
2014	13	5.9	24	2.5	15	1.2	8	0.7	6	0.3	241	1.7	435	7.5	743	2.8

Inc: incidence

Table 1. Estimated number of cases and incidence of IPD per 100,000 inhabitants by age group in 7 Italian regions (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2014.

Tabella 1. Numero stimato dei casi e dell'incidenza di IPD per 100.000 abitanti per classe d'età in sette regioni italiane (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2014.

Year of reference	2007	2008	2009	2010	2011	2012	2013
Birth cohort	2005	2006	2007	2008	2009	2010	2011
Abruzzo	30.30	34.43	39.66	40.07	40.19	49.63	56.09
Basilicata	92.68	95.23	96.34	97.27	98.46	98.60	98.73
Campania	n/a						
Calabria	57.13	68.12	75.28	81.36	86.91	94.00	44.54
Emilia-Romagna*	43.30	n/a	94.30	94.60	94.10	94.40	94.10
Friuli-Venezia Giulia*	n/a	n/a	n/a	n/a	74.90	84.00	86.53
Lazio	n/a	n/a	n/a	n/a	n/a	n/a	90.80
Liguria	85.12	89.09	90.17	91.26	91.29	n/a	93.66
Lombardia*	35.91	46.90	58.46	66.10	71.73	77.88	83.70
Marche	24.20	35.50	45.50	59.70	91.90	88.20	93.39
Molise	n/a	n/a	n/a	n/a	n/a	88.86	95.95
Piemonte*	10.85	19.31	27.80	29.11	44.68	89.61	92.68
P. A. Bolzano*	14.30	23.60	40.20	72.60	75.50	81.40	78.78
P. A. Trento*	37.72	69.55	85.13	84.03	84.58	86.10	87.64
Puglia	56.40	71.40	75.70	80.40	92.60	95.10	92.93
Sardegna	n/a	n/a	n/a	n.a.	90.73	91.24	64.76
Sicilia	83.90	88.70	90.70	93.60	95.00	94.95	92.90
Toscana	n/a	n/a	n/a	88.21	93.50	92.06	94.01
Umbria	n/a	n/a	n/a	76.90	93.30	93.88	94.86
Valle d'Aosta	n/a	n/a	85.40	89.70	92.10	89.60	89.68
Veneto*	83.70	86.10	87.50	88.30	90.30	87.90	88.4
average coverage	46.19	55.81	70.13	75.46	81.81	87.55	87.10
average coverage for the regions included in the study	42.44	51.04	65.73	70.01	75.31	85.90	87.71

*regions included in the study; n/a: not available

Table 2. Vaccination coverage (completed series) by birth cohort and region for conjugate vaccine against *S. pneumoniae*. Italy, 2007-2013.

Tabella 2. Vaccino coniugato contro *S. pneumoniae*: copertura vaccinale (ciclo completo) per coorte di nascita e Regione. Italia, 2007-2013.

tly not vaccine-preventable, we hypothesize an under-notification/under-diagnosis in some geographical areas; a recent comparison with data from hospital discharge records supports this hypothesis (data not shown).

To obtain a more realistic incidence, we selected data from seven regions (representing 43% of the Italian population) which provided 87.4% of all Italian IPD notifications in the period 2008-2014. The incidence in this group of regions is approximately double than the national one.

At first glance, several years of use of 7-valent and 13-valent PCV did not reduce the overall incidence of IPD in Italy. However, when we stratify data by age and serotype groups, we can observe the positive impact of the vaccine (a 56% incidence reduction) in children aged 0-4 years, who are the main target of PCV and, together with adults >64 years of age, the age group with the higher incidence of IPD.

Our data show a slight decrease in IPD due to VT in the older population, a possible sign of a herd immunity effect already observed in other countries.^{10,11} This trend, however, lacks statistical significance.

The incidence of IPD in the >64 age group increased by 30% as a consequence of a higher number of cases due to NVT. The interpretation of this increase is not easy and several hypotheses can be formulated: is it a true increase, as reported by other studies,¹⁰ or the result of a recent growing attention to the etio-

logical diagnosis of invasive disease in adults, or just a greater inclination to disease reporting? This study was not designed to answer this question, but theoretically the use of more sensitive diagnostic tests (i.e., PCR)¹² could lead to an increase in NVT IPD cases and hide a decrease in VT in older people. However, in our study we found that PCR was used as a diagnostic test in only 4% of IPDs in the seven selected regions. This study suggests the need of a comparison with other sources of data, like hospital discharge records, and focus on regional diagnostic attitudes and reporting practices to verify the temporal trend of pneumococcal infections.

This study has many limitations. We analyzed the data from the seven selected regions as a single entity, however PCV was introduced in the regional immunization plans at different times and VC varied among the regions; consequently, the aggregated data are not fully homogeneous.

Incidence by VT and NVT cases was estimated by applying, to the isolates with unknown serotype, the same distribution of serotypes observed in the same year for all confirmed cases; however, the distribution of serotype is slightly different among children and elderly patients, and this could affect the estimation.

The study shows the incidence trend for VT and NVT categorizing the serotypes as included or not included in PCV13; however the cohorts before 2011 were vaccinated with PCV7

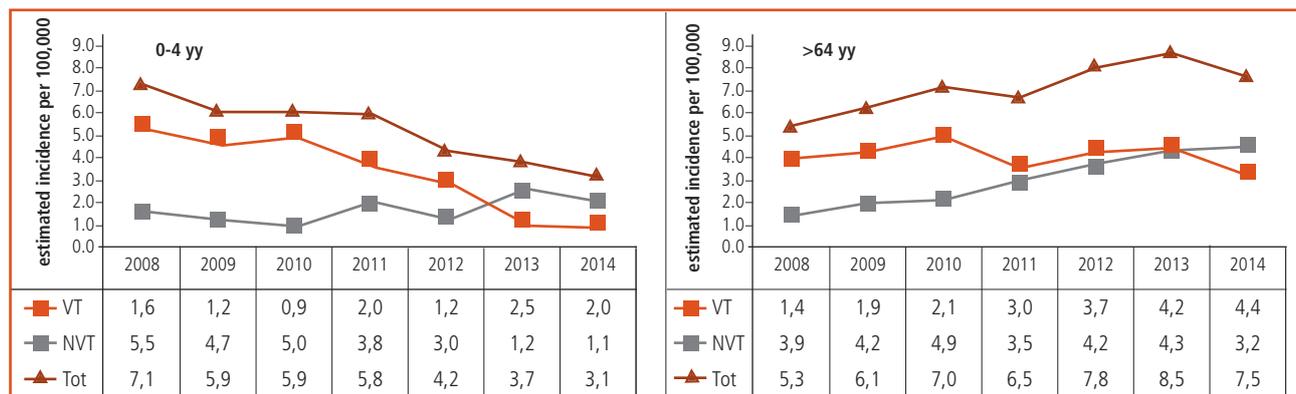


Figure 1. Estimated incidence of IPD in the 0-4 and >64 year age groups, by year of notification and serotype group in 7 Italian regions (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2012.

Figura 1. Incidenza stimata dei casi di IPD nei gruppi d'età 0-4 e >64, per anno di notifica e serotipo in 7 Regioni italiane (P.A. Bolzano, P.A. Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Piemonte, Veneto), 2008-2012.

and an unknown quota of children received one dose of PCV13; this could make it more difficult to interpret the trend of incidence by groups of serotypes.

The possibility of under-diagnosis was not investigated in the selected regions, so there is no information about whether the sensitivity of the system is homogenous among the seven regions. In conclusion, despite the limitations mentioned above, our data show a positive impact of pneumococcal conjugate vaccination in children. More studies should be performed to verify the representativeness of the surveillance system. These future efforts might also prove useful to improve the representativeness of the Italian data provided at European level; the national surveillance of invasive bacterial diseases is in charge of sending to the ECDC the IPD data, which are published in the ECDC surveillance report of invasive bacterial diseases on a yearly basis.¹³

A better knowledge of data could help to decide whether to continue to send only national data (which at the moment is providing a “diluted” incidence) or switch to a subnational sample that it is proven to produce more realistic data. Another important issue is the use of PCR in diagnosis: use of this method is slowly increasing because it allows to identify within a few hours the pathogen responsible for meningitis or sepsis, thus providing useful clinical support.

However there is no national protocol/guideline that recommends the use of this method and provides indications on how to use it (i.e., in which clinical picture to use it). At the moment, although the indication to use PCR for meningitis cases is present in many regional laboratories, our data does not indicate a widespread use of this method.

Conflicts of interest: none declared

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COMMUNICATIONS C13
Thursday 15 October
h. 8.30
Amber Room 3

Influenza and immunization: a quantitative study of media coverage in the season of the «Fluad case» Informazione: risultati di un'indagine di monitoraggio nella stagione del «caso Fluad»

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Abstract

Background. Seasonal influenza generates serious health and economic losses. In the last influenza season, the report of three deaths originally blamed on the Fluad vaccine drew widespread attention from the media and is likely to have had a major negative impact on vaccine uptake.

Objective. We quantitatively analyzed media coverage on influenza and immunization-related topics on all published issues of the Italian newspaper ranking first in circulation, over one year.

Design. We retrieved relevant key words and articles, reporting on article topic, length, position, and approach to immunization, and on other selected indicators' summary statistics, trends, and correspondence with key events.

Results. Selected key words were retrieved 798 times over the study period, 34% specifically focusing on influenza. The average number of influenza-related key words per issue was 96% higher in the four-day «uncertainty» period from when the deaths were first reported to the release of the test results disproving any causal association between the deaths and the vaccine (time frame #1), as compared to the whole study period. Ninety relevant articles were included in the analysis, 51% focusing on influenza, the average number/issue being 97% higher during time frame #1. During time frame #1, articles were also longer and located in the main sections of the newspapers. No articles were published at the launch of the seasonal influenza immunization campaign.

Conclusion. We propose an analytic model of media monitoring that could be effectively applied to support health authorities and representatives of the scientific community in conveying health education messages through the media.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 139-145)

Key words: seasonal influenza, vaccine, Fluad, immunization, media coverage and communication, media monitoring

Riassunto

Obiettivo. L'influenza ha rilevante impatto sanitario, economico e sociale. Nonostante l'offerta vaccinale, le coperture rimangono basse. I mezzi di informazione di massa sono potenti strumenti per convogliare messaggi di educazione sanitaria. Abbiamo condotto un'analisi quantitativa dell'impatto mediatico del «caso Fluad».

Disegno. L'analisi è stata effettuata su 366 numeri del *Corriere della Sera*, valutati per la presenza di parole chiave e di articoli inerenti le tematiche della patologia influenzale e delle vaccinazioni. Per ciascun articolo sono stati analizzati rilevanza (numero di parole e posizione) e approccio nei confronti delle vaccinazioni. Per le parole chiave è stato valutato il trend di frequenza nel tempo in relazione all'inizio della campagna vaccinale e al caso Fluad.

Risultati. Le parole chiave sono apparse sul quotidiano 798 volte, con una media di 16,2/giorno nei 4 giorni immediatamente successivi alla notizia delle morti sospette e prima della smentita ufficiale dell'Agenzia italiana del farmaco e dell'Istituto superiore di sanità (ISS) sulla responsabilità vaccinale dei decessi (contro 0,7/giorno nell'intero periodo analizzato). Novanta gli articoli rilevanti pubblicati, di cui 51% specifici sull'influenza, con una media di 4 articoli/giorno durante il caso Fluad, di cui 3 in prima pagina e con una lunghezza mediana del 25% maggiore rispetto ai restanti. Nessun articolo è stato pubblicato durante il lancio della campagna di immunizzazione.

Conclusioni. Proponiamo un modello analitico di monitoraggio dei media quale strumento utile per studiarne l'impatto sui comportamenti della popolazione in tema di salute e prevenzione. L'ISS ha stimato che le coperture della vaccinazione antinfluenzale siano calate drasticamente in seguito al caso Fluad. I risultati preliminari del nostro studio dimostrano come i mezzi di informazione siano stati principali mediatori di quest'associazione.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 139-145)

Parole chiave: influenza stagionale, Fluad, vaccini, mezzi di informazione, copertura mediatica, comunicazione, monitoraggio mediatico

BACKGROUND

Seasonal influenza generates serious health and economic losses for individuals and society as a whole.¹ In Italy it is estimated that, in the last season, around 11% of the general population (over 6.3 million cases) got influenza.² Influenza-related outcomes, including complications, hospitalizations, and deaths, have a relevant clinical, social, and economic burden. Despite the availability and active free-of-charge offer of influenza vaccines to subjects aged ≥ 65 and at-risk subgroups, flu vaccine coverage rates remain low and still far from the 75% target established by the Ministry of Health.³ More in general, despite immunization being among the most effective primary prevention tools ever invented, vaccines are «victims of their own success» and have recently lost public confidence.⁴ False myths related to adverse reaction risks and commercial interests are fuelling the growing phenomenon of vaccine hesitancy.⁵

Media play a crucial role in channelling health-related information. They are powerful tools for delivering health education and promoting disease prevention, including immunization. However, if misused or exploited, they can negatively influence the general population's health attitudes and behaviour towards prevention.⁶ In the last influenza season, the report of three deaths originally thought to be associated with administration of the Fludac influenza vaccine – the «Fludac case» (detailed in box 1) – drew widespread attention from the media and is likely to have had a major negative impact on influenza vaccine uptake.

OBJECTIVES

General aim of the current study was to retrospectively monitor reporting on influenza and immunization-related topics (immunization in general; vaccines other than influenza; public health issues with mention of vaccines), on all published issues of the most-read Italian newspaper, *Corriere della Sera*, over a

one-year study period. In particular, specific objectives were:

- to quantitatively analyze media coverage of the Fludac case in its temporal development;
- to quantitatively analyze media coverage of the Fludac case in comparison to media coverage of influenza and influenza-related topics during the whole influenza season;
- to quantitatively analyze media coverage of immunization-related topics;
- to explore the type of message (positive/negative/neutral) delivered by the media with regard to influenza immunization and immunization in general;
- to propose a preliminary media monitoring model and build and apply media monitoring indicators that can be used to analyze media coverage of health-related topics in the press;
- to describe the health education and communication role played by the media and reflect about its impact on the general population's health behaviours and approaches to prevention and immunization.

METHODS

We considered a one-year (366 days) study period, from 15 May 2014 to 15 May 2015, for which we retrospectively retrieved all published issues of the Italian daily newspaper ranking first in readership, *Corriere della Sera* (full digital version in portable document format, PDF).

Data extraction

Each newspaper issue was manually screened to retrieve all published articles focusing on influenza and immunization-related topics.

The screening was independently conducted by two authors, using key words related to the concepts of influenza and vaccination. Disagreements by authors were resolved by consensus. Relevant data were extracted by two authors, supervised by a third author, using a pre-defined data extraction spread-

THE «FLUAD CASE»

On 27 November 2014, the Italian Medicines Agency (AIFA) suspended the use of two batches of Fludac influenza vaccine after three deaths were reported through the National Network of Pharmacovigilance as having occurred within 48 hours from vaccine administration and deemed to be associated with it by general practitioners (GPs).⁷ The decision was taken as a precautionary measure, following the EU legislation on pharmacovigilance.⁸

The three deaths in question were reported by general practitioners and occurred in a 68-year-old who died of myocardial infarction within an hour of vaccination and in two subjects, aged 79 and 87 respectively, who died of meningoencephalitis within 48 hours of vaccination. The three administered vaccines belonged to two Fludac batches whose use was consequently suspended. After this precautionary decision, testing and analysis were initiated by the Italian Institute of Health (ISS) and AIFA, in agreement with the European Medicines Agency (EMA), both on the identified vaccine batches – to assess their safety – as well as on the case reports – to assess the nature of the association between the adverse events and the vaccine.

On 1 December, the ISS announced the first tests results; there was no presence of endotoxins and the content and characteristics of the vaccine virus antigen were compliant with quality standards.⁹ On 3 December, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there was no evidence of a causal relationship between the reported fatal events and the administration of Fludac and reassured other European countries about the safety of the flu vaccine.¹⁰ On 23 December, ISS released the final test results (abnormal toxicity test, or ATT, and sterility test) confirming the vaccine was safe, and removed the ban on the Fludac batches.¹¹

sheet. The data extraction spreadsheet was piloted on 10 randomly selected articles and modified accordingly.

Indicators and time frames taken into account and analysis

We defined and selected five key events that occurred during the study period (figure 1):

- 3rd September 2014 (Key event #1): the Ministry of Health released its 2014-2015 Circular containing recommendations for influenza prevention and control;
- 27th November 2014 (Key event #2): three deaths surmised to be associated with Flud vaccine administration were reported and the Flud batches in question were suspended;
- 1st December 2014 (Key event #3): the Italian Institute of Health released the first safety results;
- 3rd December 2014 (Key event #4): EMA released the Pharmacovigilance Risk Assessment Committee conclusion;
- 23rd December 2014 (Key event #5): the Italian Institute of Health released the final safety results.

For the sake of our analysis, we split the Flud case into two timeframes within the study period:

- a 4-day time frame (28th Nov-1st Dec): from reporting on the deaths to the release of the first safety results by the ISS – namely, when there was uncertainty about the vaccine's safety (time frame #1 – Flud case - uncertainty);
- a 27-days time frame (28th Nov-24th Dec): from reported deaths to the final safety results release (time frame #2 – whole Flud case).

We considered two units of analysis:

- key words: key words related to Italian for «vaccine/s» and «influenza»;
- relevant articles on influenza and immunization-related topics.

The following indicators were compiled:

Key word-related indicators:

- number of key words per day (per newspaper issue);
- average number of key words per time frame.

Article-related indicators:

- average number of articles per month and time frame;
- absolute number of articles per key event (media coverage was assessed *the day after* each event (4th Sept, 28th Nov, 2nd Dec, 4th Dec, and 24th Dec, respectively), as printed newspapers publish news the day after its occurrence);
- topic of the article, using four different categories:
 - articles specifically focusing on influenza and influenza immunization;
 - articles focusing on vaccines in general;
 - articles specifically focusing on vaccines other than influenza;
 - articles focusing on public health issues with mention of vaccines and immunization.
- position of the article (i.e., front page, specific section of the newspaper);
- length of the article (expressed in number of words);
- overall approach of the article, using three different categories:
 - positive approach towards vaccines;
 - negative/critical approach towards vaccines;
 - descriptive/neutral approach.

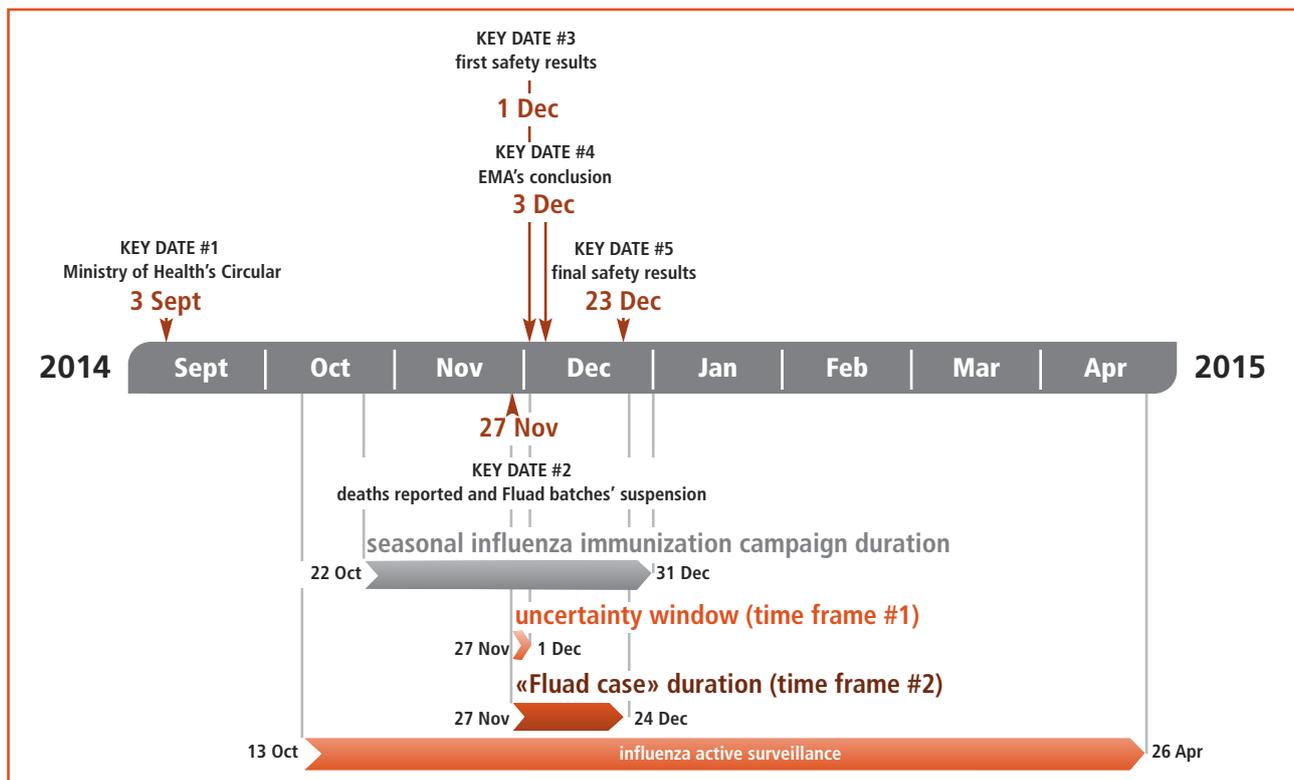


Figure 1. 2014-2015 influenza season: key dates. / Figura 1. Stagione influenzale 2014-2015: eventi chiave.

Analysis

We carried out descriptive analysis reporting selected indicators summary statistics, trends and correspondence with key events occurred during the influenza season. For both units of analysis (key word and articles) data were explored first on whole retrieved elements (all immunization-related topics) and then on elements specifically focusing on influenza.

RESULTS

Three hundred and fifty eight newspaper issues were published in the study period and were included in the study. *Corriere della Sera* was not published on 8 days during the study period due to strikes or national holidays (on 23-25 May 2014, 16 August 2014, 25-26 December 2014, 6 April 2015, 2 May 2015).

Key word analysis

During the study period, Italian words for «influenza» and «vaccine/s» were retrieved 798 times: «influenza» 273 times (34%) and «vaccine/s» 525 times (66%). Their distribution over time is presented in [figure 2](#).

The average number of key words per day was 45.5/day during time frame #1 and 10/day during time frame #2, as compared to 2.2/day during the whole study period.

When only considering «influenza»-related key words, figures were: 16.2/day during time frame #1, 3.6/day during time frame #2, and 0.7/day during the whole study period.

Looking at «influenza» key words (n=273), the distribution among the 5 identified key events ([figure 3](#)), showed the greatest share (62%, n=23) on key day # 2; key day # 3 accounted for 38%, while no key words were retrieved on key days #1, #4, and #5. Similar distribution was reported for total key words ([figure 3](#)).

Analysis of relevant articles

Ninety relevant articles were retrieved during the study period. Among them: 51% (n=46) specifically focused on seasonal influenza and seasonal influenza immunization, 13.5% (n=12) focused on vaccines in general, 14.5% (n=13) specifically focused on vaccines other than influenza and 21% (n=19) focused on public health issues and mentioned vaccines and immunization. The distribution over time of relevant articles by article type is reported in [figure 4](#).

When including all four categories of articles (total n=90), there were: 7.5 per month on average during the study period, 3.5/month when only considering those focusing on seasonal influenza and seasonal influenza immunization.

The average number of total relevant articles published per day over the study period was 0.2, increasing to 4/day during time frame #1 and 1.2/day during time frame #2. In particular, 16 articles were published during time frame #1 (four days).

A similar distribution was reported when only considering articles specifically focusing on influenza and influenza vaccine: 0.1/day for the whole study period, 1/day during time frame #2 and 4/day during time frame #1 (it must be noted that all articles published during time frame #1 were on influenza and influenza immunization).

[Figure 3](#) reports the articles' distribution over the 5 key dates: no articles focusing on influenza and influenza immunization were published on key date #1. Two articles were published around the start of the seasonal influenza immunization campaign (on 4 and 12 October). They were placed on page 31 and 53 of the newspaper; one was a 23-word long article placed at the bottom of the page, the other focused on influenza without mentioning the approaching influenza immunization campaign.

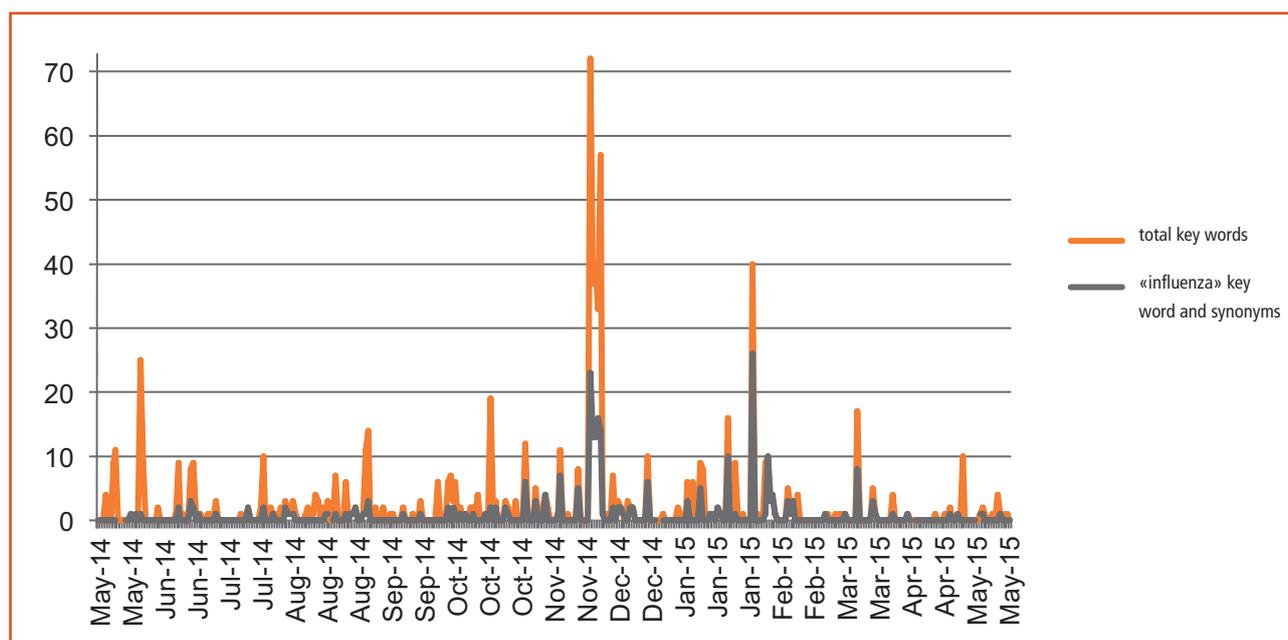


Figure 2. Distribution of key words over time (absolute number by newspaper issue)

Figura 2. Distribuzione delle parole chiave nel tempo (numero assoluto per edizione del quotidiano)

influenza immunization during time frame #1 and time frame #2 was 25% and 15%, respectively, higher than the length observed during the whole study period (317 words). Considering all retrieved articles, the median length during time frame #1 and time frame #2 was 20% higher than the length observed during the whole study period.

The share of retrieved articles placed in the main section of the newspaper increased from 13% when considering the whole study period to 38% during time frame #2 (43% if only considering articles on influenza), reaching 50% during time frame #1. Overall, 5 articles made the front page, of which 3 during time frame #1.

DISCUSSION

We assessed media coverage of influenza and immunization-related topics on all published issues of the Italian newspaper ranking highest in circulation over one year. We report that 7.5 articles per month were published on immunization-related issues, 3.5 specifically focusing on influenza. The largest share of them were concentrated around the period of the Fludac case and – this is particularly relevant – were published in the «uncertainty» period between the first reporting of the deaths suspected to be associated with Fludac vaccine administration and before the Italian Institute of Health's announcement that there was no evidence of causal association. Not only were more articles published during that period, but they were also longer and located in the main sections of the newspapers, including the front page. In addition, poor media coverage was given to the release of official safety results by national and international health authorities. Not a single article was published reporting EMA's Pharmacovigilance Risk Assessment Committee statement that there was no evidence of a causal relationship between the fatal events and the administration of Fludac, nor was a single article published reporting the final test results conducted by the National Institute of Health, proving Fludac vaccine safety. On the contrary: before health authorities announced that the Fludac vaccine was safe and encouraged the population to get vaccinated against the flu to prevent serious complications, article titles kept reporting on increasing numbers of deaths suspected to be associated with Fludac, using alarming title words such as «deadly vaccine» and «killer vaccine».

We would also like to underline that, apart from the Fludac case, very little attention was paid by the media to influenza prevention and immunization in general; no articles were published when the Ministry of Health released the annual Circular with the recommendations for influenza prevention and control, nor were any articles published around the launch of the seasonal immunization campaign promoting influenza vaccination among the elderly and at-risk populations.

The 2014-2015 seasonal influenza immunization coverage data have been recently made available by the Ministry of Health: in subjects aged ≥ 65 years vaccine coverage this year decreased by 11% as compared to the previous season, a step back to 2000-2001 coverage rates.¹² Luckily enough, the Fludac case occurred halfway through the immunization campaign:

(more than one month after its start), and this limited its negative impact, as many people had already been vaccinated. Still, a survey conducted by the Union of Italian Physicians (SMI) reported that, right after the Fludac case, influenza vaccine uptake rates decreased by 80% at the national level, ranging from -15% to -100% in different regions.⁷

In addition, the clinical burden of influenza was larger this year than in previous seasons, with the national epidemiologic surveillance system reporting 648 serious flu cases and 163 influenza-related deaths, corresponding, respectively, to an 85% and 90% increase as compared to the 2013-2014 season.² It must be noted that, of all reported serious flu cases, only 7.6% of patients were vaccinated against influenza. All available indicators point to the fact that the last influenza season was the second most severe after the 2009/2010 pandemic.¹²

Our findings suggest that the Fludac case media coverage might have had a negative impact on influenza vaccine uptake, therefore worsening influenza-related clinical outcomes and direct and indirect healthcare costs.

When health-related events make the headlines, they greatly influence the risk perceptions of the general population. In this context, institutions and health authorities should invest more in communication and their role in the press needs to be more prominent.¹³ If the Ministry of Health, the National Institute of Health, and the Italian Medicines Agency's statements and positions on the Fludac case had had greater visibility, this could have limited the circulation of alarming and misleading messages, and ultimately the decrease in vaccine uptake.¹³

Trust in vaccines and immunization is being increasingly undermined.¹⁴ As anti-vaccination arguments are widely available online and anti-vaccination movements capitalize on the potential offered by the new means of communication, public institutions and scientific societies are called to handle this growing public health concern. Along these lines, in 2013 the Italian Society of Hygiene and Preventive Medicine launched the VaccinarSi project, with the aim of exploiting the great potential offered by media to communicate and educate the general population, as well as the healthcare community at large, about vaccines.¹⁵

Our study presents both strengths and limitations. To our knowledge, this is the first study to have performed a comprehensive media monitoring on all issues of a national newspaper (ranking first in circulation) over a one-year follow up. Another major strength of our work is that we carried out a quantitative analysis of the media coverage of influenza and immunization-related topics: we built and applied a number of indicators that enabled us to quantitatively assess the number, content, and relevance of retrieved articles, as well as analyze trends and perform comparisons. Similar studies published in the literature considered shorter study periods, did not scan printed newspapers, and carried out only qualitative analyses.¹⁶ Limitations include only having considered one newspaper. However, *Corriere della Sera* is the newspaper that ranks first in readership in Italy (with a print run of 400,697 copies per day) and reaches a large and representative sample of the Italian population.¹⁷ Another limitation is that we did not include

other types of media, such as new and social media, in our analysis; nevertheless, as the target population of the influenza vaccine is the elderly, we believe they are likely to read printed newspapers rather than seek for information on the Internet. Last but not least, it would have been interesting to analyze influenza and influenza immunization media coverage trends over a longer period comprising several influenza seasons, as well as compare it with media coverage of other relevant health issues.

We carried out a retrospective analysis. We suggest that media monitoring models like ours could be applied prospectively. In case of relevant public health issues, this could be a helpful tool to plan, implement, and evaluate effective communication strategies promoting healthy behaviours.

CONCLUSION

Seasonal influenza vaccines can prevent millions of cases, thousands of hospitalizations, and hundreds of deaths, which also

produce direct and indirect-related costs and societal burden. However, influenza immunization coverage in Italy remains low and far from the targets established by the Ministry of Health. During the last influenza season, the Fluad case is likely to have negatively influenced not only influenza vaccine uptake and confidence, but immunization in general: our findings suggest that media coverage of the event might be mainly responsible for this.

Media – if misused – can have a detrimental effect on population health and prevention behaviours. Public institutions, health authorities and representatives of the scientific community should increase their efforts in conveying health education messages through the media.¹⁸

We proposed an analytic model of public health-related topic monitoring that can be effectively applied to support this.

Conflicts of interest: none declared

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Vaccine coverage in Italy and assessment of the 2012-2014 National Immunization Prevention Plan

Coperture vaccinali in Italia e valutazione dell'attuazione del PNPV 2012-2014

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LAST MINUTE SESSION
Wednesday 14 October
h. 10.00-11.00
Brown room 3

Abstract

Background. In 2012, the Italian Ministry of Health issued the National Immunization Prevention Plan (*Piano Nazionale Prevenzione Vaccinale*, or PNPV 2012-2014), with the aim of harmonizing immunization strategies across the country and ensuring equitable access to infectious disease prevention to all citizens. The Plan defines the immunization standards all regions should comply with.

Objective and methods. As new evidence has accumulated in the field of immunization, and the new National Immunization Prevention Plan is about to be launched, the aim of the current study is to: **i.** present immunization coverage data (2000-2014) for 14 vaccines included in the PNPV to be offered to the general population, **ii.** assess to what extent the PNPV coverage targets and objectives have been met, and **iii.** report on how the PNPV was transposed into regional immunization programs. Data are also available for the eight regions that piloted varicella immunization.

Results. The 2012-2014 PNPV first introduced a "lifecourse" approach to vaccination at the institutional level, and has been a milestone for prevention in the Italian health policy agenda. However, infant vaccine coverage rates have been decreasing over the last years, as has influenza immunization in the elderly. HPV vaccine coverage has been increasing for all birth cohorts, but is still far below the targets set in the Plan. Promising preliminary data show that pneumococcal and meningococcal C conjugate vaccines were well introduced in regional immunization schedules.

Conclusion. The 2012-2014 PNPV objectives have only been partially met, due to several factors, in particular increase in vaccine hesitancy. Strengthened efforts are needed to promote immunization. The new National Immunization Prevention Plan should introduce new vaccines and extend immunization programs to other target populations on the basis of the most recent scientific evidence available. It is of crucial importance that interventions of proven efficacy be planned and implemented to contrast the growing phenomenon of vaccine hesitancy and ultimately increase immunization uptake.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 145-158)

Key words: vaccine coverage, immunization, immunization programs and policies, National Immunization Prevention Plan, vaccine hesitancy, Italy

Riassunto

Introduzione. Il Piano Nazionale Prevenzione vaccinale (PNPV 2012-2014) è stato emanato nel 2012 come Intesa in Conferenza Stato-Regioni con l'obiettivo di armonizzare le strategie di immunizzazione in tutto il Paese e di assicurare un accesso equo alla prevenzione delle malattie infettive a tutti i cittadini. Il Piano definisce gli standard di immunizzazione ai quali tutte le Regioni si sono impegnate ad aderire.

Obiettivo. A più di tre anni dall'approvazione e nell'imminenza dell'uscita del nuovo Piano, obiettivo del nostro studio è stato quello di: **i.** riassumere i contenuti del PNPV 2012-2014, **ii.** descriverne le declinazioni regionali e **iii.** presentare i più aggiornati dati di copertura (2000-2014), evidenziando gli obiettivi raggiunti e le criticità riscontrate.

Risultati. Dall'analisi dei dati raccolti dal Ministero della salute emerge il calo delle coperture in quasi tutte le Regioni per le vaccinazioni dell'infanzia e nella popolazione anziana per quella antinfluenzale; coperture preliminari per le neo-introdotte vaccinazioni antimeningococco C e antipneumococco e per la vaccinazione contro la varicella nelle Regioni che l'hanno introdotta; coperture in aumento per tutte le coorti invitate alla vaccinazione anti-HPV, benché al di sotto dei target stabiliti nel Piano.

Conclusioni. I nostri dati sottolineano come gli obiettivi del PNPV 2012-2014 siano stati raggiunti solo parzialmente a causa di

diversi fattori, in particolare l'incremento dell'esitazione sui vaccini. Maggiori sforzi sono necessari per promuovere l'immunizzazione. Il nuovo Piano dovrà considerare i nuovi vaccini e l'estensione dell'offerta di quelli esistenti che già sono stati introdotti in alcune Regioni alla luce delle nuove evidenze scientifiche disponibili. Inoltre, dovranno essere realizzati interventi di informazione e comunicazione di provata efficacia per fronteggiare il fenomeno della esitazione sui vaccini e garantire il raggiungimento degli standard di copertura.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 145-158)

Parole chiave: coperture vaccinali, vaccini, politiche vaccinali Piano Nazionale Prevenzione Vaccinale, vaccine hesitancy, Italia

BACKGROUND

Immunization programs are key preventive interventions and have largely contributed, over the last century, to reduce the burden of infectious diseases and decrease related morbidity, mortality and healthcare costs.¹⁻⁴ International and national health authorities have recently renewed their commitment to promote prevention of vaccine-preventable diseases (VPDs) and strengthen immunization programs. A milestone in the European political agenda for public health, the EU has recently adopted the Council Conclusions on «Vaccinations as an effective tool in public health».⁵ Along the same line, the WHO European Region Vaccine Action Plan 2015-2020 (EVAP) – defining immunization priority action areas and targets – calls on countries to implement effective immunization policies and programs.⁶

In Italy, immunization programs are managed within the National Health Service (Servizio sanitario nazionale, or SSN). The SSN provides universal health coverage: the national level sets the health systems' fundamental principles and goals, defines the core benefit package of health services to be guaranteed to all citizens (Livelli essenziali di assistenza, or LEAs), and allocates national funds to the regions. Regions are responsible for planning, financing, and implementing healthcare services.⁷ In the field of immunization, this structure translates into each region adopting its own regional immunization plan and schedule.

With the aim of harmonizing immunization strategies between the regions and ensuring to all citizens equity in access to infectious disease prevention, the Ministry of Health issues the National Immunization Prevention Plan (PNPV): a guidance document for immunization policies intended to be of technical support to regions.

The 2012-2014 PNPV was issued by the Ministry of Health in April 2012 after the approval of the State-Regions Conference.⁸ It defines the immunization standards all regions should comply with and sets specific objectives to be reached at the national level in terms of target coverage rates, immunization information systems, infectious disease surveillance, quality and safety of immunization programs. The PNPV's crucial points are the following:

- it lists vaccines to be actively offered free of charge to the general population as part of the LEAs and includes them in the National Immunization Schedule (NIS);
- it lists immunization programs for at high-risk subjects and healthcare professionals;
- it makes reference to the need to make vaccines not included in the above-mentioned categories available with co-payment for subjects willing to get immunized.

In accordance with the national health service structure, single regions and autonomous provinces retain the responsibility of implementing and managing immunization programs.

OBJECTIVE

Since the adoption of the PNPV in 2012, new evidence has accumulated in the field of immunization which has been incorporated in a new and updated Italian National Immunization Prevention Plan about to be launched by the Ministry of Health. Three and a half years after the 2012-2014 PNPV was adopted, and before the new Plan is approved by the State-Regions Conference, the aim of the current study is to:

- present the 2012-2014 legislative process, content, and structure, underlining its most innovative aspects;
- report and analyze how different regions transposed the 2012-2014 PNPV into regional immunization plans and schedules;
- report and analyze the most up-to-date data on vaccine coverage for the immunization programs included in the National Immunization Schedule;
- critically appraise whether 2012-2014 PNPV objectives have been met;
- comment on barriers to effective implementation of immunization programs in Italy that will need to be tackled in the future by the new Plan.

METHODS

In this paper we present the 2012-2014 PNPV, we list PNPV transpositions into regional immunization plans and programs and we pool and analyze the most up-to-date immunization coverage data for the period 2000-2014.

Sources of data

Data were provided by the Prevention Directorate-General of the Italian Ministry of Health and from other selected sources, including published papers and reports. We considered the 2000-2014 study period, based on data availability. A detailed list of data sources by year is provided in [Appendix 1](#) (see supplementary material online).

Analysis

All data retrieved were compiled in a comprehensive database. We present coverage figures by single preventable disease and by vaccine. Based on data availability, we carried out descriptive analysis by region and at the national level. We report on two sets of analyses:

- first, we present current immunization coverage data, ex-

pressed as the most up-to-date coverage rates by preventable disease (cross sectional design analysis);

- then, we present immunization coverage trends over time, expressed as percentage change in vaccine coverage over two different time periods:
- 2000-2014 (the longest study period we can account for, based on data availability);
- 2012-2014 (since the PNPV was adopted).

In both sets of analysis comparisons are made with the vaccine-specific coverage targets established by the 2012-2014 PNPV, to assess whether they have been met, at the regional and national level.

Outcomes

We focused on immunization programs actively offered to the general population, as defined in the 2012-2014 PNPV. In particular, the following outcomes were considered:

- inactivated poliomyelitis vaccine coverage at 24 months for completed courses – 3 doses (IPV);
- diphtheria, tetanus, and acellular pertussis vaccine coverage at 24 months for completed courses – 3 doses (DTaP);
- diphtheria and tetanus vaccine + diphtheria, tetanus, and acellular pertussis vaccine coverage at 24 months for completed courses – 3 doses (DT-DTaP);
- hepatitis B vaccine coverage at 24 months for completed courses – 3 doses (HepB3);
- *Haemophilus influenzae* type b vaccine coverage at 24 months for completed courses – 1, 2 or 3 doses, based on age (Hib);
- measles, mumps, and rubella vaccine coverage at 24 months / measles, mumps, rubella, and varicella vaccine – first dose (MMR/MMRV);
- measles vaccine + measles, mumps, and rubella vaccine / measles vaccine + measles, mumps, rubella, and varicella vaccine – first dose (M-MMR/M-MMRV);
- pneumococcal conjugate vaccine coverage at 24 months for completed courses – 1, 2 or 3 doses, based on age (PCV);
- meningococcal C conjugate vaccine coverage at 24 months for completed courses – 1, 2 or 3 doses, based on age (MenC);
- influenza vaccine coverage in subjects aged ≥ 65 years;
- *Human papillomavirus* vaccine coverage for completed courses and for “at least one dose administered” (HPV);
- varicella vaccine coverage at 24 months – one dose.

RESULTS

The 2012-2014 PNPV

The 2012-2014 National Immunization Plan was issued by the Italian Ministry of Health and published on the Ministry of Health website in April 2012⁹ after approval of the State-Regions Conference on 22 February 2012⁸ and publication in the Italian Official Gazette no. 60, Ordinary Supplement no. 47 on 12 March 2012.¹⁰ The document was issued by the Italian Ministry of Health and composed in close consultation with the High Health Council (Consiglio superiore di sanità, or CSS), experts from the National Institute of Health (Istituto superiore di sanità, or ISS) and the Directorate General for Prevention of the Ministry of Health. The PNPV work-

ing group's methods included comprehensive reviews of the available scientific evidence on vaccines and reference to the most recently updated technical documents of the World Health Organization (WHO) and the European Centre for Disease Control and Prevention (ECDC). The draft was shared with the Italian Medicines Agency (AIFA) and the Interregional Prevention Coordination before final approval by agreement between the government, the regions, and the two autonomous provinces.

General aim of the 2012-2014 PNPV was to harmonize immunization strategies across Italian regions to ensure equity in access to infectious disease prevention to all citizens. Specific objectives were:

- to strengthen infectious disease surveillance systems and serotyping capacity and link them with other SSN and administrative flows;
- to guarantee the active, free-of-charge offer of the immunization programs to the general population included in the National Immunization Schedule (NIS, [table 1](#)) and reach the vaccine coverage targets presented in [table 2](#);
- to guarantee active, free-of-charge offer and promote immunization programs listed in the PNPV for high-risk subjects, healthcare professionals, and hard-to-reach subgroups;
- to implement immunization information systems in the whole country;
- to make vaccines not included in the PNPV available in all local health units in a co-payment regimen for subjects willing to get immunized;
- to plan and implement effective information and communication interventions to promote immunization among healthcare professionals and increase the demand for immunization in the general population.

The 2012-2014 PNPV is structured into eleven main sections. Details on the 2012-2014 PNPV content and structure are presented at page 149 ([box](#)). One of the sections contains the National Immunization Schedule (NIS) ([table 1](#)). Fourteen vaccines are scheduled in the NIS: they are actively offered to the whole population and included in the LEAs.

Previous editions of the PNPV were issued by the Ministry of Health for 1999-2000 and 2005-2007.^{11,12} The most innovative aspects of the National Vaccine Schedule as compared to the previous PNPV editions are the following:

- the “lifecourse” approach to immunization with the extension of immunization programs to adults in addition to infant and adolescents;
- the introduction of the pneumococcal conjugate vaccine and meningococcal C conjugate vaccine for infants;
- the planned introduction of the varicella vaccine into the National Immunization Schedule in 2015, after results from regions that piloted its introduction will be available.

Regional immunization plans

[Appendix 2](#) (see supplementary material online) systematically lists:

- all available legal acts of transposition of the 2012-2014 PNPV at the regional level;

2012-2014 PNPV STRUCTURE AND CONTENT

The PNPV is structured into eleven main sections:

- 1. Introduction:** this section outlines the rationale behind the need to have a national guidance document on immunization, namely the need to harmonize immunization offer, policies, and programs between different regions.
- 2. Context:** this section presents the political context in which the 2012-2014 PNPV is grounded; in particular, reference is made to key legal acts and policy documents that preceded the 2012-2014 PNPV and channelled the dialogue between state and regions on prevention.
- 3. The 2012-2014 objectives:** this section outlines the PNPV's general aim and specific objectives (which are presented in detail in the results section).
- 4. Guidelines on how to overcome regional and local differences:** in this section three tools are identified as effective to overcome regional and local differences in immunization program offer, quality standards, and performance: **i)** yearly monitoring of the core benefit package of health services (LEA), **ii)** commitment to meet the 2012-14 PNPV objectives at the regional level, and **iii)** the "solidarity between regions" instrument in its different forms.
- 5. Going beyond compulsory immunization – the conceptual framework:** in this section preliminary arguments are provided regarding legal and administrative pathways, as well as the criteria and requirements needed to go beyond compulsory immunization at the national level (already in place in one Italian region, Veneto).
- 6. Guidelines on how to introduce new vaccines in national and regional immunization schedules:** this section outlines the criteria of efficacy, safety, economic sustainability, and public health prioritization that are needed to support the introduction of new vaccines in the national and regional immunization schedules.
- 7. Guidelines on how to monitor and evaluate immunization programs:** this section presents the main items and associated indicators to be adopted by regions and local health units to monitor and evaluate immunization programs in terms of adequacy, effectiveness, and efficiency.
- 8. National immunization schedule:** this section lists the immunization programs to be actively offered free of charge to the general population in all regions as part of the LEAs and compiled in the National Immunization Schedule (NIS, [table 1](#)).
- 9. Immunization programs for high-risk subjects:** this section details the immunization programs for high-risk subjects, by vaccine and high-risk subgroup.
- 10. Immunization programs for healthcare professionals:** this section details the immunization programs for healthcare professionals.
- 11. Recommendations for PNPV-implementing technical guidance documents:** this section provides a list of PNPV-implementing technical guidance documents to be issued.

Vaccine	Birth	3 rd month	5 th month	6 th month	11 th month	13 th month	15 th month	5-6 years	11-18 years	>65 years	every 10 years
DTaP ^a		DTaP ^a	DTaP ^a	DTaP ^a	DTaP ^a	DTaP ^a	DTaP ^a	DTaP ^{a1}	Tdap ^d		Td ^{h2}
IPV ^b		IPV ^b	IPV ^b	IPV ^b	IPV ^b	IPV ^b			IPV ^b		
hepatitis B	hepatitis B ³	hepatitis B	hepatitis B	hepatitis B	hepatitis B	hepatitis B					
Hib ^c		Hib ^c	Hib ^c	Hib ^c	Hib ^c	Hib ^c					
MMR ^e							MMR ^e	MMR ^e	MMR ^{e4}		
PCV ^f		PCV ^f	PCV ^f	PCV ^f	PCV ^f	PCV ^f					
Men-C ^g							Men-C ^{g5}		Men-C ^{g5}		
HPV									HPV ⁶ (3 doses)		
influenza										influenza	
varicella									varicella ⁷ (2 doses)		

¹ For children older than 7 years the formulation with diphtheria, tetanus, and acellular pertussis vaccine for adolescents/adults (Tdap) needs to be used.
² Adults with unknown vaccine history need to complete a three dose schedule (Td-Td-Tdap), with the second dose after 4 weeks and the third after 6/12 months. After that, a booster shot every ten years is recommended.
³ For children born from HBsAg positive mothers. It has a four-dose schedule: first dose within the first 12-24 hours of life concurrently with specific hepatitis B immunoglobulins, second dose after 4 weeks, third dose after the 8th week of life, fourth between the 11th and the 12th month of life – even in combination with other vaccinations.
⁴ In case of outbreaks, in addition to catch-up strategies for 11-18 years old subjects, active immunization for susceptible unvaccinated contacts is recommended (mop up strategy).
⁵ Men-C immunization has a one-dose schedule. Administration at 11-18 years old should be considered only in subjects not vaccinated during childhood.
⁶ For 12 year-old girls. Three-dose schedule: at 0, 1 and 6 months for bivalent vaccine (against HPV genotypes 16 and 18) and at 0, 2 and 6 month for quadrivalent vaccine (against HPV genotypes 6, 11, 16, and 18).
⁷ In subjects unvaccinated or with negative history for varicella a two-dose schedule is recommended, with the second dose administered after one month.

^a diphtheria, tetanus, and acellular pertussis vaccine ^b inactivated polio vaccine ^c *Haemophilus influenzae* type b vaccine ^d diphtheria, tetanus, and acellular pertussis vaccine for adolescents/adults
^e measles, mumps, and rubella ^f pneumococcal conjugate vaccine ^g meningococcal C conjugate vaccine ^h diphtheria and tetanus vaccine

Table 1. 2012-2014 PNPV National Immunization Schedule (NIS) actively offered to the general population (translated and adapted from ref. 9).

Tabella 1. Calendario nazionale delle vaccinazioni offerte attivamente a tutta la popolazione contenuto nel PNPV 2012-2014.

- all available, updated regional immunization prevention plans and schedules adopted in the 19 Italian regions and two autonomous provinces.

For all documents, references to the original documents is provided.

Immunization coverage rates in Italy

Immunization for infants

At the national level, polio vaccine coverage in 2014 was 94.7%, the same as for diphtheria. Tetanus vaccine coverage was 94.8%, hepatitis B and pertussis vaccines coverages were 94.6% and Hib vaccine coverage was 94.2%; none of the vaccines reached the 95% coverage target set by the PNPV (figure 1A-F).

At the regional level, 11 regions met the 95% PNPV coverage target for tetanus, 10 regions met the 95% PNPV coverage target for polio and diphtheria, and 9 regions met the 95% PNPV coverage target for hepatitis B and Hib. Regional vaccine coverage ranged from 88% (in particular: 88.5% for polio and tetanus vaccines, 88.4% for diphtheria and pertussis vaccines, 88.0% for hepatitis B vaccine, and 88.7% for Hib vaccine) to 98.8% (figure 1A-F).

In the 2012-2014 period (from PNPV approval in 2012 until the most recent data available) national vaccine coverage decreased for all the above-mentioned immunization programs (figure 2A-C); the percentage decrease was highest for the hepatitis B vaccine (-1.7%) and lowest for Hib (-1.0%). The 2012-2014 percentage change in vaccine coverage at the regional level is reported in Appendix 3A-F (see supplementary material online): for all six vaccines, we report decreasing trends in almost all regions.

When considering the entire 2000-2014 study period, polio vaccine coverage decreased by 2%, diphtheria vaccine coverage by 0.7%, and tetanus vaccine coverage by 0.6%. On the contrary, pertussis vaccine coverage increased by 8.4%, hepatitis B vaccine by 0.5%, and Hib vaccine by 72% (please note that the latter was first introduced into the routine immunization programs in 1999). Figures by region are reported in Appendix 4A-F (available online).

Measles, mumps, and rubella vaccine coverage in Italy in 2014 was 86.6% (figure 1G-I). None of the regions met the 95% coverage target rates set in the PNPV; all but two Regions reached coverage rates greater than 80% for the three vaccines, regional-level range being 68.8% to 90%.

In the 2012-2014 study period, measles vaccine coverage in Italy decreased by 3.7%, with decreasing trends reported in all but one region. In 11 regions, the percentage decrease was greater than 5% (Appendix 3G-I, available online). A similar pattern was observed for mumps and rubella vaccine coverage, for which national level coverage rates decreased by 3% and 2.9% from 2012, with decreasing trends in all but one region, and a percentage decrease that was greater than 5% in 10 regions.

For the measles, mumps, and rubella vaccines altogether, coverage increased as compared to 2000: +16.8% for mumps and rubella and +12.7% for measles (2001-2014). Regional percentage changes in vaccine coverage between 2000 and 2014 are presented in Appendix 4G-I (available online).

Pneumococcal conjugate vaccine coverage at the national level was 87.3% in 2014. Only one region (Basilicata) met the 95% PNPV coverage rate target, nine regions reported coverage rates greater than 90% while – on the other extreme – two regions reported coverage rates lower than 80%. The overall regional range in 2014 was 76.6% to 98.5% (figure 1L).

Overall, pneumococcal conjugate vaccine coverage in Italy decreased by 0.4% in the 2012-2014 study period. Regional patterns are reported in Appendix 5A (available online). Two regions reported opposite peak percentage changes between 2012 and 2014: +68.5% in Abruzzo and -29% in Sardinia. Data on coverage rates earlier than 2012 are scant: they are only available from 2007 and for few regions (Appendix 5B, available online): six regions reported an increase in vaccine coverage greater than 100% since 2007.

Meningococcal C conjugate vaccine coverage rates are only available for the years 2013 and 2014: the most recent figures report an overall national vaccine coverage of 74.9%. No region met the PNPV's 95% coverage target, nine regions reported vaccine coverage rates exceeding 80%, with a regional

Vaccine	Target population	Coverage target
DTaP ^a , IPV ^b , hepatitis B, Hib ^c	newborns	≥95% completed courses (3 doses)
Tdap ^d	adolescents (age range: 11-18 years)	≥90% (1 dose)
MMR ^e	within 2 years of age	≥95% (1 dose)
MMR ^e	age groups: 4-5 and 11-18 years	≥95% (2 doses)
influenza	age group: >65 years	≥75% (minimum) ≥95% (optimal)
PCV ^f	newborns	≥95% completed courses (1, 2, or 3 doses, based on age)
Men-C ^g	newborns and adolescents (age range: 11-18 years)	≥95% completed courses (1, 2, or 3 doses, based on age)
HPV	age group: 12-year-old girls	≥70% completed courses (from 2001 birth cohort) ≥80% completed courses (from 2002 birth cohort) ≥95% completed courses (from 2003 birth cohort)
rubella	child-bearing age women	≤5% of susceptible women

^a diphtheria, tetanus, and acellular pertussis vaccine
^b inactivated polio vaccine
^c *Haemophilus influenzae* type b vaccine
^d diphtheria, tetanus, and acellular pertussis vaccine for adolescents/adults
^e measles, mumps, and rubella
^f pneumococcal conjugate vaccine
^g meningococcal C conjugate vaccine

Table 2. Immunization program's vaccine coverage; targets set in the 2012-2014 PNPV. / Tabella 2. Target di copertura vaccinale stabiliti nel PNPV 2012-2014

range comprised between 42.7% (Campania) and 88.3% (Emilia-Romagna) (figure 1M).

Varicella immunization coverage rates are reported for the year 2014 in the regions that piloted varicella universal immunization program¹³ and are shown in figure 3. They vary between 51.1% in Calabria and 84.2% in Veneto. Detailed data on varicella immunization programs in selected regions since its introduction are provided by the Interregional Group on Varicella Vaccination (IGVV).¹³

Immunization for adolescents

Figure 4 reports national HPV vaccine coverage rates by birth cohort, as reported in the most recent 2014 update of the National Institute of Health.¹⁴ At the national level, coverage rates for completed courses in 11-year old girls were 70.8% for the 1997 birth cohort, 70.9% for the 1998 birth cohort, 72.1% for the 1999 birth cohort, and 71.1% for the 2000 birth cohort. Coverage rates by region are reported in Appendix 6A-D (available online). Data for “at least one administered dose” by region are also available by birth cohort for the same study period and show similar patterns over time (Appendix 7A-F, available online). On average, 4% of girls did not complete the whole HPV immunization course. Regional data show large heterogeneity, with completed vaccine courses of 27%-86% in the 1997 birth cohort, 27%-84% in the 1998 birth cohort, 28%-82% in the 1999 birth cohort, and 31%-82% in the 2000 birth cohort.

For the 2001 and 2002 birth cohorts – for which the offer has not yet been completed in all regions – overall coverage rates were 67% and 52.4%, respectively. However, data from the two latter birth cohorts cannot be considered definitive. The 70% PNPV coverage rate target for the 2001 birth cohort was met in 9 regions, while no region has yet met the 80% coverage target for the 2002 birth cohort (Appendix 6E-F, available online).

Immunization for the elderly

In the last (2014-15) influenza season, national influenza vaccine coverage in subjects aged ≥ 65 was 48.6% – the lowest reported since the 2000-2001 season (figure 5A).

At the regional level, vaccination coverage equal or exceeding 50% was reported in six regions, but no region met the minimum (75%) or optimal (95%) coverage targets set in the 2012-2014 PNPV. The highest rates were reported in Umbria (61.8%) and Veneto (53.4%), the lowest in the autonomous province of Bolzano (36.6%) and in Abruzzo (38.5%).

Although we report an overall 17% increase in vaccine coverage as compared to the 1999-2000 influenza season (figure 5B and Appendix 8B), since 2011-2012, influenza vaccine coverage in Italy has decreased by 22% (Appendix 8A). The decreasing trend observed at the national level is consistently mirrored in all regions, with reductions exceeding 25% in 7 regions.

DISCUSSION

Overall, the 2012-2014 PNPV has been a milestone for prevention in the Italian health policy agenda for a number of reasons:

- in the ongoing epidemiologic transition and changing demographic structure, it introduced for the first time at the institutional level a “lifecourse” approach to vaccination;
- it provided technical guidance for regions to prepare and implement regional immunization plans;
- it provided ground for fruitful debate and consultation between the Ministry of Health, its technical agencies, and others stakeholders;
- it raised awareness about the need to harmonize immunization policies across the country, and, more importantly:
- it greatly contributed to disseminate the culture of immunization among national and local health authorities, as well as the general public.

Three and a half years after the adoption of the 2012-2014 PNPV we present a comprehensive overview of vaccine coverage rates in Italy, focusing on infant, adolescent, and adult immunization programs included in the National Immunization Schedule. Overall, in Italy, apart from a few exceptions, coverage rates have been decreasing since 2012 and, to date, are still below the targets established in the Plan. We report a high degree of heterogeneity between the various Italian regions and vaccines.

With regard to infant immunization (polio, TDP, hepatitis B and Hib), nearly one third of Italian regions reached the 95% coverage target set in the Plan. However, in other regions, coverage remained under 90% for compulsory vaccines. The recent decreasing trends reported at the national level are mirrored in virtually all regions. Scant data are available on the two vaccines included in the National Immunization Schedule for the first time in 2012: the pneumococcal and meningococcal C conjugate vaccines. Preliminary data suggest that – although far from meeting PNPV targets – both vaccines were well introduced in infant immunization schedules, reaching, respectively, over 87% and 74% coverage at the national level. In addition, promising trends are reported for the conjugate pneumococcal vaccine.¹⁵ Its coverage rates have increased since 2007 in all regions for which we have data. HPV vaccine coverage is below the target but has been increasing for all birth cohorts invited so far, showing a relatively successful catching up of unvaccinated girls. Influenza vaccine uptake is low in the elderly and has been decreasing over the last years, with a dramatic decreasing peak reported in the last flu season, likely to be associated to the «Fluad case».¹⁶

We systematically recorded PNPV transpositions at the regional level and referenced all available Regional Immunization Prevention Programs and Plans. As emerges from the data, the immunization offer varies widely across the country. As new evidence accumulates in the field of vaccination and new vaccines are made available – in a context of a decentralized health system – regions are implementing different immunization strategies. For example, some regions extended HPV vaccine offer to other age cohorts (7 regions offer HPV vaccine to two age cohorts and 1 offers it to four age cohorts); since 2015, five Italian regions have extended active offer of the HPV vaccine to males.^{14,17} With regard to the pneumococcal conjugate vaccine, three Italian regions offer it to all subjects older than 65

Figure 1 (A-M)

Immunization coverage rates for infant vaccines scheduled in the National Immunization Schedule. 2014 updated data by region and at the national level.

Notes: Sardegna - data not available.

Legend: *average.

Figura 1 (A-M)

Coperture vaccinali per le vaccinazioni pediatriche offerte attivamente a tutta la popolazione (PNPV 2012-2014). Dati aggiornati al 2014 per regione e a livello nazionale.

Note: Sardegna - dati non pervenuti.

Legenda: *media nazionale.

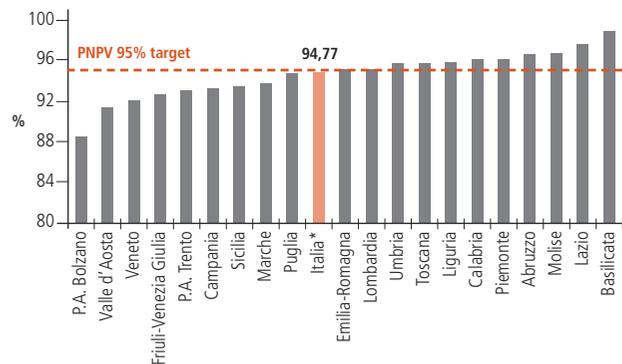


Figure 1C. Tetanus

Diphtheria and tetanus vaccine (DT) + diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage at 24 months for completed courses (three doses).

Figura 1C. Tetano

Coperture vaccinali al 24° mese per vaccini difterite-tetano (DT) + difterite-tetano-pertosse acellulare (DTPa) - ciclo di base completo (3 dosi).



Figure 1A. Poliomyelitis

Inactivated polio vaccine (IPV) coverage at 24 months for completed courses (three doses).

Figura 1A. Poliomielite

Coperture vaccinali al 24° mese per vaccino antipolio inattivato (IPV) - ciclo di base completo (3 dosi).



Figure 1D. Pertussis

Diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage at 24 months for completed courses (three doses).

Figura 1D. Pertosse

Coperture vaccinali al 24° mese per vaccino difterite-tetano-pertosse acellulare (DTPa) - ciclo di base completo (3 dosi).



Figure 1B. Diphtheria

Diphtheria and tetanus vaccine (DT) + diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage at 24 months for completed courses (three doses).

Figura 1B. Difterite

Coperture vaccinali al 24° mese per vaccini difterite-tetano (DT) + difterite-tetano-pertosse acellulare (DTPa) - ciclo di base completo (3 dosi).



Figure 1E. Hepatitis B

Hepatitis B vaccine (HepB) coverage at 24 months for completed courses (three doses).

Figura 1E. Epatite B

Coperture vaccinali al 24° mese per vaccino anti-epatite B (HepB) - ciclo di base completo (3 dosi).



Figure 1F. Haemophilus influenzae type B (Hib) disease

Haemophilus influenzae type b (Hib) coverage at 24 months for completed courses (1, 2 or three doses, based on age).

Figura 1F. Patologia da Haemophilus influenzae tipo B

Coperture vaccinali al 24° mese per vaccino anti-Haemophilus influenzae tipo B (Hib) - ciclo di base di 1, 2 o 3 dosi secondo l'età.

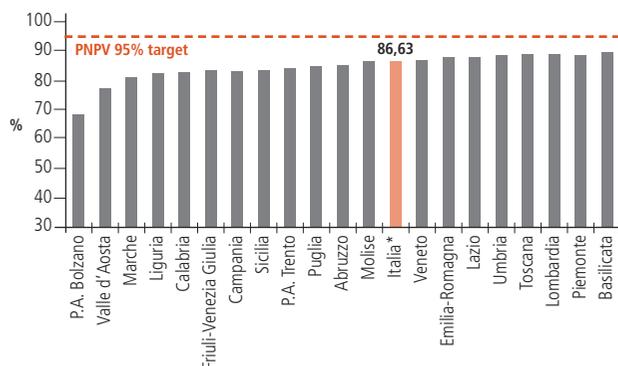


Figure 1I. Measles

Measles (M) vaccine + measles, mumps, and rubella vaccine / measles, mumps, rubella, and varicella vaccine coverage at 24 months - first dose (M-MMR / M-MMRV).

Figura 1I. Morbillo

Coperture vaccinali al 24° mese per vaccini anti-morbillo + anti-morbillo-parotite-rosolia / morbillo-parotite-rosolia-varicella (M-MPR / M-MPRV) - prima dose.

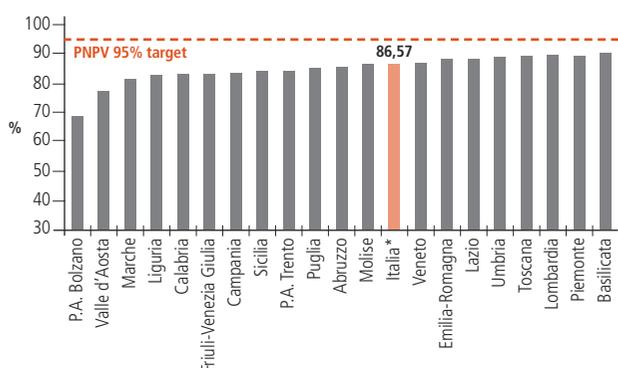


Figure 1G. Mumps

Measles, mumps, and rubella vaccine / measles, mumps, rubella, and varicella vaccine coverage at 24 months - first dose (MMR/MMRV).

Figura 1G. Parotite

Coperture vaccinali al 24° mese per vaccino anti-morbillo-parotite-rosolia / morbillo-parotite-rosolia-varicella (MPR/MPRV) - prima dose.

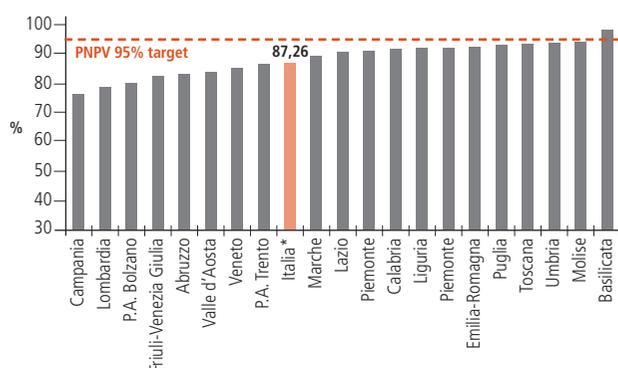


Figure 1L. Pneumococcal disease

Pneumococcal conjugate vaccine coverage at 24 months (birth cohort: 2012) for completed courses (1, 2, or 3 doses, based on age).

Figura 1L. Patologia pneumococcica

Coperture vaccinali al 24° mese per vaccino anti-pneumococco coniugato - ciclo di base di 1, 2 o 3 dosi secondo l'età.

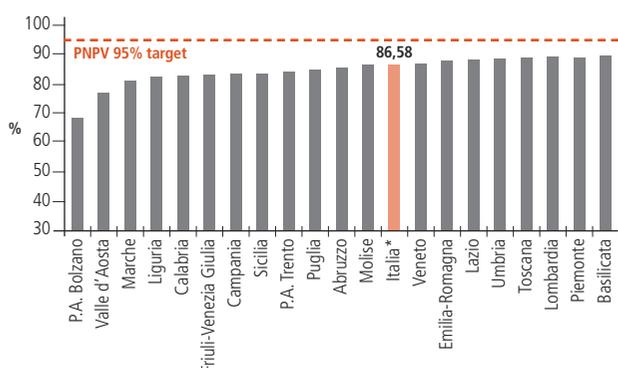


Figure 1H. Rubella

Measles, mumps, and rubella vaccine / measles, mumps, rubella, and varicella vaccine coverage at 24 months - first dose (MMR/MMRV).

Figura 1H. Rosolia

Coperture vaccinali al 24° mese per vaccino anti-morbillo-parotite-rosolia / morbillo-parotite-rosolia-varicella (MPR/MPRV) - prima dose.

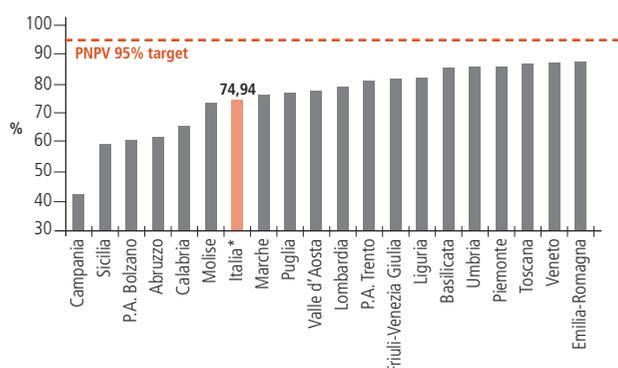


Figure 1M. Meningococcal disease

Meningococcal C conjugate vaccine (Men-C) coverage at 24 months (birth cohort: 2012) for completed courses (1, 2, or 3 doses, based on age) [data not available for Lazio].

Figura 1M. Patologia meningococcica

Coperture vaccinali al 24° mese per vaccino anti-meningococco C coniugato (Men-C) - ciclo di base di 1, 2 o 3 dosi secondo l'età [dati non pervenuti per il Lazio].

Figure 2 (A-C)
Immunization coverage rates over time for selected vaccines(2000-2014).

Figure 2 (A-C)
Coperture vaccinali: trend temporali per alcuni vaccini (2000-2014).

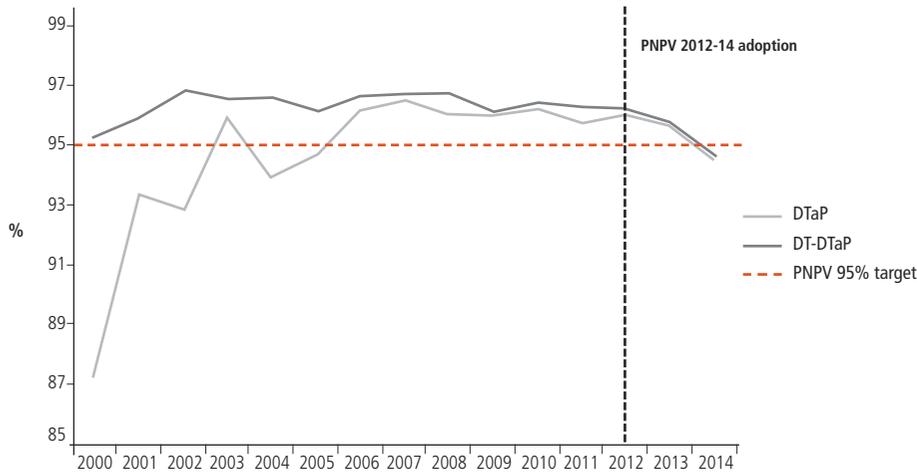


Figure 2A.
Diphtheria - Tetanus - Pertussis
Diphtheria and tetanus vaccine (DT) + diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage at 24 months for completed courses (three doses).

Figura 2A.
Difterite - Tetano - Pertosse
Coperture vaccinali al 24° mese per vaccini difterite-tetano (DT) + difterite-tetano-pertosse acellulare (DTPa) - ciclo di base completo (3 dosi).

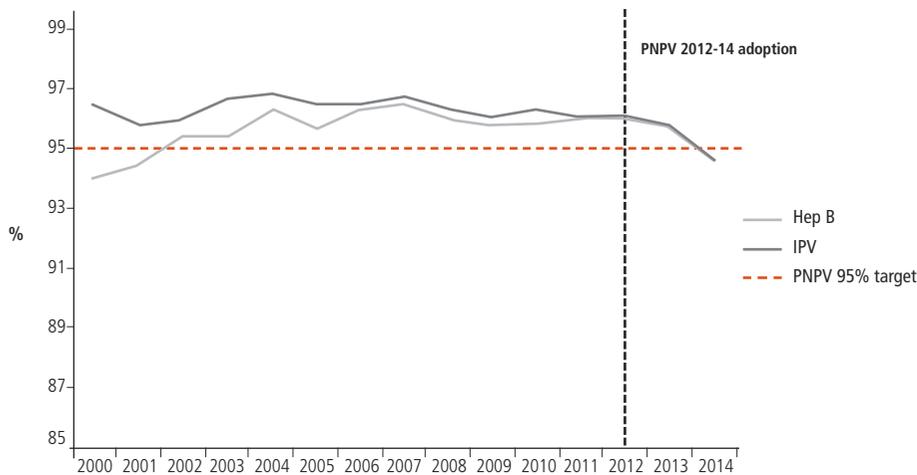


Figure 2B.
Poliomyelitis - Hepatitis B
Inactivated Polio vaccine (IPV) and hepatitis B vaccine (HepB) coverage at 24 months for completed courses (three doses).

Figura 2B.
Poliomielite - Epatite B
Coperture vaccinali al 24° mese per vaccini antipolio inattivato (IPV) e anti-epatite B (Hep B) - ciclo di base completo (3 dosi).

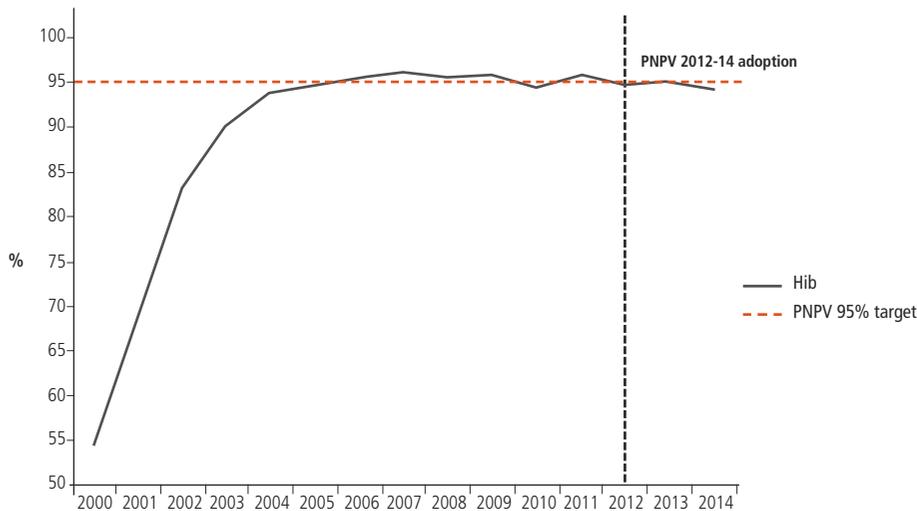
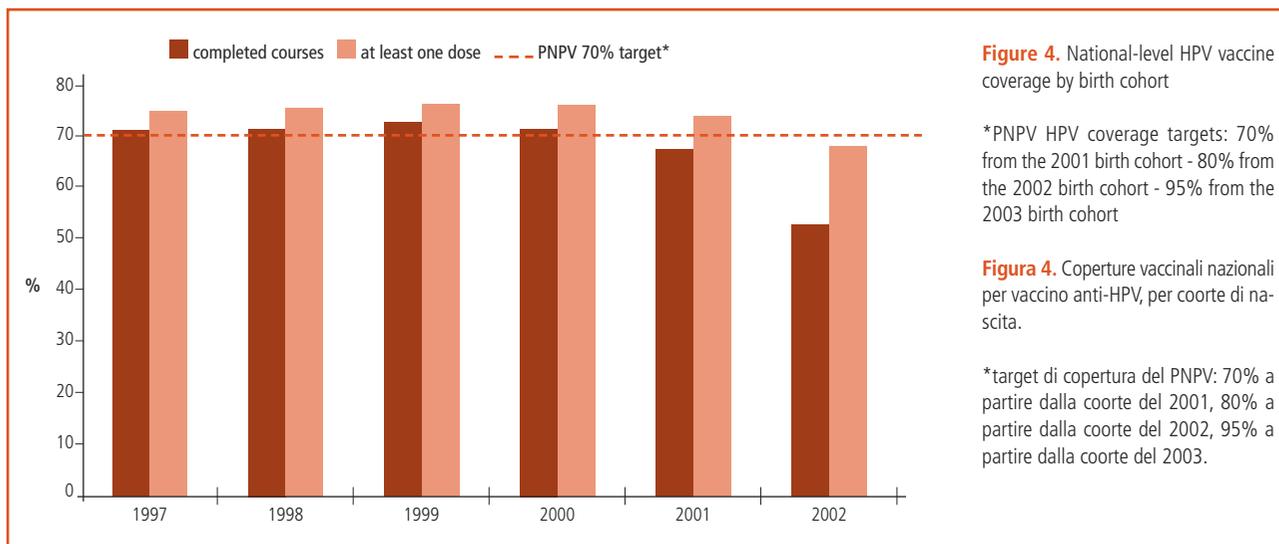
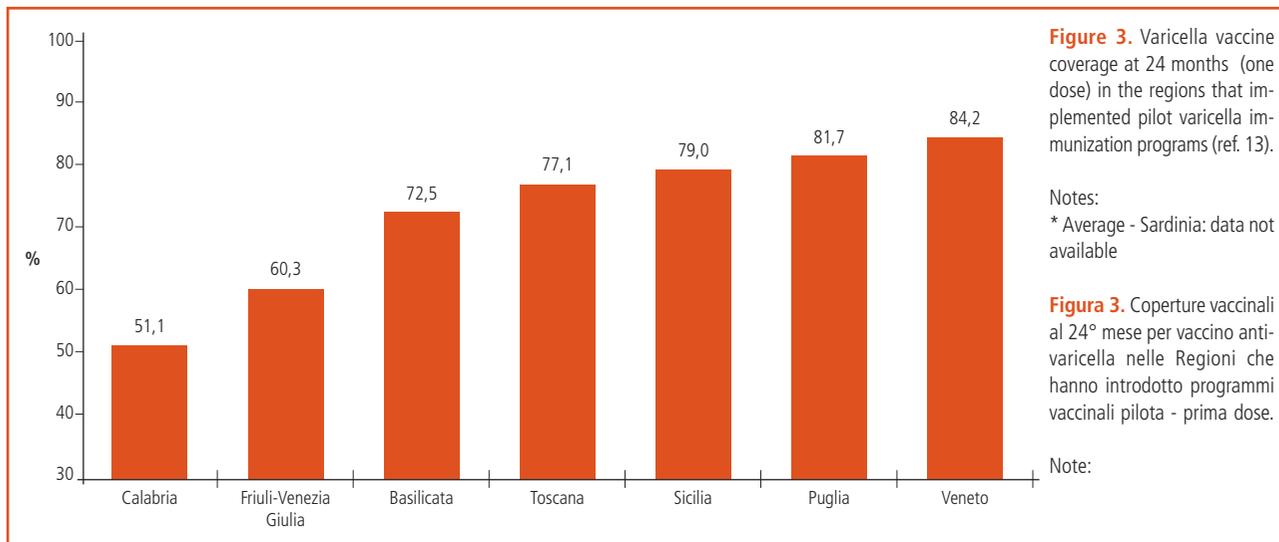


Figure 2C.
Haemophilus influenzae type B (Hib) disease
Haemophilus influenzae type B (Hib) coverage at 24 months for completed courses (1, 2, or 3 doses, based on age)

Figura 2C.
Patologia da Haemophilus influenzae tipo B
Coperture vaccinali al 24° mese per vaccino anti-*Haemophilus influenzae* tipo B (Hib) - ciclo di base di 1, 2 o 3 dosi secondo l'età.



years, others to selected older birth cohorts, others only to at-risk subgroups. Since serogroup B meningococcal (Men B) vaccine was licensed in Europe and became available in Italy, eight Italian regions and one autonomous province have introduced it in their regional immunization schedules for children under one year of age.¹⁸ Furthermore, over the past few years, eight regions have implemented a two-dose schedule varicella immunization program; preliminary vaccine coverage data over time are available and will inform the introduction of universal varicella vaccination at the national scale.¹³ It is worth underscoring that the wide variability of coverage among regions is not a new phenomenon and has historical reasons, such as dissimilar organizational models in the offer of vaccinations by Local Health Units, different attention and commitments from politicians and decision-makers at the local level, different vaccine culture in the population. In any case, there is no doubt that the decreasing coverage for several vaccines reflects an international trend recorded in the past few years and is mainly due to what is known as «vaccine hesitancy». A more complete, comprehensive vaccination of-

fer does not hamper the attainment of coverage targets for other vaccines, rather it could convey a stronger message of trust in active immunization. Such consideration is supported by data on measles and rubella coverage rates in regions that already introduced a universal varicella vaccination program compared to regions who did not. The 4 regions with the lowest MMR coverage in 2014 were not in the pilot group of universal varicella vaccine implementers. Three out of the 8 pilot regions have MMR coverage rates higher than the national average, an additional 4 were only slightly under the national average (data for Sardinia not available). Furthermore, among the 5 regions that registered the worse percent decrease in coverage for MMR in the last 3 years, only one (Puglia) offered universal varicella vaccination between 2012 and 2014. In other words, MMR coverage rates and trends are not negatively influenced by a simultaneous offer of universal varicella vaccination. Our study has a number of limitations. First, more data would have been useful to further explore immunization coverage rates in Italy: whereas certain vaccine coverage rates are routinely collected by the Ministry of Health for other vaccines,

Figure 5. Influenza immunization coverage rates in subjects aged ≥ 65 years by region and at the national level.

Figura 5. Coperture vaccinali per vaccino antinfluenzale nei soggetti ≥ 65 anni, per Regione e a livello nazionale.

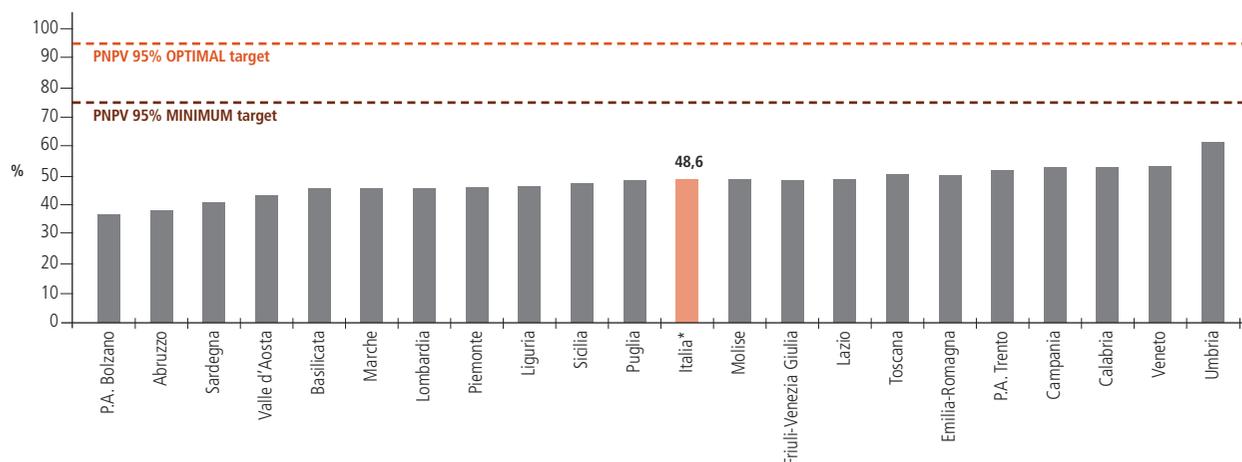


Figure 5A. Influenza vaccine coverage by region for flu seasons 2014-2015.

Figura 5A. Coperture vaccinali per la stagione influenzale 2014-2015, per Regione.

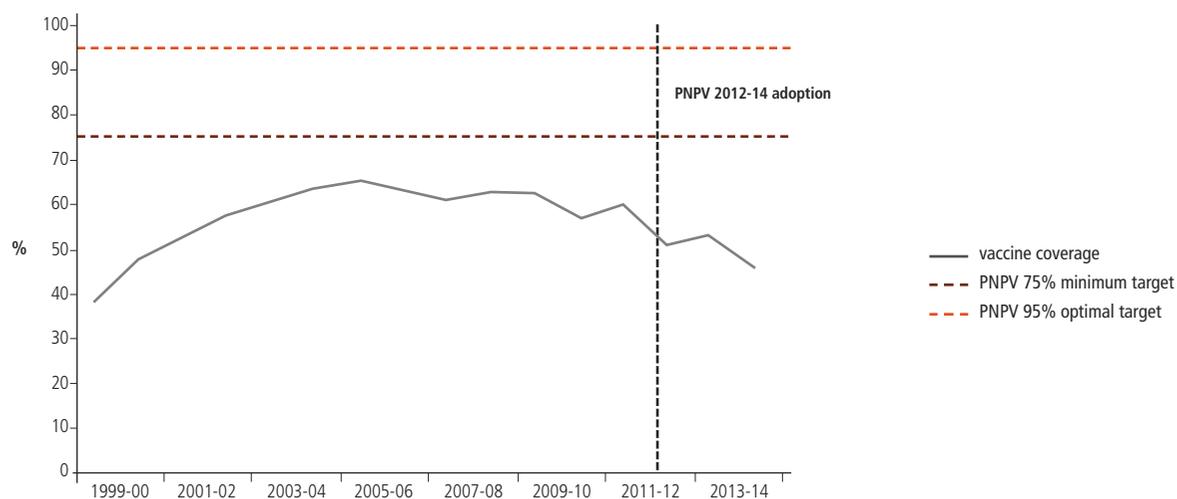


Figure 5B. National-level influenza vaccine coverage over time (from 1999-2000 to 2014-2015).

Figura 5B. Coperture vaccinali nazionali: trend temporali (stagioni influenzali da 1999-2000 a 2014-2015).

namely the pneumococcal, meningococcal, and varicella vaccines, no routine coverage surveillance system has been in place in recent years and coverage data are only collected in *ad hoc* projects.¹⁹ Pneumococcal and meningococcal vaccines routine coverage started in 2014. Influenza immunization data are collected and transmitted to the ministerial level mostly by general practitioners while HPV data were routinely collected by ISS and, as stated in the Ministerial Circular of 24 April 2014, will be routinely collected by Ministry of Health starting from 2015.¹⁴ In addition, the data we presented did not allow us to distinguish between different available

conjugate meningococcal, conjugate pneumococcal, and HPV vaccines or between two- and three-dose HPV vaccine schedules. Last but not least, the available data are not sufficient to monitor all the PNPV coverage targets and objectives. Another limitation is our descriptive approach. Although we acknowledge that accounting in our analysis for environmental factors that might have an impact on vaccine uptake over time and in different regions in an analytic approach might have provided us with elements that would help us understand how vaccine coverage could be increased, that was not the aim of this study. Our objective was to describe immunization

coverage rates in Italy in a comprehensive, transparent way, and assess whether PNPV objectives have been met.

Finally, we did not present the VPD burden in terms of notifications and hospitalization, nor did we speculate on the extent to which the VPD burden was prevented through immunization – the most important indicators to assess immunization program effectiveness – as this would have broadened the scope of our work too much. Further studies will explore these issues in depth.

CONCLUSION

Overall, the 2012-2014 PNPV objectives have been only partially met. We have already discussed the coverage target goals. With regard to the other PNPV objectives, a great deal still needs to be done to improve surveillance systems and serotyping capacity, link VPD notifications and immunization coverage data with other administrative data flows, and implement immunization information systems across the country. Of crucial importance, in times where vaccines are losing public confidence and the World Health Organization warns against the growing phenomenon of vaccine hesitancy,²⁰ renewed efforts should be devoted to plan and implement effective information and communication interventions to promote immunization among healthcare professionals and increase the demand for immunization in the general population. In particular, the potential offered by information and communica-

tion technologies and new media should be leveraged by institutions and the public health community to inform and educate the general public on the benefits of vaccination.²¹⁻²⁵ This is no time to decrease our preventive efforts, but rather to rekindle trust in all immunizations of proven efficacy, effectiveness, and public health impact.

The new National Immunization Prevention Plan is about to be launched. It has been drafted in consultation with representatives of several scientific societies. In particular, the “lifetime immunization schedule” recommended by the Italian Society of Hygiene, Preventive Medicine, and Public Health (SItI), the Italian Society of Paediatrics (SIP), the Italian Federation of Paediatricians (FIMP), and the Italian Federation of General Practitioners (FIMMG) constituted a solid basis for discussion.²⁶ Taking into consideration the most recent scientific evidence available, the new National Immunization Schedule will include new vaccines of proven efficacy and extend vaccine offer to additional target populations. Several lessons have been learned in the last three and a half years, and the data we presented and the findings we derived have greatly informed the definition of the new Plan’s objectives and strategies. As we praise the work done so far to strengthen and harmonize immunization policies in Italy, we need to roll up our sleeves and prepare for the work ahead.

Conflicts of interest: none declared

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