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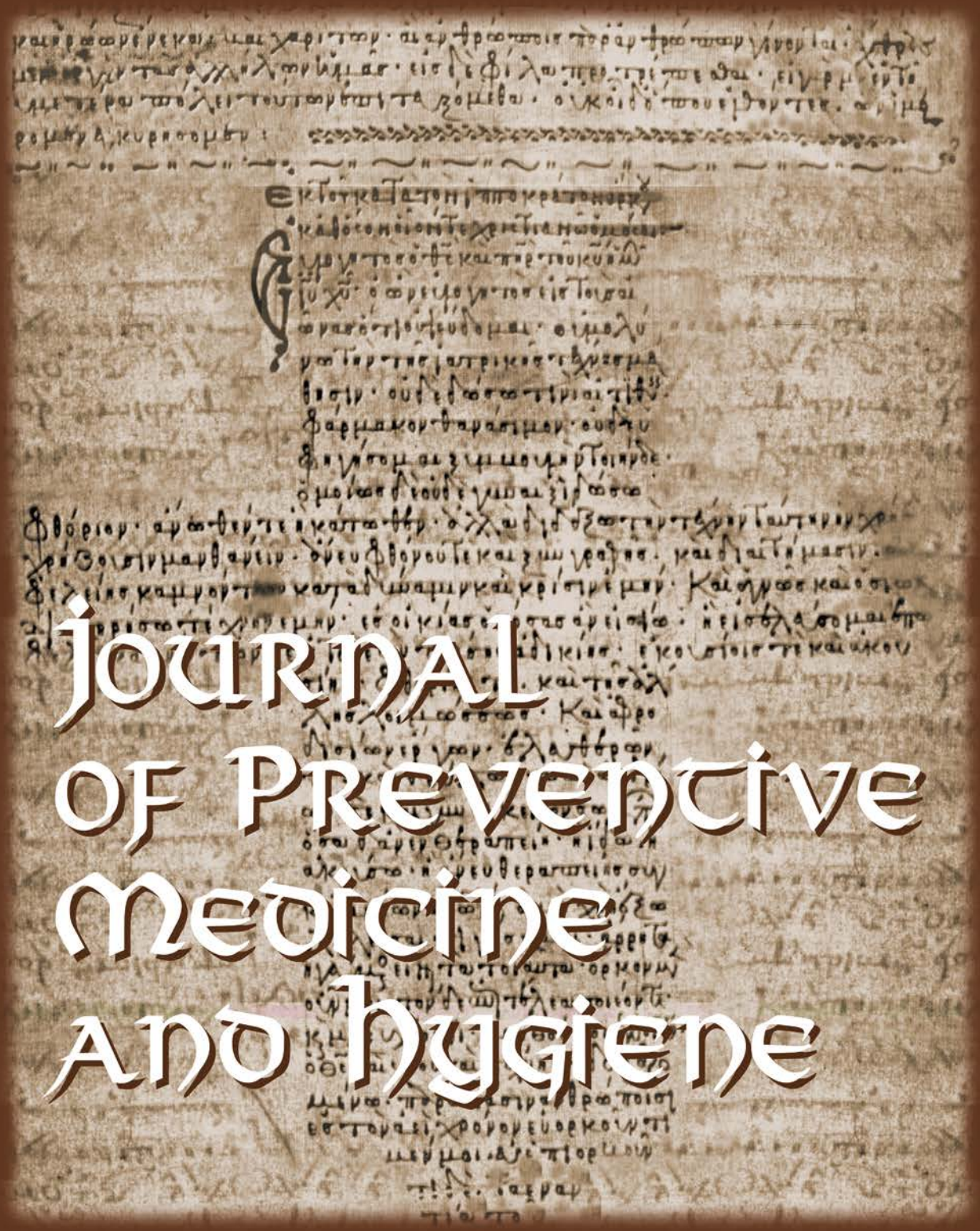

The original document of Hippocrates' oath

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CONTENTS

Influenza vaccination: from epidemiological aspects and advances in research to dissent and vaccination policies

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Keywords

Influenza • Influenza vaccine • Dissent

Summary

Influenza is a serious public health problem, since seasonal epidemics affect approximately 5-10% of the population and thus give rise to a heavy social and healthcare burden. The heavy burden of disease is due to several factors, one of which is the biological features of the pathogen. Indeed influenza viruses display high mutation rates and undergo frequent genetic reassortment. Minor variations cause seasonal epidemics and major variations, which result from the hybridization of viruses typical of different animal species, can lead to pandemics.

Vaccination remains the most efficacious means of mitigating the harmful healthcare and social effects of influenza. Influenza vaccines have evolved over time in order to offer broader protection against circulating strains. Trivalent vaccines containing two A viruses and one B virus are currently available. However, given the co-circulation of both B virus lineages (B/Yamagata and B/Victoria), quadrivalent vaccines have recently been developed. The new quadrivalent vaccines constitute a great advance, in that they can offer broader strain coverage.

Despite the availability of effective and safe influenza vaccines, the Italian public's trust in vaccination has declined and, in the last few years, influenza vaccination coverage rates have decreased both among the elderly and among at-risk adults. It is therefore necessary that users, in their own interests, regain trust in this important means of disease prevention.

In order to mitigate the damage wreaked by influenza, it seems important to: (i) improve clinical-epidemiological and virological surveillance of the disease; (ii) promote the development of new efficacious vaccines, as has recently been done through the introduction of the quadrivalent vaccine; (iii) extend free vaccination to the entire population, as in the US and Canada; (iv) ensure that general healthcare professionals are properly informed and always updated with regard to vaccination; (v) promote public campaigns to raise the population's awareness of the importance of vaccination; (vi) inform politicians and other decision-makers of scientific results in the field of vaccination; (vii) fight the anti-vaccination lobbies with every available weapon.

Influenza, which is caused by the homonymous virus belonging to the *Orthomyxoviridae* family, is a disease characterized by fever, respiratory and other systemic symptoms. In both the northern and southern hemispheres, the disease occurs annually, during the cold season (seasonal influenza). Periodically – at intervals of 20-30 years – antigenically new viruses may appear and cause a pandemic [1].

Influenza is a serious public health problem, since seasonal epidemics affect approximately 5-10% of the population and thus give rise to a heavy social and healthcare burden. Influenza-related direct costs are very high and mostly linked to severe disease complications and deaths, which are usually observed among at-risk subjects (elderly, subjects with chronic diseases and pregnant women). Moreover, a typical epidemic peak is associated with high rates of absenteeism, which, from the societal point of view, cause a heavy economic burden and hamper public services, especially those offered by the National Health System [1].

The heavy burden of disease is due to several factors, one of which is the biological feature of the pathogen. Indeed, the biology of the influenza virus is complex and conditions the epidemiology of the disease. Three types of virus are known: A, B and C. While types A and C can infect man and many animal species, B viruses almost exclusively infect humans [2]. Under the electron microscope, the virus generally has a roughly spherical shape, from which emerge two glycoproteins (hemagglutinin and neuroaminidase) that are essential to the biology of the virus [3]. Indeed, these enable the virus to adhere to the specific receptors of the cells of the respiratory mucosa and allow the release of the virus that has multiplied inside the cell [4, 5]. Survival of the virus is ensured by the wide variability of its glycoproteins (antigens). Specifically, influenza viruses undergo very frequent point mutations of the genome, which is dispersed in 8 segments of RNA (minor variations). This phenomenon occurs in both A and B viruses, while the genome of A viruses may undergo far more drastic variations (major variations). While minor variations are random, major variations are the result of the hybridization of viruses typical of different animal species (man, swine, birds) [6]. Theoretically, there are 198 possible

combinations of hemagglutinin and neuroaminidase, according to the types of the two known glycoproteins [7]. If, however, minor variations are considered, the number of combinations far exceeds 1 billion. For instance, the virus responsible for the last pandemic, which occurred in 2009/2010, was the result of a quadruple reassortment with two swine virus genes, European and Asian, an avian gene and a human gene [8]. A pandemic usually displays an atypical epidemiological trend (e.g. young adults are particularly affected) [9] and can, according to the pathogenic features of the new virus that causes it, determine even millions of deaths [10, 11].

In the last years of the 20th century and the first years of the 21st, a considerable challenge was posed by the H5N1 virus, which underwent major variations, such as H5N6 and H5N8. Moreover, the possibility currently exists that new subtypes of viruses typical of animals may adapt to humans, as in the case of the H7N9 subtype, which, from March 2013 to April 2015, caused 662 human cases and 262 deaths (lethality: about 40%) [12].

Seasonal influenza generally displays a less severe behavior. Nevertheless, the World Health Organization (WHO) has estimated that the disease causes from 3 to 5 million cases of severe disease and from 250,000 to 500,000 deaths each year, worldwide [13].

Vaccination remains the most efficacious means of mitigating the harmful healthcare and social effects of influenza [14]. Advances in epidemiology, viral genetics, immunology and molecular biology have given a great boost to the preparation of increasingly safe and efficacious vaccines. Thus, influenza vaccines purified by means of chemical methods and containing whole inactivated viruses have given way to split vaccines, subunit vaccines, adjuvated vaccines and live attenuated vaccines [15]. Moreover, the high reliance on supplies of embryonated hen eggs, which are used in traditional vaccine production, has been overcome by the development of vaccines obtained by multiplying the virus in *in vitro* cell cultures [16]. However, notwithstanding the great progress of vaccinology, vaccine efficacy is blunted by the great variability of the pathogen and the need to update vaccine preparations each year in response to the antigen modifications of the virus.

Influenza vaccines have evolved also markedly over time in order to offer broader protection against circulating strains. Indeed, in the early 1960s the vaccine was bivalent, i.e. it contained an H3N2 virus and a B virus; subsequently, trivalent vaccines containing two A viruses and one B virus were developed, and recently, given the co-circulation of both B virus lineages (B/Yamagata and B/Victoria), quadrivalent vaccines were developed.

The recent availability of quadrivalent vaccines constitutes a great advance, in that they can offer broader strain coverage. Indeed, the frequency with which B viruses were isolated by the Italian NIC (National Influenza Center) in the period 2003-2015 ranged from 0.8% to 58.0%, with a mean of 20.5% (95% CI: 0-38%) [17]. Thus, considering that influenza cases in Italy vary on average from 5 to 6 million each year [18], and assuming 38% frequency of B viruses (the upper value of 95% CI) and total B-mismatching, we can suppose that the maximum additional percentage of protection provided by the quadrivalent vaccine may allow us to avoid 2,280.000 cases (at 100% vaccine efficacy; some studies [19, 20] have reported this level of efficacy, albeit rarely) or 1,140.000 cases (50% efficacy). This latter level of efficacy is closer to that reported in most studies. Indeed, a recent meta-analysis conducted by Osterholme revealed mean efficacy levels of 59% in subjects aged between 18 and 65 years, and of 83% in children aged between 6 months and 7 years [21].

Despite the availability of effective and safe influenza vaccines, the Italian public's trust in vaccination has declined. In the last few years, Italian vaccination coverage rates have decreased both among the elderly and among at-risk adults. In the elderly, vaccination coverage declined from 55.6% in the 2013-2014 season to 49.0% in the 2014-2015 season: a fall of 6.6%. However, in comparison with the 2005-2006 season, when coverage was close to 70% (a rate approaching the ideal coverage for subjects aged > 64 years [75%]), the percentage drop was much greater (-21%) [22]. It may plausibly be claimed that one of the reasons for this reduction was poor communication on the part of the Ministry of Health during the pandemic caused by the virus A/California/07/09 [23]; another may have been the excessive prudence of the AIFA, which, for reasons of caution, suspended the use of a commercially available vaccine for two consecutive years [24, 25]. These events were emotively amplified by the press and mass media, and were exploited by anti-vaccination lobbies and consumer associations. As a result, vulnerable subjects were not immunized and were therefore more exposed to the serious complications of the disease. Thus, it is necessary that users, in their own interests, regain trust in this important means of disease prevention. In order to rebuild trust, it must be borne in mind that those who refuse vaccination fall within different categories. Indeed, some oppose vaccination on ideological grounds; some are skeptical of the utility and safety of vaccines; others simply neglect their health, while others again are marginalized individuals. There is also a need to raise awareness among members of the medical profession, since their recommendations are essential to orienting patients towards the right health choices.

Moreover, we cannot ignore the fact that the "anti-vaccinators" hoodwink the gullible with fantastic false accusations that are totally bereft of scientific evidence. Numerous such fallacies have been circulated, such as, for example: "vaccines make women sterile; vaccines shrink the ovaries; vaccines cause testicular cancer; vaccines are contaminated by amoebas present in the air in laboratories; vaccines paralyze the immune system; vaccines cause: Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, transverse myelitis, optical neuritis, diabetes, rheumatoid arthritis, asthma; and so on and so forth. But the greatest of falsehoods spread by the anti-vaccinators is undoubtedly that vaccines cause autism. This lie, which masqueraded as the result of a scientific study, was put about by Dr. Andrew Wake-

field in an article published by the scientific journal The Lancet [26]. It soon emerged, however, not only that Dr. Wakefield had utilized rather unethical para-scientific methods, but also that the results served his own personal interests; he was subsequently struck off the register of British physicians [27]. It is interesting that the anti-vaccinators' claims that vaccines cause neurological or psychiatric disorders are linked in a subtle manner to the "plot hypothesis". Indeed, these people maintain that the plotters (or Illuminated Ones, as they call them) have infiltrated all levels of decision-making in order to foist mass vaccination on the population. The plotters' aims are said to be twofold. First, they want to stultify the majority of the world's people, in order to dominate them more easily, and, at the same time, favor unvaccinated subjects, whose intellectual skills would remain intact as a result of natural selection; second, they want to get rich alongside their industrial allies – the vaccine producers.
The American Institute of Medicine (IOM) has repeatedly demonstrated that there is no scientific evidence to support the much-touted association between vaccines and the above-mentioned diseases [28]. Moreover, in most of the neurological diseases of early onset, the application of molecular biology to neurology is increasingly revealing the importance of transmissible or new-onset genetic disorders, and it has been demonstrated that cases of disease erroneously attributed to vaccination, such as Dravet's syndrome, are actually linked to genetic damage [29].
Vaccination is recognized as one of the most cost-effective in the fight against diseases. However, it is tragic that more than 2½ million children worldwide die each year, despite efficacious and safe vaccines are currently available [30].
In the most advanced countries, such as the USA, vaccination campaigns have always been implemented. However, when a vaccination strategy works well, its results often go unnoticed by the majority of the population. Indeed, only when events occur that threaten public health and arouse mass fears (e.g. measles outbreaks, bioterrorist attacks such as that of the envelopes containing spores of *Bacillus anthracis*, or the threat of biological weapons), does it become clear just how important it is to immunize the population [31]. In Italy, people are now beginning to realize this, in the wake of the various outbreaks of meningococcal invasive disease that have occurred in Tuscany since 2015 [32].
With regard to vaccination policies, it should be pointed out that preventive strategies, despite their great success, have always been an extremely marginal item of expenditure in the Italian National Health Service budget. Indeed, of the total annual expenditure of about € 111 billion, only about € 291 million (0.26%) is spent on vaccination (about € 40 million on influenza vaccines) [33, 34].
In conclusion, in order to mitigate the damage wreaked by influenza, it seems important to strengthen the following interventions:

- improve clinical-epidemiological and virological surveillance of the disease;
- promote the development of new efficacious vaccines, as has recently been done through the introduction of the quadrivalent vaccine;
- extend free vaccination to the entire population, as in the US and Canada [35];
- ensure that general practitioners, pediatricians and other healthcare professionals are properly informed and always updated with regard to vaccination;
- promote public campaigns to raise the population's awareness of the importance of vaccination, not least by using new means of communication such as apps for smartphones and tablets [36, 37];
- inform politicians and other decision-makers of scientific results in the field of vaccination [38];
- fight the anti-vaccination lobbies with such weapons as: counter-information (e.g. what would happen if this or that vaccine had not been invented?), irony, satire, humor, logic, scientific evidence and common sense.

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European decision-maker perspective with regard to influenza prevention policies

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Keywords

Vaccination • Public Health policy • European Union • Epidemiological monitoring

Summary

Influenza is a public health priority in Europe. The impact of influenza pandemics on public health is very high, but seasonal influenza also constitutes an important burden in terms of hospitalisation and excess deaths. Influenza vaccination is a fundamental pillar of disease prevention. In the absence of a clear decision-making process for vaccination policies, EU institutions have, in recent years, fostered collaboration among Member States. Such collaboration was closer during the 2009 pandemic, which constituted a clear cross-border threat to EU citizens' health. The EU institutions have been supporting national vaccination programmes by providing evidence of the effectiveness and safety of influenza vaccination. Decision 1082/2013 was a major step toward EU collaboration, in that it highlighted the role of pandemic vaccination in the field of preparedness and emergency response, in which concerted action is clearly valuable.

Introduction

Influenza prevention is a public health priority worldwide. In Europe, seasonal influenza causes between 4 and 50 million symptomatic cases each year and the death toll associated with influenza is estimated at between 15,000 and 70,000 every influenza season, in terms of excess deaths [1]. The impact of influenza is even greater in the case of pandemics, when large population age-groups – if not the entire population – are immunologically naïve toward the pandemic viral strain. During the 2009 H1N1 pandemic, 2,900 deaths directly related to influenza were reported by the European Union (EU) Member States during the first 12 months [2], but the increase in mortality rates related to the pandemic virus is estimated to be larger. In addition, the high number of cases occurring in a short period of time places a heavy load on the healthcare system during the influenza season.

Preventive measures to limit the spread of influenza include both individual and public health interventions. Frequent hand-washing and correct respiratory hygiene have proved to be effective in preventing respiratory illnesses, including influenza [3, 4]. However, influenza vaccination is still the main tool for preventing the spread of influenza spread and limiting the burden on public health. In the US, routine annual influenza vaccination is recommended for all persons aged ≥ 6 months who do not have contraindications [5]. Recommendations are more limited in the EU, and vary widely among Member States [6].

This paper presents an overview of the European approach to influenza prevention and describes the point of view of European decision-makers regarding both seasonal and pandemic prevention policies.

The EU decision-making process with regard to vaccination policies

In the EU, responsibility for immunisation programmes, including immunisation schedules, their mandatory or voluntary character and their financing, lies with the individual Member States. As clearly stated in art. 168 of the Lisbon Treaty, harmonisation of national laws and regulations in the field of human health promotion is excluded. On the other hand, the same article reads "The Union shall encourage cooperation between the Member States […] and, if necessary, lend support to their action. It shall in particular encourage cooperation between the Member States to improve the complementarity of their health services in cross-border areas" [7]. Definitively, even though decisions on vaccination issues are taken essentially at the national level, there may nevertheless be some room for action at the European level in terms of support and cooperation between national and EU decision-makers.

During the last few years, for the first time since the foundation of the EU, some pieces of legislation have been delivered by EU institutions in the specific area of vaccination programmes. Specifically, in 2011 and 2014, two Council Conclusions were delivered during the Employment, Social Policy, Health and Consumer Affairs Council meeting under, the Hungarian and Italian Presidencies, respectively. These two Council Conclusions both move in the direction of fostering the ef-

forts of EU Member States to strengthen vaccination programmes, thus underlining the great importance and societal value of immunisation [8, 9]. More importantly, in December 2009, a few months after the declaration of the H1N1 pandemic, a recommendation on seasonal influenza vaccination was issued by the Council of the EU [10]. In this recommendation, EU Member States "are encouraged to adopt and implement […] action plans or policies […] aimed at improving seasonal influenza vaccination coverage, with the aim of reaching, as early as possible and preferably by the 2014-2015 winter season, a vaccination coverage rate of 75% for 'older age-groups' and, if possible, for other risk groups […]. Member States are also encouraged to improve vaccination coverage among healthcare workers". Moreover, Member States should draw up specific action plans aimed at monitoring influenza vaccine coverage and investigating the reasons for low adherence to vaccination. Even though Council recommendations are not binding on the Member States, this recommendation on influenza vaccination is nevertheless the first of its kind in the field of vaccines, and demonstrates the great interest of European decision-makers in influenza prevention. Indeed, the seasonal influenza coverage rates reported by EU Member States are widely variable and mostly suboptimal. There is no statutory system for collecting and monitoring adherence to influenza vaccination in the EU. For this reason, a network of experts (VENICE consortium, Vaccine European New Integrated Collaboration Effort) [11] supported by a grant from the European Centre for Disease Prevention and Control (ECDC) started a regular survey in 2006 to collect, among other data, information on influenza vaccine coverage. The results of the VENICE influenza surveys are publicly available at the VENICE website [11]. Two major issues arise from the analysis of vaccine coverage data. Firstly, only in the Netherlands and some parts of the United Kingdom is the target of 75% of vaccination coverage among elderly people reached. Moreover, data are available from 23 Member States only, and not from all influenza seasons. On the other hand, comparison of the available data on vaccination coverage in the general population in 2008-2009 (seasonal) and in 2009-2010 (pandemic), reveals some evidence that, during a pandemic, vaccination levels are very similar to those reached during a normal influenza season. It would appear that the same people who receive seasonal influenza vaccines are reached during pandemic vaccination programmes. Therefore, pandemic influenza vaccination is better implemented where a well-functioning seasonal influenza vaccination programme is already in place. This evidence supports the need to strengthen seasonal influenza vaccination programmes as part of preparedness plans for future pandemics. Pandemic influenza preparedness plans are a clear area of intervention for EU institutions, since an influenza pandemic is a typical cross-border threat [7]. Therefore, in addition to the clear benefits yielded by a strong seasonal influenza vaccination programme, this is a good reason for the EU to support Member States in improving their programmes.

How EU can support national influenza programmes

The EU decision-maker has limited power to influence national vaccination policies. On the other hand, influenza prevention is perceived as a priority at the EU level because of the potential pandemic threat and its subsequent cross-border issues. As a consequence, the role of the EU – also fostered by the 2009 Council Recommendation – has been to support national vaccination programmes by providing evidence of the effectiveness and safety of influenza vaccination. The perceived low effectiveness of influenza vaccines and the fear of alleged adverse events are considered the main obstacles to improving vaccination adherence. Providing national vaccination programme managers with reliable data on post-marketing evaluation of influenza vaccines may constitute an evident added value. To this end, the ECDC has funded the I-MOVE project [12]. Since the 2008-9 influenza season, I-MOVE has provided estimates of vaccine effectiveness that are usually available a few months after the end of the season. Thanks to a standardised protocol and a fairly large number of participating study sites, these estimates have good geographical representativeness [13]. In addition, only as a result of European collaboration can the study population reach a size large enough to yield robust estimates.

As expected, influenza vaccine effectiveness is strongly dependent on the quality of matching between vaccine strains and circulating virus strains. This was particularly evident during the 2009 pandemic, when the only circulating strain was the pandemic one and vaccine effectiveness was particularly high, reaching 78.4% (95% CI 54.4-89.8) in patients aged < 65 years [14]. Definitively, vaccine effectiveness estimates obtained from such collaborative studies can provide good-quality evidence to support communication. A real perception of the effectiveness of influenza vaccines is a prerequisite to communicating the real benefits of influenza vaccination to the public. Indeed, suboptimal effectiveness – during some seasons it may be even lower than 50% – may be negatively perceived at the individual level, even though the impact of the vaccination programme on public health may be considerable in terms of the lowered global burden of disease.

Vaccine safety issues are another potential obstacle to influenza vaccine acceptance. Indeed, vaccines, unlike other drugs and medical interventions, are administered both to healthy subjects and to fragile individuals, such as very young children and elderly people. For this reason, any potential safety issue is usually overestimated and the fear of alleged adverse events following immunisation (AEFI) is the main reason why many people are sceptical towards vaccination. Vaccine safety monitoring is strictly regulated in the EU, with the European Medicine Agency (EMA) playing a crucial role, especially during the pre-marketing phase [15]. On the other hand, monitoring and assessing vaccine safety during the post-marketing phase may present some challenges in the absence of a clear commitment. Responsibility for

post-marketing surveillance is shared between pharmacovigilance authorities and vaccine producers. The basic system of AEFI surveillance is constituted by the statutory pharmacovigilance system – shared with all other drugs – present in all EU Member States and coordinated by the EMA through the Eudravigilance system [16]. This is a routine passive surveillance system, which is good enough to detect clear safety signals, but not sufficiently well designed to support vaccine programme managers who deal with vaccine hesitancy or anti-vaccine lobbies. For this purpose, pre-emptive strategies are needed, and good evidence on alleged adverse events should be rapidly available to vaccine managers.

Post-marketing studies to assess vaccine safety are complex and expensive. EU-wide collaboration in this field is a clear added value, as recently demonstrated after the marketing of A(H1N1) pandemic vaccines. The VAESCO consortium (Vaccine adverse events surveillance and communication) – a consortium of public health institutions sponsored by the ECDC [17] with the purpose of starting a European collaboration in the field of post-marketing vaccine surveillance – assessed the risk of Guillain-Barré syndrome (GBS) by means of a multinational case-control study [18] followed by a prospective self-controlled case series study [19]. The conclusion of both studies was that the risk of GBS was not significantly elevated after influenza A(H1N1) pandemic vaccination; this research was made possible only by EU collaboration, which ensured a population size large enough to achieve the necessary study power [19]. Finally, the valuable role of the EU was clearly shown when an unexpected increase in narcolepsy cases was reported in Finland and Sweden in 2010, after vaccination with Pandemrix® [20]. In that case, too, the EU committed a substantial amount of resources to assessing the narcolepsy signal. The VAESCO consortium conducted an ECDC-sponsored study in six EU Member States, which provided evidence of the association between narcolepsy cases in adolescents and Pandemrix® vaccination [21].

Vaccination as a preparedness measure against cross-border threats

Although the EU institutions cannot make any attempt to harmonise human vaccination practices, they should foster cooperation between Member States with regard to cross-border health threats. The level of cooperation and the limits of EU coordination in this field were recently defined by the Decision of the European Parliament and of the Council N° 1082/2013/EU on serious cross-border threats to health [22]. The Decision, which is binding and is to be implemented at the national level, provides the EU Member States with four benefits: 1) preparedness planning capacity should be reinforced, to ensure that all Member States are adequately prepared in the event of an emerging crisis; 2) risk assessment and management should be improved at the national level, with the support of the EU agencies responsible (ECDC, EMA etc.); 3) a new mechanism for the joint procurement of vaccines and medicines in the event of a health emergency is in place, in order to ensure the provision of emergency vaccine/medications in all Member States; 4) the response at the EU level will be coordinated by the Health Security Committee, which has a solid legal mandate to quickly take decisions in the event of an emergency.

Decision 1082 constitutes a major step toward EU collaboration in the field of infectious disease prevention. In particular, two main principles regarding vaccination are evident: a) vaccines are an important component of emergency preparedness; b) a mechanism for purchasing vaccines through EU joint procurement is in place, which also provides a clear advantage deriving from the economy of scale. In particular, seasonal influenza vaccination should be an important component of pandemic preparedness, since a strong vaccination system for seasonal influenza is clearly necessary in order to achieve good coverage during a pandemic. In addition, the joint procurement mechanism has been specifically set up to support the weaker Member States, which may have difficulty purchasing pandemic vaccines. This demonstrates that the EU decision-maker does acknowledge the strategic role of influenza vaccination in preparing Europe to tackle the pandemic threat.

Conclusions

EU decision-making in the field of influenza prevention, as well as of all other vaccination policies, is not clearly established. Nevertheless, there is quite large room for collaboration, especially in the field of post-marketing vaccine surveillance. In addition, there is a clear added value in the area of emergency preparedness and response, in which common EU policies, and even the joint procurement of vaccines, are ensured in the event of a pandemic.

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The sustainability of influenza vaccination programs: considerations and perspectives from Italy

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Keywords

Influenza • Vaccine sustainability • Elderly

Summary

Influenza constitutes an annually recurring threat to society, from both the clinical and economic points of view. The impact of influenza is often underestimated, especially among frail elderly people, who are at increased risk of serious complications, including hospitalization and death. In Italy, around 10 million individuals aged 65 years and older are at risk of contracting influenza, and it can be estimated that the lack of a vaccination strategy would lead to more than 2 million cases and about 30,000 deaths. However, adherence to routinely recommended adult immunizations remains suboptimal despite the availability of safe and effective vaccines. Indeed, a monitoring program from the National Institute of Health in Italy has shown that influenza vaccination coverage in the elderly dropped to 49% in the 2014-2015 season, which is far below the maximum values (68%) recorded in the 2005-2006 season. The current situation in Italy imposes a need for greater sustainability in order to face the challenges related to the changing epidemiological situation, demographic transition and social transformations. Our review sums up the key elements of influenza vaccine sustainability and makes suggestions for improving the organizational structure of the present initiatives.

Introduction

Influenza is considered a highly contagious respiratory illness, mainly because unstable viruses periodically drift and shift their antigens from one season to another to evade the immune system.

Annual winter outbreaks of influenza are a major cause of morbidity and mortality, especially among frail elderly people, who are at increased risk of serious complications, including hospitalization and death [1].

Although the public perception in many countries is that seasonal influenza is a mild illness, with a low to negligible impact on health and economies, annual influenza attack rates range from 5-10% in adults to 20-30% in children, generating high healthcare costs and placing a significant clinical and economic burden on patients and society [2].

Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths [3]. From 1976 to 2007, individuals aged ≥ 65 years accounted for approximately 90% of all influenza-related deaths in the USA. Furthermore, during the period 1999-2010, it was estimated in the UK that 2.5-8.1% of deaths among those aged ≥ 75 years were due to influenza [4].

Founded in 1999, Influnet is an Italian network of sentinel physicians, it aims to monitor seasonal trends in influenza-like syndromes (influenza-like illness, ILI) in the population. According to the estimates made from the data gathered, ILI affects 4-12% of the population each year, with an average of 7.5% recorded in the period 2011-2014 [5].

The clinical impact of seasonal influenza epidemics in Europe has recently been extrapolated from American data. According to these estimates, in Italy about 6,000 deaths and 38,000 excess hospitalizations are attributable to influenza [6].

The economic impact of influenza primarily involves healthcare resource utilization by elderly and high-risk groups and work absenteeism among otherwise healthy working adults [7]. In 2013, the costs attributable to the four main adult Vaccine-Preventable Diseases (VPD) in the United States were estimated to be around $ 26 billion, with influenza accounting for the majority of cases of adult VPD (81% of adults aged 50 and older and 77% of adults aged 65 and older). Moreover, the highest annual costs (medical and indirect costs) were indeed related to influenza. Influenza accounted for $ 16,0 billion (60%) of the cost among adults older than 50 years and $ 8,3 billion (54%) among those aged 65 and older [8].

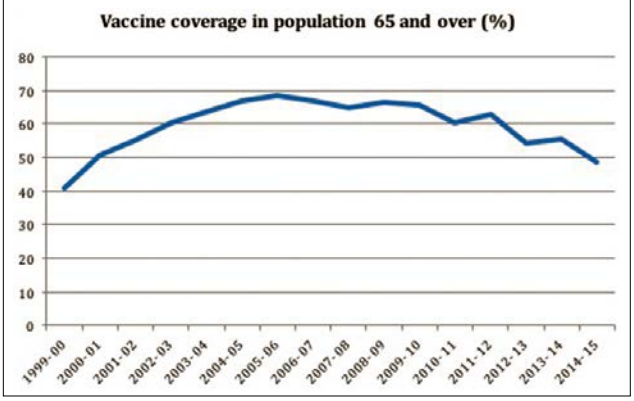
From the patient perspective, an average episode of ILI and clinically diagnosed influenza in the out-of-hospital Belgian general population costs € 51-53 in direct medical costs, 4 days of absence from work or school and the loss of 0.005 quality-adjusted life-years [9]. In Italy, the average length of absence from work or school is around 4.8 days, and 10% of all work absences are due to influenza. The total cost of each case of influenza is estimated to be about € 330 [10], with indirect costs accounting for a further € 364-774 (values from 2011) [11].

Considering that in Italy there are nearly 10 million individuals aged 65 years and older who are at risk of contracting influenza, it can be estimated that the lack of a vaccination strategy would lead to more than 2 million cases and about 30,000 deaths. Indeed, vaccination has the potential to reduce the number of cases to 1,3-1,5 million. Hence, the reduction in the number of hospital admissions would eventually lead to a reduction in healthcare costs of up to € 80 million (specifically, after administration of vaccines containing adjuvants) [10]. In this regard, one Italian study analyzed data gathered from the cohort of elderly individuals in the Liguria Region; the authors estimated that the costs resulting from hospitalization due to influenza were 5 times higher among non-vaccinated subjects than vaccinated subjects [12].
Moreover, vaccination targeting people from 50 to 64 years old in Italy has the potential to avoid about 100,000 cases of ILI (about 10% of the total), 3,000 hospitalizations (60%), 232 deaths (out of a total of 989) and more than 110,000 days of lost work [6].

European and national strategies and sustainability of influenza vaccination

Bearing in mind the clinical, economic and social impacts of influenza, the World Health Organization has proposed vaccination as a cost-effective and a cost-beneficial tool for preventing serious forms and complications of influenza, and reducing premature mortality in groups at increased risk of serious illness.
In Italy, the 2012-2014 National Immunization Prevention Plan introduced influenza vaccination for the elderly (65 years and over), with coverage targets of 75% (minimum achievable goal) and 95% (optimal goal in the target population). The objective was to reduce individual risk of illness, hospitalization and death, and the related social costs. In addition, several countries have lowered the age threshold to 60 or 50 years for free-of-charge influenza vaccination. These decisions were based on pharmacoeconomic evaluations, which proved that this age-based approach was sustainable, cost-effective and also cost-saving, owing to the increased probability of adherence to vaccination by the population. This approach, together with the analysis published in 2012 by the Italian Society of Hygiene (SItI) [13], prompted the Italian Ministry of Health to launch a thorough discussion among all stakeholders, in order to assess the possibility of progressively reducing the age threshold in the upcoming national anti-influenza recommendations.
Although infectious diseases in older adults have a huge burden, adherence to routinely recommended adult immunizations across Europe remains suboptimal, despite the availability of safe and effective vaccines [1]. Still, vaccination is considered the most efficacious public health tool currently available to protect elderly individuals against influenza [4].
European data indicate that vaccination coverage in groups at risk (patients with concomitant disease) is around 35% [10]. In Italy, monitoring carried out by the National Institute of Health has shown a progressive decline in coverage from the maximum value (68%) recorded in the 2005-2006 season. The lowest levels, reached in the 2014-2015 influenza season, indicated that national coverage had dropped to 49%, another 5 percentage points below the previous season (Fig. 1). This decline in coverage is affecting all Italian regions, with reductions ranging from a minimum value in Lombardy (-3.3%) to a maximum value in Abruzzo (-28.0%), and is depressing Italian coverage rates to the levels estimated fifteen years ago. This situation is making it increasingly difficult for Italy to achieve the European target coverage [14] and must surely prompt profound reflection. Indeed, it is essential to implement measures aimed at turning this situation around; a prerequisite to achieving this is understanding why vaccination, which has been unquestionably successful, is shunned by so many people.
While disaffection with vaccination can be partly attributed to the growing number of anti-vaccination campaigns, it stems in large part from the difficulties that the National Health System has in allocating the human/financial resources needed to carry out effective information campaigns directed towards citizens and healthcare workers. The problem of resource allocation is common to many prevention activities that involve immediate costs but yield medium/long-term results. Moreover, these results are often hardly visible, as the success of such initiatives lies in the non-occurrence of a negative event, and therefore a "non-event". This presumably explains why the funding of prevention programs in Italy has traditionally been even lower than the already limited 5% established in the planning documents.
While the European Union has more than doubled its funds for immunization worldwide, from € 10 million to € 25 million for the period 2014-2020, Italy is experiencing a decrease in expenditure on vaccines and a series of difficulties in approving a new national preventive vaccination plan [10]. Indeed, last year's data from OSMED (National Observatory on Drug Use) indicated a 21.2% reduction in spending on influenza vaccines:

Fig. 1. Influenza vaccination: vaccination coverage in the elderly (age > = 65 years) (per 100 inhabitants) Seasons 1999-2000/2014-2015 (Source: Ministry of Health – ISS, based on the summaries submitted by the Regions and Autonomous Provinces of Italy).



around € 39 million in total [15, 16]. At the same time, however, around 41.0% of subjects diagnosed with a viral infection of the upper respiratory tract (influenza, cold, acute laryngotracheitis) received an inappropriate antibiotic prescription. This exemplifies how the initial failure to pay for vaccine administration later impacts on patients in terms of increased disease risk and treatment costs.

Bearing in mind the need for the widespread administration of influenza vaccine and the complexities of its distribution, it is obvious just how crucial it is to have a comprehensive communication plan and well-designed infrastructure in order to ensure a maximally effective system of influenza prevention [17]. A clear influenza vaccination policy is essential and the lack of one is a key obstacle to influenza programs. Each country currently handles its own vaccination program/policy, and the lack of international coordination results in the wide variability of vaccine supplies and population targets, thereby potentially exacerbating inequalities at the international and national levels. Furthermore, discrepancies in several choices may be difficult for citizens to understand and could facilitate the activities of the anti-vaccination movements.

Communication supports the development and implementation of these policies and transforms them into a language that will resonate with policy-makers, partners and the public. A recent study on vaccine programs for European citizens aged 60 years and older showed that, in addition to improved access to vaccines, communication and the awareness of vaccine-preventable diseases, as promoted through an efficient system of reminders, recalls and information, are the main parameters leading to success in establishing a vaccine program [18]. Strategies targeted at increasing positive attitudes, such as health education by means of educational videos, may enhance vaccine acceptance and improve knowledge and attitudes in the elderly [19].

Strengthening the communication capacities of the various contributors to influenza programs should ensure that all stakeholders, especially the public and the media, have access to available resources, tools and scientific expertise. Also, promoting communication between scientists and practitioners should create a suitable environment for transparent information sharing with all the stakeholders. Moreover, communication needs to be adapted to the various local and cultural situations (language, content of information, and means of communication). Not only should communication be go beyond pure messaging and providing information; monitoring and evaluation of the communication process is also critical. Various tools could be used for these purposes, such as social network analysis, surveys, interviews etc., and the results should be used to adjust decision-making processes at the political, programmatic and technical levels.

Reaching out to the subjects that need to be involved is generally not enough to gain public support for prevention programs. The training of health workers, who ought to be motivated and committed to the individual and collective interests of vaccinations, is essential. Indeed, non-adherence to vaccination often stems more from the lack of motivation of educational trainers than from opposition on the part of families. The key role of healthcare workers in promoting access to and awareness and acceptance of, influenza vaccination should not be taken for granted, and strengthening the role of healthcare providers is of the highest importance. At the same time, it is very important that people living with or caring for aging adults get vaccinated. Healthcare personnel are in regular contact with at-risk populations, and strategies for improving vaccination rates among health employees are absolutely essential [20].

Vaccine services should have an efficient organizational structure in order to satisfy the needs of the population and ensure the success of vaccination programs. In this regard, the evaluation of vaccination coverage enables identification of the areas where infectious diseases may occur more easily. Therefore, the influenza vaccination coverage is a key indicator for assessing the effectiveness of vaccine supply, especially in such target population groups as the elderly.

Implementing a computerized system of vaccine registries (computerized immunization registries) connected with municipal registry offices should be seen as a prerequisite to increasing the quality of immunization services, and should be integrated with other existing databases, such as those of sentinel sites, population-based studies, hospitals and out-patient clinics and regional authorities. Indeed, the absence of an accurate surveillance system is considered one of the main obstacles to establishing evidence-based policies to reduce the impact of influenza nationally.

Conclusions

Influenza constitutes a serious health threat, especially for vulnerable populations such as older adults. The importance of promoting healthy aging and increasing vaccination coverage, by sustaining a life-course immunisation approach to limit the burden of the disease, is evident. The current economic and socio-political climate, which is characterized by scant resources and cost-cutting, imposes on our healthcare system the need for a new model of sustainability – one which would be able to face the new challenges related to the changing epidemiological situation, demographic transition and great social transformations. In this regard, financial difficulties could be seen as an opportunity to enhance vaccine prevention as part of a system that makes good health investments that impact positively on direct and indirect healthcare costs.

In addition, not only should the costs of a vaccination campaign be programmed; they could also be notably lower than the unpredictable costs of the disease that is to be avoided, thus confirming that investment in prevention promotes the efficient use of human and financial resources.

The need to support public health and to stress the social and economic value of vaccination is now greater than ever. Communication and the awareness of vaccine-preventable diseases in the general community is an important starting point, and all healthcare professionals and public health/social workers can play a key role in this regard.

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Influenza vaccination in high-risk groups: a revision of existing guidelines and rationale for an evidence-based preventive strategy

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Keywords

Influenza vaccination • Elderly • Chronic diseases • Pregnancy • Healthcare workers

Summary

Influenza, an infectious respiratory disease, is one of the main causes of excess winter deaths (EWDs) in Europe. Annual flu epidemics are associated with high morbidity and mortality rates, especially among the elderly, those with underlying health conditions and pregnant women.
Health Care Workers (HCWs) are also considered at high risk of both contracting influenza and spreading the virus to vulnerable patients.
During the 2014/2015 season, the excess winter mortality rates observed in countries of the northern hemisphere (EuroMOMO network) and in Italy (+13%) were strongly related to the intensity of influenza circulation.
Influenza vaccination is the most important public health intervention to prevent seasonal influenza transmission and infection. However, to date, influenza vaccination coverage reported in Europe (including high-risk groups) is still largely unsatisfactory. This study analyzes some international and European guidelines on influenza vaccination and the rationale that underlies evidence-based public health intervention for the prevention of influenza among the principal high-risk groups: a) the elderly (subjects aged 65 years or older); b) subjects with underlying health conditions; c) pregnant women; d) healthcare workers.
Only by achievement recommended influenza vaccination coverage among high-risk groups in all European countries can we reduce the burden of disease.

Introduction

Influenza, an infectious respiratory disease caused by influenza viruses, is one of the main causes of excess winter deaths (EWDs) in Europe [1-3]. Annual flu epidemics are associated with high morbidity and mortality rates, especially among the elderly and those with underlying health conditions; these groups are particularly at risk of developing influenza complications, such as bacterial pneumonia [3, 4].
During the last winter season (2014/2015), the excess of deaths due to all causes observed in fourteen European countries among people ≥ 65 years old coincided with an increase in the detection of influenza A(H3N2) viruses by the European influenza surveillance system [5]. In particular, in England and Wales the highest number of EWDs since 1999/2000 was recorded, while in Italy a 13% rate of EWDs was reported [6, 7].
Influenza vaccination is the most important public health intervention to prevent seasonal influenza transmission and infection [3, 4]. In Europe, guidelines and preventive policies for influenza vaccination are primarily focused on protecting individuals at higher risk, both directly by vaccinating these subjects and indirectly by vaccinating those who could infect them [3].

This review aims to analyze international and European guidelines on influenza vaccination and the rationale that underlies evidence-based public health intervention for the prevention of influenza. In particular, we will discuss the evidence regarding influenza vaccination among the four principal groups at risk, which constitute key target for preventive strategies: the elderly (subjects aged 65 years or older), subjects with underlying health conditions, pregnant women and healthcare workers.

Influenza vaccination among the elderly

In the temperate zones, an increase in expected mortality levels is frequently observed among the elderly during the winter season; this increase, however, largely depends on the season or country [5, 8, 9].
Excess mortality may be related to two main factors: a) seasonal influenza, especially during seasons with a prevalent circulation of influenza A(H3N2), and other respiratory tract infections; b) environmental conditions (e.g. cold spells) [6, 9].
In recent years, several studies have shown the worldwide impact of influenza infection on excess winter mortality rates in the elderly (Tab. I) [5-11].

Tab. I. Influenza-attributable excess winter mortality (EWDs) in the elderly.

Authors	Country	Age-class	Years	Prevalence of EWDs attributable to influenza	Influenza virus type
Matias et al. [10]	USA	≥ 75 years	1997-2009	71%	A(H3N2)
	USA	≥ 75 years	1997-2009	50-95% (during all seasons)	B
Nielsen et al. [9]	Denmark	≥ 65 years	1994-2010	82%	A(H3N2)
Thiberville et al. [8]	France	≥ 65 years	1999-2010	6.27 to 13.23 (per 100,000 inhab)	A(H3N2)

In Europe, a network named EuroMOMO (European monitoring of excess mortality for public health action network) monitors weekly and "real-time" all-cause age-specific excess mortality in European countries through a standardized approach that allows pooling of results [12].
In February and March 2012, an increased number of excess deaths among the elderly was observed in European member countries of the EuroMOMO [12]. This reported excess mortality coincided with late increased influenza activity and was related to a prevalent detection of influenza A(H3N2) by both sentinel and non-sentinel sources (approximately 95%) [11]. This profile of isolation was very different from previous influenza seasons, when influenza A(H1N1) was predominantly isolated; in these seasons, only a minor impact on mortality among the elderly was observed in countries of the northern hemisphere [6, 11]. More recently, a greater number of excess deaths among the elderly was observed during the last winter season (2014/15) and was strongly related to the intensity of influenza circulation, showing a correlation between weeks with excess mortality and medium or high influenza activity (80%) [5-7]. Moreover, the last influenza season in the northern hemisphere was similar to the 2011/2012 season, in that A(H3N2) virus was predominant (56% of detections across the European Community) [13]. It is expected that a winter season in which influenza A(H3N2) is predominant will have a higher impact on mortality among the elderly than a season with predominant influenza A(H1N1) or a season with low influenza A transmission [5, 9]. Influenza A(H3N2) virus has been recognized as having a noticeably greater effect on the elderly than influenza virus A(H1N1), which is particularly virulent in younger people [6]. In addition, in the 2014/15 influenza season, most influenza A(H3N2) viruses characterized in Europe exhibited antigenic differences in comparison with those included in the vaccine formulation; higher morbidity and mortality rates were observed in vaccinated populations [14, 15]. Finally, during the last influenza season in Europe, a lineage B mismatch of the influenza vaccine was frequently observed, which contributed to reducing vaccine efficacy [16, 17]. These data provide strong support for the inclusion of both influenza B lineages in seasonal influenza vaccines [17].
Trends in influenza circulation are strongly correlated with excess winter mortality among the elderly in the northern hemisphere and Europe, highlighting the heavy burden of disease [5]. In this context, influenza vaccination guidelines issued by the principal public health authorities recommend 75% coverage of seasonal influenza vaccination for individuals aged ≥ 65 years [18-20]. However, in the 2011/2012 and 2012/2013 seasons, vaccination coverage in the elderly reached this threshold only in two European countries (the United Kingdom and the Netherlands). All other EU member states reported lower vaccination coverage, varying from 60% (Italy and Spain) to 5-10% (Estonia and Latvia) [21, 22]. In Italy during the last influenza season, influenza vaccination coverage was estimated to have decreased by 25-30% from the overall 2014 level [7, 22]. These data suggested that only high vaccination coverage rates can reduce influenza circulation, the impact of infection and possible variations in vaccine effectiveness among the elderly [18, 19].

Influenza vaccination among subjects with chronic diseases

Individuals with underlying health conditions are the core target of influenza vaccination. Every disease exacerbates the risk of influenza infection and, in particular, of influenza complications or death [19]. The association of several chronic diseases could constitute a serious risk factor for unvaccinated subjects during the influenza season [22].
According to public health guidelines, all individuals aged > 6 months with at least one chronic illness that constitutes a risk factor for influenza or its complications should be vaccinated [20, 21]. The comorbidities in which influenza vaccination is recommended are reported in Table II.
Despite the strong recommendation to vaccinate subjects with comorbidities, the observed coverage rate remains low. Indeed, there is great debate inside the scientific community, especially among general practitioners and medical specialists, regarding the efficacy and safety of influenza vaccines in chronically ill subjects. One concern regards vaccine efficacy (VE), as such comorbidities are claimed to determine a lower immunological response. However, research has demonstrated a good efficacy profile of influenza vaccines among these population groups [22-25].
An extensive review and meta-analysis published in 2012 assessed influenza vaccination among immuno-

Tab. II. Chronic diseases that increase the risk of contracting influenza, for which influenza vaccination is strongly recommended (mod. from Ministero della Salute, 2016 [21]).

Chronic diseases
Respiratory and pulmonary diseases (COPD, asthma, cystic fibrosis etc.)
Heart diseases (all congenital or acquired heart conditions)
Diabetes mellitus or any other metabolic diseases (including individuals with BMI > 30)
Chronic renal or adrenal gland failure
Any type of cancer (also during radio- and chemotherapy)
Hematological diseases or hemoglobinopathies
Congenital or acquired immunodeficiency (pharmacological, AIDS etc.)
Chronic inflammatory bowel disease and inadequate intestinal absorption syndrome
Chronic hepatic diseases
Neuromuscular diseases or any disease at risk for aspiration of respiratory secretions

compromised patients [26]. The study demonstrated that transplant recipients and patients with human immunodeficiency virus (HIV) infection or cancer had significantly lower odds of contracting influenza-like illness after vaccination. Moreover, compared with patients receiving placebo or no vaccination, vaccinated HIV-positive patients had lower odds of laboratory-confirmed influenza. Influenza vaccination was generally well tolerated [26].

Another prospective, non-interventional cohort study was conducted during the 2010/2011 influenza season among more than 800 adult cancer patients in Israel [27]. A lower mortality rate was observed among vaccinated cancer patients than unvaccinated ones, even though a statistical association with complications due to influenza infection was not demonstrated [27]. Furthermore, a large (7,772 subjects with COPD aged ≥ 55 years) cohort study conducted from 1996 to 2008 in Taiwan by Sung et al. found a reduction in hospitalizations for acute coronary syndrome among vaccinated people [28]. The protective effects were observed in both sexes and all age-groups examined (55-64, 65-74, ≥ 75), regardless of influenza seasonality. When the patients were stratified according to the total number of vaccinations, the adjusted Hazard Ratios (HRs) for acute coronary syndrome hospitalization were 0.48 for patients who received 2-3 vaccinations and 0.20 for patients who received ≥ 4 vaccinations [28].

Influenza vaccination was also associated with a 24% reduction in stroke risk in a case-control study conducted in the UK from 2001 to 2009 [29]. Specifically, stroke risk was significantly lower following early (September to mid-November), but not later, influenza vaccination (mid-November onwards) [29].

Influenza vaccination among pregnant women

Influenza may be a frequent infection during pregnancy [30, 31]. In particular, pregnant women appear to have an increased risk of severe disease, especially during annual epidemics and pandemics [32, 33]. As reported by Louie et al., the pandemic influenza A(H1N1) in 2009 caused severe illness and death especially among pregnant and postpartum women [34]. Conducted in California, their study analyzed all women hospitalized during the first wave of pandemic influenza (from April to August 2009), 42.6% (N = 102/239) of whom were pregnant or in postpartum. Overall, 18 pregnant and 4 postpartum women (22%) required intensive care, while 8% died [34]. The severity of influenza among pregnant women observed in California is consistent with an increased risk of severe disease and the disproportionate number of influenza-associated deaths that has been documented for seasonal influenza and previous pandemics [35-37] The main difference was the rapid clinical deterioration observed in some patients in comparison with the typical course of seasonal influenza [34].

Moreover, in the Hungarian case-control surveillance of congenital abnormalities conducted from 1980 to 1996, Nandor et al. found a higher prevalence of maternal influenza during the second and/or third month of pregnancy in newborns with cleft lip-palate, neural-tube defects and cardiovascular malformations. The authors supposed that the teratogenic effect due to influenza viruses was probably associated with fever, as this risk was reduced by the use of antifever drugs [38].

On the other hand, several studies have demonstrated the efficacy and safety of influenza vaccination during the second and third trimesters of pregnancy. With regard to efficacy, Thompson et al. conducted a population-based case-control study during two consecutive influenza seasons (2010-2011 and 2011-2012) and showed a lower risk of Acute Respiratory Illness (ARI) associated with laboratory-confirmed influenza in vaccinated pregnant women [35]. The reported VE was similar to that observed among all adults during these seasons (VE against influenza A and B: 44%; 95% confidence interval 5-67%) [35, 36]. Moreover, a double-blind, randomized, placebo-controlled trial of influenza vaccine conducted in South Africa in 2011 demonstrated that influenza vaccine was immunogenic in both HIV-uninfected and HIV-infected pregnant women and provided partial protection for infants who were not exposed to HIV [37]. With regard to safety, Ludvigsson et al. found no excess mortality in the offspring of women who had been vaccinated against influenza A(H1N1)pdm09 during pregnancy. Moreover,

the authors noted that maternal A(H1N1) vaccination during any trimester of pregnancy had no adverse effects on children in either the early neonatal period or early childhood [39]. In 2015, McMillan et al. published a review on safety outcomes of influenza vaccination during pregnancy. In their quantitative analysis, maternal influenza vaccination was not associated with an increased risk of fetal death, spontaneous abortion or congenital malformations [40].
For all these reasons, international and national guidelines now strongly recommend influenza vaccination for all pregnant women in the second and third trimesters, in order to protect them and their children during late pregnancy and to protect their infants during the first six months after birth through the induction of immunity that would otherwise not be achievable [19-21].

Influenza vaccination among health-care workers

Influenza vaccination among health-care workers (HCWs) is considered to be the most important strategy for preventing the transmission of influenza viruses to vulnerable patients and minimizing absenteeism among HCWs during annual epidemics [19, 41, 42]. Indeed, hospitalized patients may acquire influenza not only from other patients or visitors but also from hospital employees. Elder et al. estimated a 20% influenza infection rate among HCWs each season [43]. Many HCWs continue working while infected, thereby spreading the virus [43]. Therefore, vaccinating medical personnel against influenza is the most effective strategy for preventing nosocomial influenza transmission and reducing influenza-like illness (ILI) mortality among elderly and high-risk patients [42, 44]. Although this is recognized and emphasized by all public health agencies worldwide, influenza vaccination coverage among HCWs remain lower than 75% [19-21].
Adherence to influenza vaccination does not seem to depend on physicians' age or specialty [45-48]. In some non-European countries, mandatory vaccination plays a decisive role in the vaccination of HCWs, and the immunization rates observed in such countries are very far from those observed in Europe [49, 50]. However, it is difficult to apply mandatory vaccination in the European context, for such reasons as staff morale, civil liberty and professional autonomy [51]. Indeed, some studies have reported that HCWs prefer other strategies for promoting influenza vaccination; specifically, it has been demonstrated that appropriate training through multidisciplinary courses, adequate university education and proactive attitudes on the part of coworkers can improve influenza vaccination coverage [51, 52].
One of the main goals of public health authorities should be to promote proper attitudes towards and knowledge of influenza vaccination among HCWs, since this is the best means of protecting both them and their patients. Moreover, HCWs should have appropriate skills in counseling patients with regard to the importance of influenza vaccination, especially among the high-risk classes of individuals analyzed in this review [52].

Conclusions

On the basis of the winter mortality rates observed in recent years both in countries of the northern hemisphere and in Italy, influenza is one of the leading causes of death. In particular, the elderly, subjects with comorbidities, pregnant women and HCWs are at higher risk of contracting influenza and its complications. Worldwide, vaccination is the only recognized strategy for preventing influenza circulation, transmission and infection, and all principal sanitary authorities recommend vaccination for these high-risk groups.
In the future, the most important target for preventive medicine will to achieve the recommended influenza vaccination coverage in all European countries, in order to reduce the burden of disease and minimize mortality [5-7, 53].

Competing interests

Francesco Vitale was a member of the advisory board on behalf of Glaxo Smith-Kline®, Pfizer®, Novartis® and Sanofi-Pasteur®. He has also spoken at International, National and Regional Conferences on the invitation of Glaxo Smith-Kline® and Pfizer®. Claudio Costantino has spoken at National and Regional Conferences on the invitation of Glaxo Smith-Kline®.

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The new pandemic influenza A/(H1N1)pdm09 virus: is it really "new"?

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Keywords

Influenza • Pandemic • A/(H1N1)pdm09

Summary

In June 2009, the World Health Organization (WHO) issued a pandemic alert concerning the spread of an influenza A (H1N1) virus that showed distinctive genetic characteristics vis-à-vis both seasonal influenza strains and vaccine strains. The main mutation occurred in the gene coding for hemagglutinin (HA). Mathematical models were developed to calculate the transmissibility of the virus; the results indicated a significant overlap with the transmissibility of previous pandemic strains and seasonal strains. The remarkable feature of A/(H1N1)pdm09, compared with seasonal strains, is its high fatality rate and its higher incidence among younger people. Data provided by the WHO on the number of deaths caused by A/(H1N1)pdm09 only include laboratory-confirmed cases. Some authors suggest that these data could underestimate the magnitude of the event, as laboratory confirmation is not obtained in all cases.

It is important to bear in mind that the A/(H1N1)pdm09 virus is still circulating in the population. It is therefore essential to maintain its epidemiological and virological surveillance.

Influenza pandemics in history

The cyclic occurrence of epidemic and pandemic phenomena attributable to influenza A virus is related to the ability of the virus to modify its two main surface proteins, hemagglutinin (HA) (which allows the virus to adhere to epithelial cells in the upper respiratory tract) and neuraminidase (NA), both of which play a very important role in the pathogenesis of the disease. Antigenic variability of influenza A virus may occur as antigenic drifts (minor variability) or antigenic shifts (major variability). Antigenic drifts (such as nucleotide substitutions, deletions and insertions of HA and NA genes) are responsible for seasonal epidemics of influenza virus, while antigenic shifts cause pandemics. The most important changes are due to the reassortment of viruses of swine and avian origin with viruses of human origin, like those responsible for the pandemics that occurred in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2) [1, 2]. The H1N1 virus reappeared in 1977, and is still circulating in humans, while the H3N2 virus was the most common up until 2009 [3, 4].

The "new" pandemic

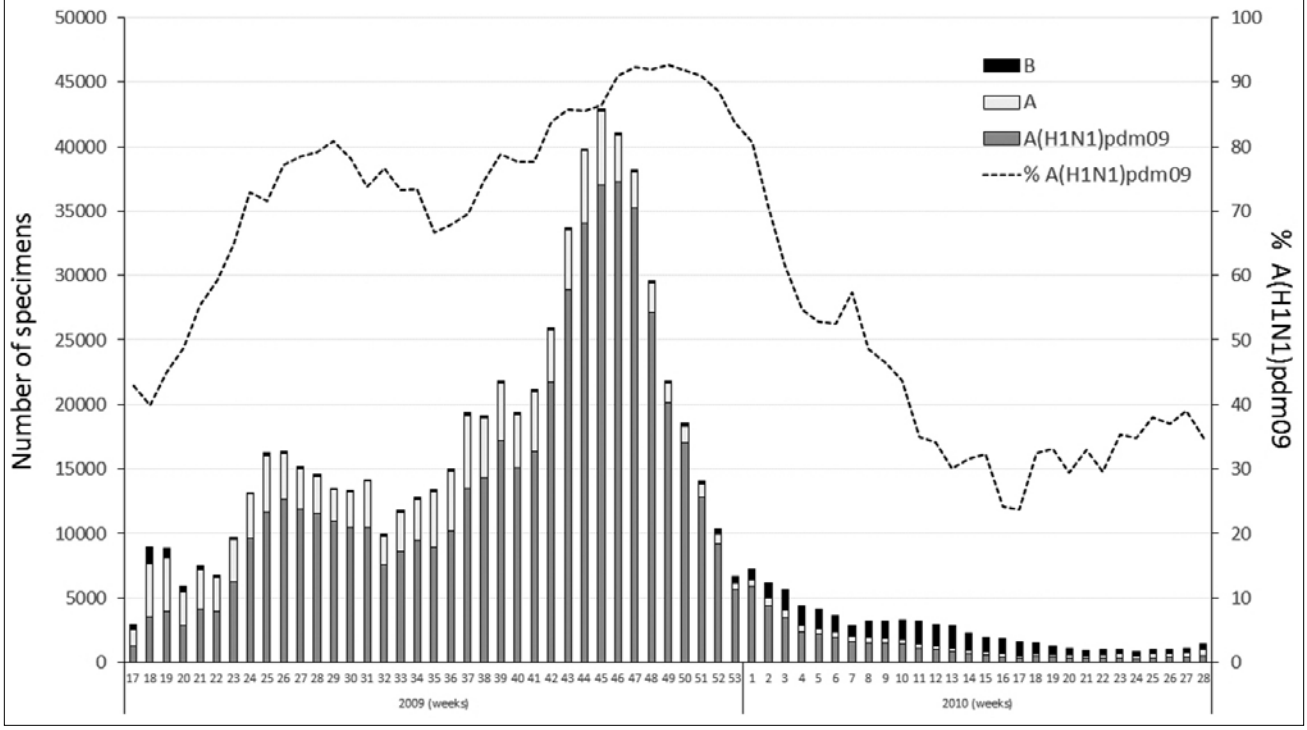
In April 2009, a new virus appeared in Mexico and California (US), and was responsible for the first pandemics of the 21st century. It spreads rapidly from person to person, and is not related to any circulating inter-pandemic viruses. The new virus was labeled A/(H1N1) pdm09. It is a quadruple reassortant virus, consisting of two swine-origin viruses, one avian-origin virus and one human-origin virus. To be more precise, molecular studies have identified the North American H3N2 triple reassortant viruses circulating among swine, a classic swine H1N1 virus, and an "avian-like" swine H1N1 virus circulating in Europe and Asia [5]. This "new" virus has proved remarkably different from the classic seasonal influenza H1N1 viruses and the viruses used to prepare vaccines [6].

The new virus spread rapidly around the world, primarily infecting children, young adults and individuals with lung and heart diseases, though the majority of cases were of low-grade severity and were self-limiting. The first epidemics occurred in Veracruz (Mexico), starting on 12 April 2009, and the virus was isolated by the Centers for Disease Control (CDC) on April 14th. By the end of April, the WHO had declared a phase-5 pandemic alert, and on 11 June this was upgraded to phase 6 (Tab. I), owing to the large number of individuals and na-

Tab. I. A/(H1N1)pdm09 pandemic timeline.

Date	Step
12th April 2009	Epidemic starts in Mexico (Veracruz)
17th April 2009	CDC isolates A/(H1N1)pdm09 virus
25th April 2009	Public health alert is declared
27th April 2009	Pandemic phase-4 alert
29th April 2009	Pandemic phase-5 alert
11th June 2009	Pandemic phase-6 alert
11th August 2010	Post-pandemic phase is declared

Fig. 1. Number of specimens positive for influenza by subtypes (from 19 April 2009 to 24 July 2010).



tions involved. In June 2009, the WHO reported 94,512 cases (including 429 deaths) and 135 nations were involved.

Burden of disease

From April 2009 to August 2010 (when the pandemic was declared to be over) [7], the number of laboratory-confirmed cases amounted to 651,449: 75.4% of these (491,382 cases) attributable to the A/(H1N1)pdm09 virus; 1.4% (35,069 cases) to the A(H1N1) seasonal influenza virus; 12.4% (81,070 cases) to non-typed A viruses; and the remaining 5.3% (34,481 cases) to the influenza B virus. The trend over the period analyzed is shown in Figure 1 [8].

The mean age of the individuals affected was 18.1 years: 64% of the cases occurred in 10- to 29-year-olds, and only 1% were aged 60 and over; 18.4% of the patients had chronic comorbidities.

The clinical manifestations were unexceptional, the most common symptoms being cough (84.9% of cases), high temperature (84.7%), headache (66.5%), runny nose (60.1%), and joint and muscle pain (58.1%). Despite these nonspecific clinical manifestations, some authors recommend considering cough and high temperature as the only parameters for identifying cases [9].

Mortality

During the pandemic, a total of 18,631 deaths were reported among the laboratory-confirmed cases, yielding a fatality rate of 2.9% (95% CI 0.0-6.7%), with an estimated fatality rate of 0.02% among all infected individuals [10]. Although this fatality rate cannot be considered a valid indicator, it prompted some to claim that the public health measures taken to deal with the pandemic had been excessive. It is important to bear in mind, however, that these figures are probably underestimated, as not all deaths involved laboratory-confirmed cases (as is usually the case during inter-pandemic periods). A recent study estimated that between 123,000 and 203,000 people died during the pandemics, and 62-85% of these were under 65 years old (and often under 14 years old): these figures suggest that the mortality rate for the 2009 influenza pandemic was in fact 10 times higher than the mortality rate resulting from the laboratory-confirmed cases. If the same method of calculation were applied to seasonal influenza epidemics, the virus would be responsible for 148,000-249,000 deaths, but would involve a larger proportion of elderly people. Indeed, only 19% of deaths involve patients under 65 years old during seasonal influenza epidemics. This epidemiological pattern gives the impression that the 2009 pandemic was more severe than seasonal influenza endemics – an assumption that may be confirmed when it is possible to obtain an estimation in terms of life years lost [10].

The fatality rate during a pandemic is calculated from the number of deaths due to the virus type investigated in relation to the number of cases in a given population. Analysis of the data shows marked heterogeneity in the fatality rates due to the A/(H1N1)pdm09 virus, which range from 1 to 10,000 deaths per 100,000 infections. In other words, the severity of pandemics is unpredictable and hard to estimate on the basis of fatality rates [11].

In-hospital mortality

Among the indicators of a pandemic's severity, the in-hospital mortality rate should be taken into account. In the case of the A/(H1N1)pdm09 pandemic, this rate varied considerably (from 0 to 52%) depending on the type of hospital involved and the gross domestic product of the country considered. In high-income countries, where standards of treatment are higher, the estimated in-hospital mortality rate ranged between 1% and 3%, and did not depend on the type of hospital or the type of ward.
In all countries, the burden of hospitalization was higher among children and younger adults, though the in-hospital mortality rate was always higher among elderly patients, mainly because they often had comorbidities. Despite their lower risk of infection, older people had higher fatality rates than younger patients in the event of hospitalization [12].

The situation in Italy

In Italy, the influenza surveillance network (INFLUNET) actively follows up 2.1% of the Italian population. Comparing data on seasonal influenza epidemics, the network showed, during the 2009 pandemic period, that the infection peaked in the 50th week (while this usually happens in the 4th to 8th week), with an intensity that was similar to other years. The network also found an increase in hospital admissions due to influenza-related complications, with 1,100 hospitalizations, 592 of which were severe cases (admission to intensive care unit, acute respiratory distress syndrome, need for intubation or extra-corporeal membrane oxygenator); 204 patients died [13].
The A/(H1N1)pdm09 virus continued to circulate after the pandemic of 2009. It was estimated that both the A (84%) and the B (16%) influenza viruses were circulating simultaneously during the 2014-2015 seasonal influenza. Specifically, the A/(H1N1)pdm09 virus accounted for 52% of all laboratory-confirmed cases, and for 76% of all severe clinical manifestations. This is the epidemic with the highest number of severe cases reported since the 2009 pandemic [14].

Features related to severity

The severity of influenza epidemics varies, depending on the geographical area involved, and can be measured by estimating the burden of disease at both the individual and community levels. The extent of a pandemic is influenced by several different factors, which depend on the features of the population affected, and severity assessment on a global level is not as straightforward as on the local level. It therefore becomes essential to implement a surveillance system in order to accurately monitor epidemiological trends and detect changes in the pattern of illness, as well as the characteristics of the infectious agent. Surveillance is essential for the prevention and control of influenza illness. Being able to recognize the specific circulating strain and the characteristics of the seasonal epidemic is important in order to identify viruses to be used in vaccines and to detect novel influenza viruses with potential for pandemic spread. Furthermore, combining virological surveillance with epidemiological surveillance gives us the chance to collect useful information for developing severity indicators.

Virological characteristics

Virological surveillance is essential in order to detect changes in the viral genome that may have an impact on the pathogenicity of the virus and on the effectiveness of influenza vaccines. Vaccine effectiveness decreases when the viral strains in the vaccine and the circulating viruses do not perfectly match [15, 16].
Mutations may be irrelevant; alternatively, they may modify the structure of epitopes (antibody-binding sites), thus giving rise to new serotypes and becoming critical in causing clinically relevant symptoms.
Critical mutations are those occurring in hemagglutinin (HA), the non-structural proteins (NS1), and polymerase (PB2). If these mutations occur simultaneously, increased virulence can be expected. Amino acids 187 and 222 in HA are involved in determining receptor-binding affinity and tissue-specific tropism: D187/D222 for α(2,6) in receptors on the human respiratory tract, D187/G222 for α(2,6) and α(2,3) in swine, and E187/G222 for α(2,3) in avian species. The new pandemic virus was characterized by major genomic mutations. Two have been identified: the so-called D222G and D222N, in which aspartic acid (D) is substituted by glycine (G) or asparagine (N), respectively. The D222G mutation is responsible for a change in receptor-binding affinity; this change enables the virus to bind to sialic acid receptors α(2,6), located on the ciliated epithelial cells in the upper respiratory tract, and to sialic acid receptors α(2,3), located on the ciliated epithelial cells in the lower respiratory tract [17]. A recent review showed a correlation between the D222G mutation in HA and the most severe and fatal cases of influenza. It also established that viral strains isolated during the pandemic did not carry other mutations in genes associated with increased virulence [18].

Epidemiological characteristics

Transmissibility is an important aspect of a pandemic. It is related both to intrinsic features of the agent causing the disease and to the public health measures adopted to deal with it. It can be measured by calculating the R0, i.e. the ability of an index case to infect other susceptible individuals. This indicator depends on the risk of transmission by contact (β), the average number of contacts per unit of time (κ), and the duration of the virus's infectiveness (D), which is agent-specific. R0 is calculated by means of the formula: $R0 = \beta * \kappa * D$. All possible public health measures may modify the R0, in which case the R0 is replaced with a Reproduction Control (RC) number. The RC depends on both the R0 and the public health measures taken, and is obviously always lower than the R0. If the RC is lower than 1, the epidemic will stop; if it is higher than 1, the epidemic will only decline

in intensity. The R0 value calculated for influenza viruses varies: in the case of the viral strain responsible for the pandemic in 1918-1919, for instance, it was about 2 (ranging from 1.4 to 2.8), while for a strain responsible for a seasonal influenza epidemic it is 1.3 (ranging from 0.9 to 2.1). These values do not differ greatly from the R0 value calculated for the A/(H1N1)pdm09 virus, which was 1.4-1.6. Since all these values overlap significantly, it is reasonable to assume a similar transmissibility among the strains considered [19].

Conclusions

The influenza A/(H1N1)pdm09 virus revealed some unique features in comparison with other circulating influenza viruses. These characteristics, combined with the state of immunity of the populations affected, accounted for the first pandemic of the 21st century. The viral and infectivity characteristics of A/(H1N1)pdm09 were entirely comparable to the characteristics of seasonal influenza strains, but the virus affected a larger proportion of children and young adults. It was consequently responsible for a heavier burden of disease, despite its similar virulence.
The picture was much the same in Italy, where the influenza epidemic peaked earlier than usual in 2009-2010.
It is important to bear in mind that the A/(H1N1)pdm09 virus is still circulating in the population. It is therefore essential to maintain its epidemiological and virological surveillance.
In conclusion, A/(H1N1)pdm09 is a new virus which is similar to seasonal influenza viruses in terms of disease incidence and transmissibility, but different in terms of its sudden appearance, rapid spread and severity of clinical manifestations in young people.

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The impact of influenza virus B in Italy: myth or reality?

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Keywords

Influenza impact • Epidemiology • Influenza B • Vaccination • Vaccine mismatch

Summary

We describe the burden of influenza B infections in Italy over a 12-year study period. Influenza A and B viruses co-circulated throughout the period, with numbers of influenza B cases approaching or exceeding those of influenza A during three influenza seasons. Influenza B virus infections led to fewer admissions to an intensive care unit (ICU) and a lower mortality rate than influenza A from 2010 to 2015. However, only 16% of those admitted to ICU with influenza B had been immunized. This highlights the need for consistent influenza vaccination for identified risk groups. Our study demonstrates that influenza B virus infections are associated with substantial morbidity and that influenza surveillance and interventions including vaccination and treatment are still suboptimal. Our findings have important public health implications. Incorporating virus and epidemiological data will help obtain more accurate estimates of influenza disease burden and result in a better selection of influenza prevention and control strategies.

Introduction

The societal burden of seasonal influenza epidemics is quite heavy, with approximately 3-5 million cases and 250,000-500,000 estimated deaths worldwide every year [1] and a large economic impact, which includes both direct and indirect costs [2, 3]. Conventionally, attention has been directed toward influenza A, which accounts for the majority of influenza cases in most seasons [4-7]. However, influenza B can account for a considerable proportion of total cases [8]. Since the 1980s, influenza B viruses have belonged to two antigenically distinct lineages, called the Victoria and Yamagata lineages [9]; this has constituted a challenge for seasonal influenza vaccines, as only one influenza B strain is included in the trivalent vaccine. Studies in the United States have shown that the frequent influenza B vaccine mismatches of recent years have been associated both with substantial increases in cases, hospitalizations and deaths (up to 970,000 cases, with 8200 hospitalizations and 485 deaths annually, in the USA) [10], and with high influenza-related medical costs and costs due to productivity loss [11].

Despite the important role of influenza B, much of the published scientific literature regarding the epidemiology of influenza has focused on influenza A, and we still have a relatively poor understanding of the global epidemiology and disease burden of influenza B. Several studies have reported on the burden of disease attributable to influenza B in a single season, or during consecutive seasons in a single country [12, 13]. In order to improve our understanding of the burden and epidemiology of influenza B, we reviewed the influenza B viruses circulating in Italy from 2000 to 2015.

Materials and methods

The National Influenza Sentinel Surveillance System

In Italy, the Influenza Sentinel Surveillance System (INFLUNET) was implemented nationwide in the 1999-2000 season by the Influnet working group [12]. INFLUNET is based on the voluntary participation of an average of 830 (range 648-902) general practitioners (including paediatricians) per year, covering about 1.5-2% of the national population in all Italian regions. The system aims to monitor the incidence of influenza-like illness (ILI) and to determine the extent, timing and severity of seasonal epidemics. GPs are asked to report ILI cases (defined as acute onset of fever + respiratory symptoms + one of the following symptoms: headache, general discomfort, asthenia) weekly (from week 42 to week 17) using standardized forms. Specific information regarding age (0-14, 15-64, > 64 years) and influenza vaccine status are also collected. We excluded the first years of data collection and focused the analysis on Influnet data collected from the 2005/2006 to 2014/2015 seasons.

The National Virological Surveillance System

Influenza virological surveillance in Italy is routinely carried out, between week 46 and week 17 of the following year, by the National WHO (World Health Organization) Influenza Centre at the Istituto Superiore di Sanità (NIC-ISS), in collaboration with a network of 15 peripheral laboratories located in 14 of the 21 Italian regions. The main objective of these activities is to rapidly characterize the influenza viruses circulating in

the country and to identify antigenic variants emerging in human populations during the winter season, in order to update the vaccine composition, in collaboration with the WHO and ECDC (European Centre for Disease Prevention and Control). During the virological surveillance period, sampling kits are sent out to a random sample of GPs participating in the INFLUNET surveillance system, who collect throat swabs from the first ILI patients seen each week. Collected swabs are then sent to the regional Reference Laboratories for influenza diagnosis, and the isolated strains are characterized at the Regional Laboratory or directly sent to the NIC-ISS for further molecular and antigenic analyses. Overall results obtained throughout the country are reported to the NIC-ISS weekly by means of web-based electronic forms.
Every year, approximately 2000 samples are collected, with a proportion of positive specimens of about 34%. Our analysis included virological surveillance data collected from the 2000/2001 to 2011/2012 seasons.

Surveillance of laboratory-confirmed severe cases

A web-based data collection form for the surveillance of severe confirmed hospitalised cases and deaths due to pandemic influenza was drawn up in mid-September 2009. Since then, regional and local authorities have filled in forms during the influenza season (October-April); the data are analysed weekly at the national level (by the ISS and the Ministry of Health). Our analysis included virological surveillance data collected from the 2010/2011 to 2014/2015 seasons, as all confirmed cases during the 2009/2010 season were due to A/H1N1pdm09 virus.

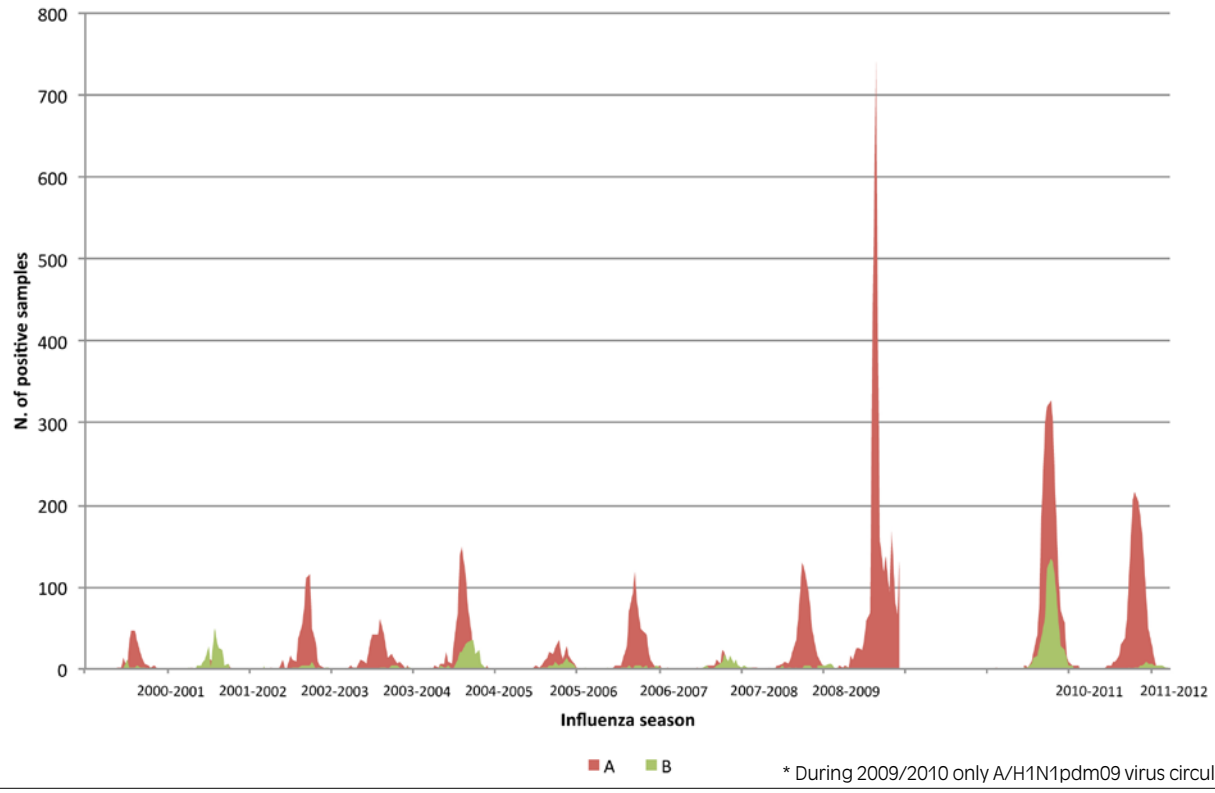
Results

From the 2005/2006 to 2014/2015 seasons, an estimated average number of approximately 4,800.000 ILI cases were reported to the surveillance system (Tab. I). Most were in the 0-5-year age-class. The national database that was used for the analysis included 40,000 ILI cases, with testing of samples from cases that occurred between 2000/2001 and 2011/2012. During the study period, several waves of infections by influenza A and B viruses were observed in Italy

Tab. I. Distribution of estimated influenza-like illness cases and cumulative incidence by season, Italy, 2005/2006 – 2014/2015.

Season	Peak week	Cumulative incidence	Estimated ILI cases
2005/2006	12	3.9	2,400.000
2006/2007	5	5.7	3,700.000
2007/2008	7	6.9	4,700.000
2008/2009	4	7,2	4,100.000
2009/2010	46	9.7	5,600.000
2010/2011	5	10.3	5,400.000
2011/2012	5	8.6	5,000.000
2012/2013	6	10.5	6,200.000
2013/2014	6	7.8	4,500.000
2014/2015	4	10.8	6,300.000

Fig. 1. Number of influenza A and B virus infections, Italy, 2000/2001 – 2011/2012.



* During 2009/2010 only A/H1N1pdm09 virus circulated

(Fig. 1). In detail, 11,488 influenza cases were confirmed in the study period: 9,842 influenza A cases and 1,646 influenza B cases. Influenza A and B viruses co-circulated during most influenza seasons, with numbers of influenza B infections approaching or exceeding those of influenza A virus during three seasons in the study period considered (2001/02, 2007/08 and 2012/13). The number of samples tested for influenza viruses by PCR in Italy increased by a factor of 1.5 over this period, from an average of 2,774 per season in the period 2000-2007 to an average of 4,312 per season in 2008-2012. Influenza B appeared to be relatively more frequent among older children; A(H1N1)pdm2009 among young and older adults, and A(H3N2) among the elderly. On average, the proportion of influenza B cases on the total of tested samples was 23% (range < 1-78%) (Fig. 2).

Severity of influenza B

From 2010/2011 to 2014/15, on a total of 1,545 severe confirmed influenza cases reported to the surveillance system (Tab. I), 102 were confirmed influenza B virus-infected individuals admitted to ICU; 2 were pregnant (both in the third trimester); 7 needed extracorporeal membrane oxygenation (ECMO) treatment, and 24 died. The median age was 63 years (range 0-92), 58 were male, and 16 were vaccinated almost 15 days before symptom onset. The median age of the individuals who died was 76 (range 39-85). Of the 102 severe influenza B patients, 73 belonged to groups recommended for vaccination (65 years and older or a clinical risk group), but only 16 had actually received the seasonal influenza vaccination. Most of the influenza B cases were reported during the 2012/2013 season, when the B virus co-circulated with the A/H1N1pdm09.

Tab. II. Distribution of confirmed severe cases, by influenza virus, Italy, 2010/2011 – 2014/2015.

Season	A/H1N1v	A/H3N2	A/non sub-typed	B	Total
2010/2011	517	0	11	10	538
2011/2012	7	33	1	1	42
2012/2013	143	8	7	61	219
2013/2014	61	23	7	1	92
2014/2015	494	87	44	29	654
Total	1,222	151	70	102	1,545

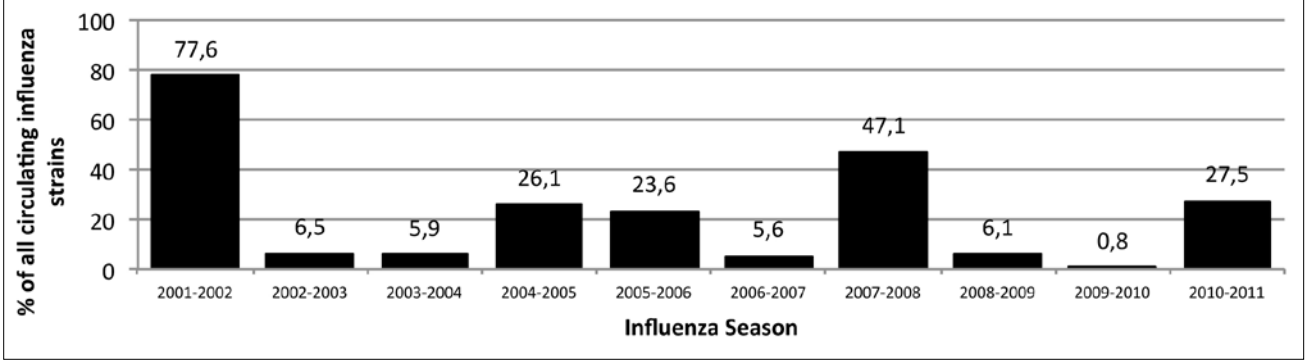
Discussion

Our results on influenza B virus infections in Italy are timely, in view of the recent introduction of a tetravalent influenza vaccine containing influenza B viruses of both the Victoria and Yamagata lineages. Our study reveals that influenza B virus was the predominant overall cause of influenza in two of the 13 influenza seasons from 2000/01 through 2012/13. However, circulation of the B virus during the inter-pandemic season was always demonstrated. Similar patterns of influenza B virus circulation have been described in the US, Europe and Hong Kong [12-13]. In Italy, the proportion of influenza B cases in the study period averaged 23% (range < 1-78%), a value similar to the European (23% (1-60%)) and US (24% (< 1-44%)) averages [14].

In our study, < 1% of all ILI cases are tested for influenza each season, and very few B viruses were antigenically and genetically characterized, thus reducing the opportunity to identify the co-circulation of the two lineages in Italy. However, evidence from two Northern Italian regions clearly demonstrated a complete or partial mismatch in the 2001/2002, 2004/2005, 2005/2006, 2007/2008, 2008/2009, 2010/2011, and 2011/2012 seasons; this was almost always due to co-circulation of the two lineages [15-17].

Influenza is generally recognised as an important disease which causes high excess mortality among the elderly, although children have been shown to play an important role in its transmission [18-19]. Unlike the influenza A(H3N2) virus, the B virus predominantly infects children and young adults and is generally recognised as a mild influenza virus [20]. Data on severe influenza B virus infections and mortality are limited. A large study conducted in the US reported that 25% of all influenza-related mortality could be attributed to influenza B virus [21]. This is higher than the percentage seen in the present study, in which influenza B in-

Fig. 2. Influenza B circulation as a proportion of the total percentage of all circulating influenza strains, Italy 2001/2002 – 2010/2011 seasons.



fections accounted for 6% of all influenza virus-related deaths (24/428) during the period considered, but is similar to figures reported for Scotland [22]. Among those admitted to ICU with influenza B infections, 7% needed ECMO treatment, 2% were pregnant, and 23.5% died.

Influenza immunisation is recommended in Italy for specific groups with an increased risk of complications following influenza infection (e.g. > 65 years old, > 6 months with chronic conditions, healthcare personnel, pregnant women in their second or third trimester etc.) [23]. Only 16% of those treated in ICU who should have been vaccinated had received the seasonal influenza vaccine, and 70% of those treated in ICU were included in the target categories of national recommendations.

The magnitude of the problem created by mismatching between circulating influenza B strains and the influenza B lineage contained in the vaccine varies by season. The most striking recent examples occurred during the 2005-2006 and 2007-2008 seasons. In 2005-2006, the influenza B component of the northern hemisphere influenza vaccine was of the B/Yamagata lineage, but 81-91% of the circulating influenza B viruses antigenically characterized in the US and Europe were of the B/Victoria lineage, and influenza B was found in 34-60% of all samples [14]. Similarly, in 2007-2008, the influenza B component of the vaccine was of the B/Victoria lineage, but 98-99% of the circulating influenza B viruses characterized in the US and Europe belonged to the B/Yamagata lineage [14].

Unfortunately, as very few B influenza viruses in Italy were genotyped, information on the antigenic characteristics of circulating B viruses was not available at the national level.

Our study demonstrates that influenza B virus infections are associated with substantial morbidity and that influenza surveillance and interventions including vaccination and treatment are still suboptimal. Our findings have important public health implications. Incorporating viral and epidemiological data will help obtain more accurate estimates of influenza disease burden and result in a better selection of strategies for influenza prevention and control [25].

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Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden

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Quadrivalent influenza vaccine • Safety • Immunogenicity • Cost-effectiveness

Summary

Influenza illness is caused by influenza A and influenza B strains. Although influenza A viruses are perceived to carry greater risk because they account for the majority of influenza cases in most seasons and have been responsible for influenza pandemics, influenza B viruses also impose a substantial public health burden, particularly among children and at-risk subjects.
Furthermore, since the 2001-2002 influenza season, both influenza B lineages, B/Victoria-like viruses and B/Yamagata-like viruses have co-circulated in Europe.
The conventional trivalent influenza vaccines have shown a limited ability to induce effective protection when major or minor mismatches between the influenza B vaccine component and circulating strains occur. For this reason, the inclusion of a second B strain in influenza vaccines may help to overcome the well-known difficulties of predicting the circulating B lineage and choosing the influenza B vaccine component.
Two quadrivalent influenza vaccines, a live-attenuated quadrivalent influenza vaccine (Q/LAIV) and a split inactivated quadrivalent influenza vaccine (I/QIV), were first licensed in the US in 2012. Since their introduction, models simulating the inclusion of QIV in influenza immunization programs have demonstrated the substantial health benefits, in terms of reducing the number of influenza cases, their complications and mortality.
In the near future, evaluations from simulation models should be confirmed by effectiveness studies in the field, and more cost-effectiveness analyses should be conducted in order to verify the expected benefits.

Introduction

Influenza is an acute viral illness of the respiratory tract, and constitutes a substantial public health burden in terms of morbidity, mortality and related costs. About 3-5 million cases of severe illness occur each year worldwide, resulting in about 250,000 to 500,000 deaths per year, high hospitalization and mortality rates, and considerable loss of productivity [1-3].
From a microbiologic point of view, type A and type B Influenza viruses differ markedly in terms of their hosts and epidemiology. Influenza A viruses have other animal reservoirs, in addition to humans, and display high antigenic variability, which mainly involves their surface glycoproteins: hemagglutinin (HA) and neuroaminidase (NA). Antigenic shift and antigenic drift are the two well-known mechanisms responsible for major and minor variations; antigenic shift is the main cause of the appearance of new influenza A strains with pandemic potential. Antigenic drift determines annual seasonal influenza epidemics [4].
Influenza B viruses, for which humans are the sole host of epidemiological relevance, do not undergo antigenic shift, but they can undergo antigenic drift. Since at least 1983, two parallel evolutionary B pathways with little antigenic cross-reactivity have been recognized, thus allowing two distinct genetic lineages to be identified: the B/Victoria/2/1987 (Victoria) and B/Yamagata/16/1988 (Yamagata) strains [5-6]. Since 2002, the two distinct influenza B lineages have frequently co-circulated, with one of the two predominating over the other in each season [7]. For example, in ten consecutive influenza seasons in Italy – from 2003-2004 to 2012-2013 – variations in the prevalence of circulating B lineages were reported: in 2007/2008 and 2012/2013, B viruses accounted for 47.7% and 58%, respectively, of viruses isolated, while in other seasons B viruses co-circulated with virus A, although with a lower prevalence [8].
Vaccination is the most effective means of reducing the number of influenza cases and related complications. Annual influenza immunization is, in particular, recommended in elderly subjects, children aged six months or more, pregnant women and individuals with chronic conditions, such as respiratory/heart/liver diseases, diabetes, or a weakened immune system. Indeed, these categories are at heightened risk of influenza-related complications and mortality [9].
In Italy, the National Ministry of Health annually publishes influenza prevention recommendations, specifying the groups to whom vaccination is offered free of charge. In addition, the Ministry sets a minimum target of vaccination coverage of 75% and an optimal target of 95% [10].

Tab. I. Influenza vaccination strains and viruses circulating in the northern hemisphere in the seasons from 1995/96 to 2015/2016.

Season	Influenza vaccination strains, Northern Hemisphere			Virus circulating in Europe and US		
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
1995/96	Texas/91	Johan/94	Beijing/93	Texas/91	Johan/94	Beijing/93
1996/97	Bayern/95	Wuhan/95	Beijing/93	Bayern/95	Wuhan/95	Beijing/93
1997/98	Bayern/95	Wuhan/95	Beijing/93	Bayern/95	Syd/97	Harbin/94
1998/99	Beijing/95	Syd/97	Beijing/93	Bay/95+Beij/95	Syd/97	Beijing/93
1999/00	Beijing/95	Syd/97	Beijing/93	NewCal/99	Syd/97	Beijing/93
2000/01	NewCal/99	Pan/99	Yaman/98	Bay/95+NC/99	Syd/97	Sichuan/99
2001/02	NewCal/99	Pan/99	Sich/99 (Y)	NewCal/99	Pan/99	Sic/99+HK01
2002/03	NewCal/99	Pan/99	HK/01 (V)	NewCal/99	Fuj/02(Pan/99)	Sic/99+HK01
2003/04	NewCal/99	Pan/99	HK/01 (V)	NewCal/99	Fuj/02	Jiangs/03
2004/05	NewCal/99	Wyom/03	Jiangs/03 (Y)	NewCal/99	Calif/04	J/03+Mal/04
2005/06	NewCal/99	Calif/04	Jiangs/03 (Y)	NewCal/99	Cal/04+Wis/05	J/03+Mal/04
2006/07	NewCal/99	Wiscons/05	Malays/04 (V)	NC/99+Sal/06	Wisc/05	J/03+Mal/04
2007/08	Salom Is/06	Wiscons/05	Malays/04 (V)	Sal/06+Bris/07	Wisc/05+Bris/07	Bri/07+Mal/04
2008/09	Bris/07	Bris/07	Florida/06 (Y)	Bris/07	Bris/07	Florida/06+Brisb/08
2009/10	Bris/07	Bris/07	Bris/08 (V)	-	Bris/07	Bris/08 (V)
2009/10	Calif/09			Calif/09		
2010/11	Calif/09	Perth/09	Bris/08 (V)	Calif/09	Perth/09	Bris/08 (V)
2011/12	Calif/09	Perth/09	Bris/08 (V)	Calif/09	Vict/11+Brisb/11	Bris/08+Wisc/10
2012/13	Calif/09	Vict/11	Wiscons/10 (Y)	Calif/09	Vict/11+Texas/12	Bris/08 (V)+Mass/12 (Y)
2013/14	Calif/09	Vict/11	Mass/12 (Y)	Calif/09	Texas/12	Bris/08 (V)+Mass/12 (Y)
2014/15	Calif/09	Texas/12	Mass/12 (Y)	Calif/09	Switzerl/13 +Texas/12	Phuk/13(Y)+Mass/12(Y)
2015/16	Calif/09	Switzerl/13	Phuk/13(Y)	Calif/09	Hong Kong/14	Bris/08 (V)+Phuk/13 (Y)

Legend: in yellow: minor mismatches; in red: major mismatches; in green: new influenza A strains with pandemic potential.

The World Health Organization (WHO) annually recommends vaccine composition on the basis of global virological surveillance. Annual trivalent influenza vaccines (TIVs) contain two influenza A strains (H1N1 and H3N2) and only one influenza B virus. The effectiveness of TIVs therefore depends on the degree of matching between the vaccine strain and circulating viral strains.

In the last two decades, four major and at least eight minor mismatches between vaccine and circulating B viruses have occurred in the northern hemisphere, thus impairing the performances of TIVs (Tab. I) [6]. Specifically, Ambrose CS and colleagues observed that, in Europe, a B-mismatch between vaccine and circulating strains occurred in 5 of 10 seasons between 2001 and 2011 [7]. The effect of antigenic mismatching between vaccine and circulating strains on vaccine effectiveness has emerged from observational and experimental studies [6, 11-14]. A recent meta-analysis by the Centers for Disease Control and Prevention (CDC) and the Marshfield Foundation reported that trivalent subunit or split influenza vaccines displayed good effectiveness in preventing lab-confirmed influenza illness when matching was good, but that vaccine effectiveness decreased when a drifted strain dominated the epidemiological picture [15]. Therefore, inaccurate prediction of the predominant influenza B lineage leaves many vaccinated individuals with suboptimal protection against influenza B disease caused by the influenza B lineage not included in the licensed trivalent vaccine [11].

To minimize the impact of B-mismatch on vaccine effectiveness, in February 2009 the Food and Drug Administration (FDA), for the first time, considered the inclusion of an additional influenza B strain in the antigenic composition of seasonal influenza vaccines [16]. Subsequently, in February 2012, the WHO recommended the production of quadrivalent influenza vaccines (QIVs) for seasonal immunization. In 2012, the European Medicines Agency (EMA) also highlighted the need for a quadrivalent vaccine that could overcome the lack of protection against the influenza B lineage not present in the trivalent vaccine. Finally, in February 2013, the WHO issued its first guidelines recommending that both expected B-strains be included in the vaccine composition [17-18].

In recent years, scientific research has addressed this need, and two quadrivalent influenza vaccines (QIVs) have been developed: a live-attenuated quadrivalent influenza vaccine (Q/LAIV) and a split inactivated quadrivalent influenza vaccine (I/QIV) [19].

Main evidence from pre- and post-marketing evaluations of licensed quadrivalent influenza vaccines

The immunogenicity, safety and tolerability of quadrivalent influenza vaccines have been evaluated in children, adults and the elderly in several clinical trials.

Live-attenuated quadrivalent influenza vaccine (Q/LAIV)

Q/LAIV has mainly been tested in children. A phase-III, randomized, double-blind study performed on 2,312 children aged 2-17 years demonstrated that the immunogenicity of an investigational Q/LAIV was non-inferior to that of two licensed T/LAIVs, one containing a B strain from the Yamagata lineage and the other containing a strain from the Victoria lineage. Moreover, this Q/LAIV proved safe and well tolerated [20].
Since 2014/2015, Q/LAIV has been used in a universal pediatric vaccination programme in the United Kingdom (UK). In this real-life scenario, the vaccine was seen to provide significant protection against drifted circulating influenza B viruses [21].

Inactivated quadrivalent influenza vaccine (I/QIV)

Children and adolescents

With respect to I/QIV, a phase II study was conducted in two groups of children aged 18-47 months: the first group was constituted by children who had received two doses of TIV in the previous season and who received one dose of TIV or I/QIV in the study season; the second group was composed of unprimed children who received two doses of I/QIV or TIV 28 days apart during the study season. In comparison with the TIV, the I/QIV displayed superior immunogenicity towards the alternative-lineage B strain, without impairing the immune responses to shared strains. Moreover, the two vaccines proved similar in terms of reactogenicity and safety [22]. These results were confirmed in a randomized phase III study conducted by Domachowske JB and colleagues in healthy children aged 3-17 years [23]. Langley and colleagues also investigated the immunogenicity and safety of a I/QIV candidate versus TIVs, in a phase-III randomized controlled trial involving 3,094 children aged 3-17 years. The I/QIV was non-inferior to the TIVs in terms of immunogenicity towards the shared strains (A/H3N2 and A/H1N1), and, in comparison with TIV controls, elicited superior responses to the added B strains. Solicited reactions, unsolicited adverse events and serious adverse events were similar in the I/QIV and pooled TIV groups [24].

Adults and elderly

The promising results obtaining with I/QIV in children were also confirmed in clinical trials performed in adult populations.
In a phase-III clinical trial comparing I/QIV with TIV/Victoria and TIV/Yamagata vaccines, 4,659 adult volunteers received one vaccine dose. Overall, the I/QIV was highly immunogenic and, on day 21, displayed greater immunogenicity towards the additional B strain than TIV, without interfering with the antibody responses to the three shared antigens [25]. The I/QIV candidate was also tested in 1,565 adults aged ≥ 18 years in a phase III, randomized, active-controlled, multicenter trial during the 2011/2012 influenza season. For all four vaccine strains, antibody responses to the I/QIV were non-inferior to those elicited by the TIV for matched strains. For both B strains, antibody responses to the I/QIV were non-inferior to the response to the TIV for the matched strains, and were superior to the responses elicited by the TIVs that lacked the corresponding B strain. The I/QIV also confirmed its acceptable safety profile in an adult population [26].
The safety of I/QIV was investigated through a routine surveillance system in Western Australia in 2015 in a sample of 1,685 healthcare workers (HCWs). The results indicated little difference between the reactogenicity of I/QIV and that of TIV; the percentage of HCWs reporting pain or swelling at the injection site was slightly higher among those who had received I/QIV than those who had received TIV (6.9% *vs* 4.2%, respectively; $p = 0.02$) [27].
The safety of I/QIVs was verified in a review of data from the Vaccine Adverse Event Reporting System (VAERS) in the US from 7/1/2013 to 5/31/2015. The most frequent non-fatal serious adverse events were: injection site reactions, such as pain and erythema, constitutional symptoms, Guillain-Barré syndrome, seizures, and anaphylaxis, though these were rare or very rare. Adverse events reported to the VAERS following I/QIVs were similar to those following TIVs [28].
On the basis of this evidence, the two quadrivalent influenza vaccines have recently been licensed in many countries, and have been gradually replacing TIVs in the immunization programs of these countries.

Expected benefits of the quadrivalent influenza vaccines

As mentioned above, two different influenza B strains may co-circulate during an influenza season. Therefore, adding a second B strain to influenza vaccines increases the likelihood of achieving adequate protection against influenza B disease. Some recent studies have evaluated the expected benefits of including QIVs in national immunization programs. For instance, Eichner et al. compared the effects of QIVs and TIVs on influenza incidence by using an individual simulation model in which the concomitant transmission of four influenza strains, maternal protection, boosting of existing immunity, loss of immunity and cross-immunizing events between the B lineages over 50 years were considered as variables. Their study found that QIV administration could prevent 11.2% of all influenza B infections which still occur with TIV, thus reducing the influenza burden on the community [29].
The public health impact of QIVs in the United States was analyzed in a model by Crépey and colleagues in a dynamic retrospective framework with real-life vaccine mismatch.
Assuming 70% cross-protection of the efficacy of a matching vaccine, the model predicted that QIV would have prevented, on average, about 16% more B lineage

cases than TIV over the period 2000-2013 [30]. The elderly (≥ 65 years) and adults aged 50-64 years were seen to benefit most from QIV, with 21% and 18% reductions, respectively, in B lineage cases [30].
Van Bellinghen et al. conducted a lifetime economic evaluation of QIVs in comparison with TIVs in elderly people and clinical risk groups in the UK. Using a multi-cohort Markov model, they estimated that quadrivalent influenza vaccination could further reduce the disease burden of influenza. The QIVs would be expected to result in substantial health benefits, reducing the number of symptomatic influenza cases, medical visits, complications, hospitalizations for complications and deaths, in comparison with TIVs [31]. In the UK, another study by Meier et al. applied a lifetime, multi-cohort static Markov model involving seven age-groups, and obtained analogous findings [32].
Thommes EW and colleagues used an age-stratified, dynamic four-strain transmission model which incorporated strain interaction, transmission-rate seasonality and age-specific mixing in the population, in order to demonstrate the cost-effectiveness of quadrivalent influenza vaccines in Canada and the United Kingdom. The results of this analysis revealed that switching from trivalent to quadrivalent vaccines would be a cost-effective means of further reducing the burden of influenza in both countries [33].
You JH and colleagues simulated the outcomes of QIV vs. TIV in 6 age-groups: 0-4 years, 5-9 years, 10-14 years, 15-64 years, 65-79 years and ≥ 80 years. Direct cost alone, direct and indirect costs, and loss of quality-adjusted life-years (QALYs) due to TIV-unmatched influenza B infection were simulated for each study arm. In the base-case analysis, QIV was more effective than TIV in all age-groups, and proved to be cost-effective from the societal perspective in all age-groups, except for those aged 15-64 years. From the healthcare provider's perspective, QIV seemed to be cost-effective in very young (6 months – 9 years) and older (≥ 80 years) age-groups [34].
In Italy, a lifetime, multi-cohort, static Markov model was constructed, and was run in one-year cycles for a lifetime (Maximum age: 100 years). The analysis demonstrated that QIV would be cost-effective compared with TIV. Specifically, QIV would be expected to reduce the number of influenza cases (by about 1,413.887), complications (by about 169,638), hospitalizations for complications (by about 41,862) and influenza deaths (by about 20,905). The incremental cost-effectiveness ratio (ICER) was € 18,883/QALY for the base case [8].

Conclusions

Influenza B viruses have a considerable public health burden, particularly among children and at-risk subjects. The belief that influenza B illness is less severe than influenza A leads to underestimation of its real impact. However, the type B influenza virus causes 20% to 25% of influenza infections worldwide. Since the mid-1980s, surveillance data have shown frequent co-circulation of both influenza B lineages, B/Victoria-like and B/Yamagata-like, during influenza seasons. The conventional TIVs, containing only a single B strain, showed limited ability to induce effective protection when major or minor mismatches between the influenza B vaccine component and the circulating strains occurred, thus substantially reducing the clinical effectiveness of the trivalent influenza vaccine [35].
The availability of QIVs may contribute to overcoming the well-known difficulties of predicting the circulating B lineage and choosing the right influenza B vaccine component in trivalent influenza vaccines (TIVs) [36].
In recent years, two QIVs, an inactivated vaccine and a live-attenuated vaccine, have been developed and licensed for human use on the basis of the good safety, tolerability and immunogenicity profiles demonstrated during the entire pre-marketing research process [37]. In some countries, such as Canada, national guidelines now recommend QIVs in preference to trivalent vaccines for use in children and young people [38].
Available models simulating the inclusion of QIVs in influenza immunization programs support the benefits of this new preventive tool in terms of reductions in symptomatic influenza cases and related complications. Indeed, QIVs could reduce both direct costs in term of medical visits, hospitalizations and antibiotic prescriptions, and indirect costs related to working days lost by affected people and their caregivers.
However, some issues need to be addressed in the near future. In particular, estimations from simulation models should be confirmed by effectiveness studies in the field and more cost-effectiveness analyses should be conducted in order to verify the expected advantages in different epidemiological scenarios.

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Introduction of a quadrivalent influenza vaccine in Italy: a budget impact analysis

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Keywords

Influenza • Budget Impact Analysis • QIV

Summary

Every year in Italy, the Ministry of Health (MoH) offers influenza vaccination free of charge to all subjects at risk and to all subjects aged ≥ 65 year old. Until 2014-2015 immunization campaign against Trivalent Influenza Vaccine (TIVs) were the only vaccines used in Italy.
Traditional TIVs contain antigens from three viral strains: A(H1N1), A(H3N2), and one of the two B lineages: B(Victoria) or B(Yamagata). Each year, the World Health Organization (WHO) decides which viral strains should be included in the next seasonal influenza vaccine. However, accurately predicting which B-lineage strain will predominate in the upcoming season has proved to be a challenging task, owing to the co-circulation of both lineages.
To address the issue of B-mismatch, a new Quadrivalent Influenza Vaccine (QIV) containing both B-lineage strains has been developed, in order to achieve broader protection against influenza. The new QIV was approved in Italy in 2015 and included by the MoH in the national recommendations for the seasonal immunization campaign against influenza 2015-2016.
Recently, a Health Technology Assessment (HTA) Report has shown that, in comparison with TIVs, the new QIV is cost-effective (Incremental Cost-Effectiveness Ratio (ICER) = € 18,883/(QALY) Quality-Adjusted Life-Year) from the Italian National Health Service (NHS) perspective. The present Budget Impact Analysis (BIA) showed that the introduction of the QIV with a 9% market share in the vaccine mix for the 2015-2016 flu campaign would yield an annual saving of € 674,089, mainly owing to the broader protection offered by QIV vs TIVs with an estimated 49.12% B-mismatch.

Introduction

Every year the Italian Ministry of Health (MoH) offers an Influenza Immunization Program for all subjects at higher risk of flu complications on the basis of age (≥ 65 years old) or clinical and professional condition. Until 2014-2015 immunization campaign against influenza, Trivalent Inactivated influenza Vaccines (TIVs) were the only vaccines used in Italy.
Traditional TIVs contain antigens from three viral strains: A(H1N1), A(H3N2), and one of two B lineages: B(Victoria) or B(Yamagata). Each year, the World Health Organization (WHO) decides which viral strains should be included in the next seasonal influenza vaccine. However, accurately predicting which B-lineage strain will predominate in the upcoming season has proved to be a challenging task, resulting in frequent mismatches with the vaccine strain [1], owing to the co-circulation of both lineages or the predominant circulation of the non-vaccine B-lineage. During mismatch seasons, efficacy and effectiveness against the opposite B lineage are lower [2-8]. To address the issue of B-mismatch, a new Quadrivalent Inactivated influenza Vaccine (QIV) containing both B-lineage strains has been developed, in order to provide broader protection against influenza. The new QIV was available in Italy [9] and included by the MoH in the national recommendations for the seasonal immunization campaign against influenza 2015-2016 [10].
Recently, a Health Technology Assessment (HTA) Report has shown that, in comparison with TIVs, the new QIV is cost-effective (Incremental Cost-Effectiveness Ratio (ICER) = € 18,883/(QALY) Quality-Adjusted Life-Year) from the Italian National Health Service (NHS) perspective [11].
The objective of the present analysis was to estimate the budget impact of the new QIV after its introduction into the national flu immunization campaign in Italy.

Methods

A budget impact analysis (BIA) was made from the NHS perspective, in order to estimate the financial impact due to the introduction of the QIV into the vaccine mix included by the MoH in the influenza immunization campaign for the 2015-2016 flu season.
The BIA included the following input data:

- population eligible for influenza immunization and vaccine coverage (target population);
- epidemiology of influenza in Italy;
- efficacy of QIV *vs* TIV;
- vaccine mix and vaccine cost;
- direct influenza costs.

The analysis considered a single-year time horizon and focused on the first year of QIV introduction by the MoH in the 2015-2016 flu immunization campaign.
The results are shown as the net budget impact of the scenario of QIV in the flu vaccine mix (new scenario) versus the scenario in which only TIVs are used in the influenza immunization program (current scenario).

Target Population

The population targeted by the national Influenza Immunization Program was calculated on the basis of the Italian population in 2014 [12].
Every year in Italy, the MoH offers free influenza vaccination to all subjects at risk (for clinical/professional reasons) and to all subjects aged ≥ 65 year old, regardless of other risk factors.
The prevalence of at-risk subjects eligible for influenza vaccination was calculated from the data collected in 25 EU countries (including Italy) by Ryan et al. [13]. The influenza vaccine coverage data in 2014 were then applied to the Italian general population, in order to estimate the annual number of subjects undergoing influenza vaccination within the national Immunization Program [14, 15].
The target population included in the BIA is summarized in Table I.

Epidemiology of influenza in Italy

The probability of contracting influenza in an unvaccinated population was derived from the study by Turner et al. and is reported in Table II [16].
The prevalence of A and B influenza viruses circulating during a season was estimated as the average data (A virus = 74.12% and B virus = 25.88%) from ECDC Surveillance Reports from 2003 to 2012 (excluding the 2009-2010 pandemic season) [11].
The prevalence of B-lineage strains circulating during a season was estimated as the average data from ECDC Surveillance Reports from 2003 to 2012 (B-Yamagata = 50.88% and B-Victoria = 49.12%) [11].

Tab. I. Target population included in the BIA.

Age-range	Population	Overall Vaccine Coverage (%)	Population at risk (%)	Population at risk vaccinated (%)
< 5	2,724.106	2.04	15.10	9.66
5-17	7,433.899	2.30	15.18	10.86
18-49	25,543.294	3.87	16.52	17.24
50-59	8,435.388	9.50	45.36	19.30
60-64	3,361.039	9.50	45.36	19.30
65-69	3,447.791	55.40	45.63	55.40
70-74	3,044.129	55.40	46.15	55.40
75-79	2,645.596	55.40	47.31	55.40
80-84	2,013.904	55.40	50.05	55.40
≥ 85	1,863.522	55.40	57.44	55.40
Total	60,782,688	16.33	28.66	31.02

Tab. II. Probability of contracting influenza in the population broken down age-range.

Age-range	Probability (%)
< 5	19.21
5-17	19.21
18-49	6.55
50-59	6.55
60-64	6.55
65-69	6.17
70-74	6.17
75-79	6.17
80-84	6.17
≥ 85	6.17
Average	8.58

Efficacy of QIV vs TIV

In the present BIA, we assumed that:

- the efficacy of QIV *vs* TIVs in preventing influenza A viruses was the same; age-specific QIV and TIV efficacy versus influenza A viruses is reported in Table III [17-19];
- the efficacy of QIV *vs* TIVs in preventing influenza B virus was the same for the vaccine B-strain (matching) in TIVs but higher for the B-strain not

Tab. III. Efficacy of QIV *vs* TIVs in preventing influenza viruses.

	Influenza A virus		Influenza B virus			
Age-range	QIV efficacy	TIV efficacy	QIV efficacy	TIV efficacy in match	TIV in mismatch	**Overall TIV efficacy *vs* B virus**
< 5	59%	59%	66%	66%	44%	55%
5-17	59%	59%	77%	77%	52%	64%
18-49	61%	61%	77%	77%	52%	64%
50-59	61%	61%	73%	73%	49%	61%
60-64	61%	61%	73%	73%	49%	61%
65-69	58%	58%	69%	69%	47%	58%
70-74	58%	58%	69%	69%	47%	58%
75-79	58%	58%	66%	66%	44%	55%
80-84	58%	58%	66%	66%	44%	55%
≥ 85	58%	58%	66%	66%	44%	55%
Total	59%	59%	66%	66%	44%	55%

Tab. IV. Unit prices and market shares of the vaccines in the BIA.

Vaccine	Current scenario		New scenario	
	Market share (MS)	Unit price	Market share (MS)	Unit price
Split	49%	2.55 €	52%	2.55 €
Intradermal	26%	5.36 €	25%	5.36 €
Adjuvanted	25%	5.33 €	14%	5.33 €
QIV	0	0	9%	6.00 €
Total	100%		100%	

Tab. V. Cost of influenza: direct costs included in the BIA and probabilities that patients with influenza will generate these costs.

Health resource	Probability of generating the cost for patients with influenza (%)	Cost	Source
GP consultation	60%	20.66 €	[21]
Antibiotic therapy	47.3%	3.53 € (< 18 years)/ 3.06 € (≥ 18years)	Final cost on multiplying the initial cost by the likelihood of receiving antibiotics [22, 23]
Antiviral therapy	0.17%	17.3 € (< 5years) / 38.5 € (≥ 5years)	[24, 25]

included in TIVs, (mismatching); these are reported in Table III. In both cases, the efficacy of QIV *vs* TIVs was derived from the meta-analysis by Tricco et al. [20];
- the B-mismatch value considered in order to estimate the overall efficacy of TIVs *vs* influenza B was 49.12%.

The overall efficacy of TIVs *vs* influenza B virus in the present analysis was derived by applying the following formula:

TIVs Overall efficacy *vs* influenza B-virus = (TIV efficacy in match*B-matching) + (TIV efficacy in mismatch*B-mismatching)

For example, if, in subjects aged 5-17 years, the efficacy of TIVs *vs* B is 77% in the scenario of matching and 52% in the scenario of mismatching, on considering an average TIV B-match of 49.12%, the overall efficacy of TIVs *vs* influenza B in that age-group is:

TIV Overall Efficacy *vs* influenza B virus = (77%*100%-49.12%)+(52%*49.12%) = 64%

Vaccine mix and vaccine cost

The BIA was conducted by comparing two scenarios:
Current scenario: this scenario included only TIVs in the vaccination strategy, and the vaccine mix was based on the TIV doses included in the allotments requested by the 20 Italian Regions for the 2014-2015 flu season (when QIV was not yet available on the market); specifically, the vaccine mix in the analysis included:
- inactivated trivalent split influenza virus vaccine (Split);
- intradermal influenza vaccine (Intradermal);
- adjuvanted influenza vaccine (Adjuvanted).

New scenario: this scenario included the QIV as an alternative to TIVs and the vaccine mix was based on QIV and TIV doses included in the allotments requested by the 20 Italian Regions for the 2015-2016 flu season; specifically, the vaccine mix in the analysis included:
- inactivated trivalent split influenza virus vaccine (Split);
- intradermal influenza vaccine (Intradermal);
- adjuvanted influenza vaccine (Adjuvanted);
- inactivated tetravalent split influenza virus vaccine (QIV).

It was assumed that in both scenarios the B-strain included in TIVs was Yamagata, in accordance with TIV antigen composition in the 2014-2015 and 2015-2016 flu seasons.
Vaccine prices in the analysis were based on the average regional tender price in the 2015-2016 flu season.
The vaccine mix and vaccine prices in both scenarios are summarized in Table IV.

Direct influenza cost

The analysis estimated one-year health resource consumption related to influenza, with or without the introduction of QIV into the National Influenza Immunization program.
Table V reports the direct costs included in the analysis and the probabilities that patients with influenza will generate these costs.
The analysis also took into account the frequency and the cost of influenza patients with complications:
- the frequency of complications in patients with influenza, regardless of age, was 29.46%; this was estimated from the data reported by Sessa et al. [21];
- the frequency of complications requiring hospitalization was 11.56% for subjects at risk and 7.15% for subjects not at risk [26];
- in the analysis, it was assumed that 90.77% of these complications requiring hospitalization were respiratory, and that 9.23% were other complications unrelated to the respiratory tract.

Tab. VI. Costs of influenza complications: inpatient and outpatient settings.

Respiratory complications	Inpatient cost < 18 years	Inpatient cost ≥ 18 years	Outpatient
Bronchitis	1,538 €	1,832 €	90 €
Pneumonia	1,948 €	2,291 €	90 €
Upper Respiratory Tract Infections (URTI)	5,768 €	€4,422	€90
Other complications not related to respiratory tract	2,777 €	2,900 €	83 €

Table VI reports the costs of complications in inpatient (hospitalization) and outpatient settings, based on DRG tariffs.

Results

The objective of this analysis was to estimate the budget impact of the new QIV after its introduction into the National Immunization campaign in Italy.
In the base-case scenario, we assumed that, in the 2015-2016 flu season:

- the TIVs used contained the Yamagata B-strain;
- the prevalence of A and B viruses circulating during the 2015-2016 flu season was 74.12% and 25.88%, respectively, and that of the Yamagata and Victoria B-strains circulating during the same year was 50.88% and 49.12%, respectively;
- the QIV was used in 9% of the population eligible for the National Influenza Immunization campaign in Italy;
- the price of a single dose of QIV was 6.00 €.

The results of the base-case scenario are shown in Tables VII and VIII. The base-case scenario simulated the impact of QIV introduction on the basis of the real volumes of influenza vaccines requested by the Italian Regions for the 2015-2016 flu season, in comparison with the vaccine mix without QIV and based on the TIV volume requested by the Italian Regions for the 2014-2015 flu season (when QIV was not yet on the market).
Comparison of the two scenarios (new versus current) revealed that, according to the estimates in the present analysis (49.12% B-mismatch), the introduction of QIV would prevent 1,601 influenza events (including 1,031 with complications), as a consequence of the broader protection of QIV against B-strain virus.
This broader protection of QIV *vs* TIVs in the new scenario resulted in a saving of € 419,389 in the annual influenza treatment costs borne by the NHS. Although the cost of introducing QIV at 9% (858,538 units) was € 5,151.230 (due to the higher purchase cost of QIVs *vs* TIVs), it was fully offset by the 3% increase in the MS of the split vaccines and the 12% decrease in the MS of the intradermal vaccine and adjuvanted vaccine, which yielded a saving of € 5,405.930. Thus, the net result of introducing QIV on the cost of vaccination was a saving of € 254,700.
The estimated net budget impact of the introduction of QIV into the National Influenza Immunization program in the flu season 2015-2016 was a saving of € 674,089 *vs* the scenario with no QIV.

Tab. VII. Impact of the introduction of a QIV in Italy on influenza cases: base-case results.

	Current scenario	New or alternative scenario	Δ (avoided cases with new scenario)
Subjects covered by vaccination	9,539.315	9,539.315	
With TIVs	9,539.315	8,680.777	
With QIV	0	858,538	
Influenza events without complications in immunized subjects	255,703	254,102	-1,601
Influenza events with complications in immunized subjects	166,596	165,565	-1,031
Bronchitis in immunized subjects	69,924	69,491	-433
Pneumonia in immunized subjects	6,351	6,312	-39
Upper respiratory tract infections (URTI) in immunized subjects	74,944	74,481	-464
Other complications not related to respiratory tract in immunized subjects	15,377	15,282	-95
Hospitalization in immunized subjects	16,073	15,973	-100

The BIA considered two alternative scenarios in addition to that of the base-case:
no B-mismatch:

- prevalence of A and B influenza virus circulating during a season: A virus = 74.12% and B virus = 25.88%;
- prevalence of B-lineage strains circulating: B-Yamagata = 100% and B-Victoria = 0%;
- the QIV was used in 9% of the population eligible for the National Influenza Immunization campaign in Italy;
- the price of a single dose of QIV was € 6.00;
- TIVs contained the Yamagata B-strain.

Tab. VIII. Impact of the introduction of a QIV in Italy on direct influenza costs: base-case results.

	Current scenario (€)	New Scenario (€)	Δ (€)
Vaccination cost	37,924.500	37,669.800	-254,700
TIVs	37,924.500	32,518.570	
QIV	0	5,151.230	
Cost of influenza	3,559.199	3,536.906	-22,293
GP consultation	3,169.698	3,149.846	-19,852
Antibiotic therapy	372,881	370,543	-2,337
Antiviral therapy	16,620	16,516	-104
Cost of influenza with complications	63,844.008	63,446.912	-397,096
Inpatient cost	50,394.190	50,080.269	-313,920
Outpatient cost	13,449.818	13,366.643	-83,176
Total	105,327.707	104,653.618	-674,089

full B-mismatch:

- prevalence of A and B influenza virus circulating during a season: A virus = 74.12% and B virus = 25.88%;
- prevalence of B-lineage strains circulating: B-Yamagata = 0% and B-Victoria = 100%;
- the QIV was used in 9% of the population eligible for the National Influenza Immunization campaign in Italy;
- the price of a single dose of QIV was € 6.00;
- TIVs contained the Yamagata B-strain.

Figures 1 and 2 summarize the results from these two additional scenarios versus the base-case.

In the No B-mismatch scenario, there was no impact of QIV introduction in preventing influenza cases versus TIVs, owing to the complete match between the B-strain circulating and the B-strain contained in the TIVs. Nevertheless, the net budget impact in this scenario was favourable, because the incremental cost due to QIV introduction was fully offset by increased use of split vaccine (Market Share (MS) +3%) and the decreased use of intradermal vaccine and adjuvanted vaccine (MS -12%), produced a net saving of € 254,700 in a year.

In the Full B-mismatch scenario, the influenza cases avoided through the introduction of QIV was 3,120. In this scenario, the broader protection offered by QIV *vs* TIVs was maximized by the 100% mismatch between the B-strain circulating and the B-strain contained in the TIVs. The net budget impact in this scenario was highly in favour of the introduction of QIV, with € 1,087.382 saved in one year. The majority of this saving came from the reduction in influenza treatment costs produced by QIV versus TIVs, owing to the full B-mismatch (-€ 832,692).

Discussion

The WHO and European Health Authorities encouraged the development of QIV in order to achieve broader protection against influenza by reducing the impact of

Fig. 1. Number of avoided cases of influenza due to QIV introduction in the 3 scenarios included in the BIA.

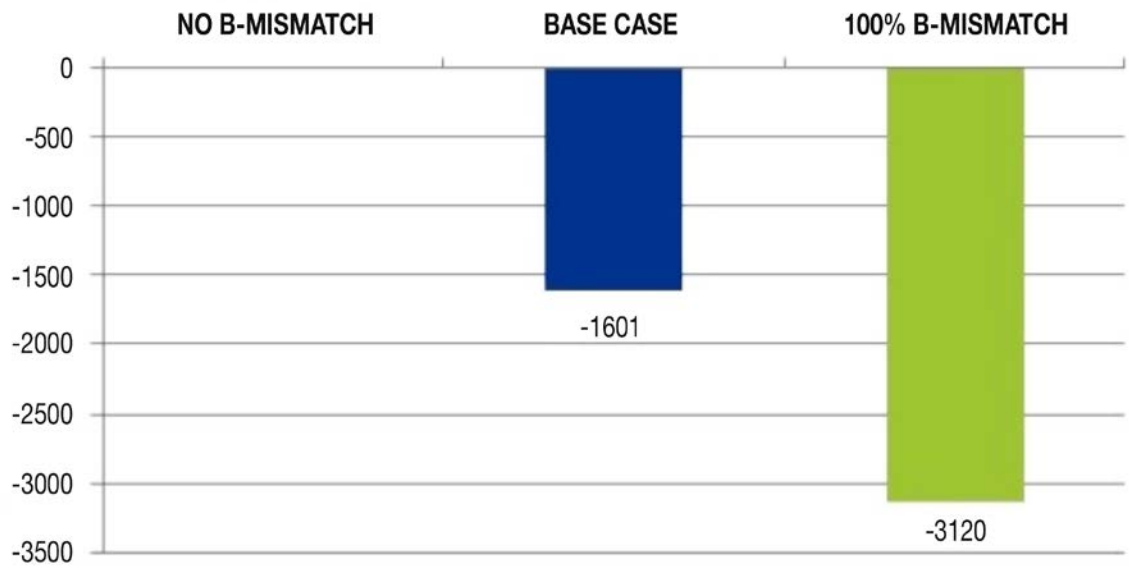
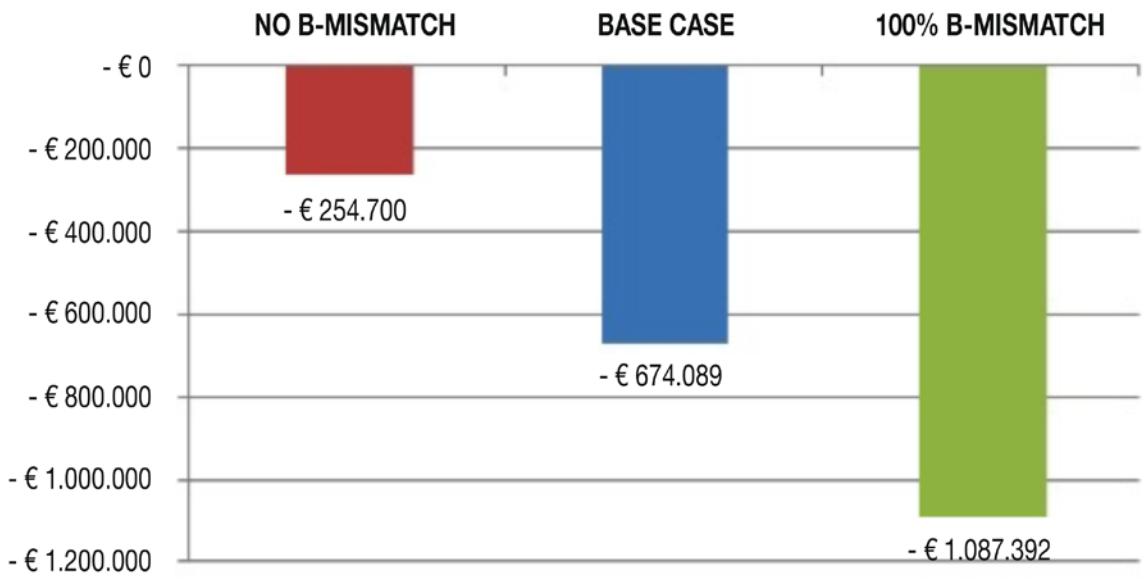


Fig. 2. Number of avoided costs due to QIV introduction in the 3 scenarios included in the BIA.



B-Mismatch. Until 2014-2015 immunization campaign against influenza, only TIVs were available for the National Influenza Immunization campaign in Italy. Traditional TIVs contain antigens from three viral strains: A (H1N1), A (H3N2), and one of two co-circulating B lineages: B(Victoria) or B(Yamagata). Each year, the WHO decides which viral strains should be included in the next seasonal influenza vaccine.

However, accurately predicting which B-lineage strain will predominate in the upcoming season has proved to be a challenging task, resulting in frequent mismatches with the vaccine strain. During mismatch seasons, efficacy and effectiveness against the opposite B lineage are lower because of the lack of cross-protection of the B-strain contained in the TIVs *vs* the circulating B-strain, when they differ.

In 2015, the first QIV was approved by the Italian Drug Agency (AIFA), and was included in the National Influenza Immunization campaign by the MoH for the 2015/2016 flu season.

An HTA Report showed that this new QIV was more cost-effective than TIVs (ICER = € 18,883/QALY) from the Italian NHS perspective.

In the present analysis, we estimated the BIA after the introduction of QIV as an alternative to TIVs. The BIA showed that, with a 9% MS in the vaccine mix for the 2015-2016 flu campaign, the introduction of the QIV yielded an annual saving of € 674,089, mainly due to the broader protection offered by QIV *vs* TIVs with an estimated 49.12% B-mismatch.

QIV is an effective and safe alternative to TIVs, offering broader protection when B-mismatch occurs in the flu season. From the NHS perspective, QIV is cost-effective in Italy; our budget impact analysis estimated that the introduction of QIV into the influenza immunization campaign in 2015/2016 would produce a net annual saving ranging from € 254,700 (0% B-mismatch, Incremental cost of QIV fully offset by the saving due to the increased MS of split vaccines and the decreased MS of intradermal and adjuvanted vaccines) to € 1,087,392 (100% B-mismatch).

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Available influenza vaccines: immunization strategies, history and new tools for fighting the disease

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Influenza vaccines • Immunization strategies • Quadrivalent influenza vaccine • Cost-effectiveness

Summary

The main public health strategy for containing influenza-related disease is annual vaccination, which is recommended for the elderly and others belonging to risk-factor categories, who present the highest morbidity and mortality, as reported by the World Health Organization (WHO) Recommendations.
The availability of different influenza vaccine formulations makes the choice of the best immunization strategy a challenge for stakeholders and public health experts.
Heterogeneity in at-risk categories included in national influenza vaccine recommendations still exists, in particular among European countries. Broader consensus is expected, which should positively impact on influenza vaccination coverage.
The availability of quadrivalent vaccines, containing both influenza B lineages, offers the potential to improve protection by overcoming the drawbacks of wrongly predicting which B lineage will predominate in a given year.

Introduction

The main public health strategy for containing influenza is annual vaccination, which is recommended for the elderly and others belonging to risk-factor categories, which present the highest morbidity and mortality, as reported by the World Health Organization (WHO) Recommendations [1].
Influenza viruses are constantly changing, mainly as a result of so-called "antigenic drift", which consists of the continuous, spontaneous modification of viral surface composition, and regards hemagglutinin (HA) and neuraminidase (NA) proteins. For this reason, the vaccine composition has to be adapted annually to integrate viral strains as similar as possible to the epidemic strains.
The degree of similarity or difference between the circulating viruses and the viruses included in the vaccines is often referred to as "vaccine match" or "vaccine mismatch".
Vaccine effectiveness, i.e. the ability to prevent influenza cases, is determined both by the degree of vaccine matching and by the characteristics of the subjects immunized, such as their age and health status.
The degree of antigenic drift and the frequency of drifted viruses in circulation can change from one season to another, in comparison with each of the strains included in the seasonal flu vaccine. Since 1973, surveillance systems have enabled the WHO to issue recommendations for the composition of influenza vaccines.
Careful analysis of epidemiological data based on the antigenic identification of strains, pathogenic potential and transmissibility is a valuable means of evaluating the persistence and dissemination of new influenza strains [2-4].
Since 1999, the WHO has issued two different sets of recommendations every year: one for the northern and one for the southern hemisphere; these recommendations are issued several months before the influenza season begins, in order to allow timely production of the upcoming seasonal influenza vaccine in conformity with the manufacturers' recommendations.
Even when circulating influenza viruses are mildly or moderately drifted in comparison with the vaccine, available evidence suggests that people may still receive some protective benefit from vaccination [5].

Historical evolution of influenza vaccines

Two main types of influenza vaccine are currently available: inactivated vaccine and live attenuated vaccine. The first inactivated influenza vaccine (IIV) was monovalent and was protective against the A (H1N1) strain. In 1940, however, a different influenza virus was isolated (influenza B) and the first bivalent vaccine was subsequently tested in healthy adults [2].
Current inactivated vaccines are mostly produced by means of propagation in embryonated hens' eggs. However, the availability of embryonated hens' eggs is a limiting factor in vaccine production, and global production is not expected to be able to meet the increased demand for doses in the pandemic season [6].
At the end of the 1970s, a new strain of influenza A with different HA and NA was identified. Since then, two influenza A strains (H1N1 and H3N2 subtypes) and one

influenza B (Victoria or Yamagata lineages) strain have been included in most influenza vaccines, called trivalent influenza vaccines (TIV) [7].
The first trivalent live attenuated influenza vaccine (LAIV) was licensed in Russia in the late 1970s and in North America in 2003. Europe recently recommended its use in children aged 2 years. The aim of vaccination with a live attenuated virus is to induce a secretory and systemic immune response that more closely resembles the immune response detected after natural infection [8]. However, the immunological mechanisms of action and correlates of protection remain largely unclear [9].
In more recent years, improvements were made, primarily in production technologies and use of adjuvants, while innovative formulations were based on two principles: the production of reassortant strains between wild-type viruses (for their antigenic properties) and culture-adapted strains (for their replication properties).
Alternative routes of delivery have been also investigated, in particular intradermal (ID) administration. An ID TIV received marketing authorization in the EU in February 2009, and was licensed by the European Medicines Agency (EMA) for adults older than 60 years in the 2010/11 season in Europe, and in Canada in September 2010. In the US, the same vaccine was approved by the Food and Drug Administration (FDA) on 10th May 2011 and has been available in the US since the 2011/2012 influenza season for subjects older than 64 years.
In 2013, the WHO recommendations included a second influenza B strain in the vaccine composition, allowing member countries to make their own decision on the possibility to recommend a TIV or a quadrivalent (QIV) influenza vaccine in their immunization programs.

Influenza vaccination recommendations

WHO recommendations define the criteria for identifying risk groups and other groups targeted for vaccination. Age is considered a risk factor for flu infection, as the elderly are at high risk of complications such as morbidity, hospitalization and mortality. Vaccination is recommended for the elderly worldwide, though age specifications differ from one country to another.
In the last decade, research has focused on increasing the protection of elderly subjects and improving their immune response, which has been shown to be lower than that of younger adults [1]. A number of studies have demonstrated that MF59-adjuvanted vaccine and ID influenza vaccine confer greater immunogenicity than non-adjuvanted vaccines in the elderly [10-14]. For this reason, it is advisable to immunize these vulnerable subjects with non-conventional vaccines. Other categories of at-risk subjects have been identified, and, on the basis of the latest clinical evidence and guidelines from scientific societies, it is recommended that they should be vaccinated against influenza every year. In this regard, it has been demonstrated that influenza-vaccinated patients with rheumatoid arthritis or systemic lupus erythematosus are less likely to contract pneumonia, acute bronchitis or viral infections than unvaccinated patients [15].
In most studies, neither DMARDs nor TNF inhibitors have hampered humoral immune responses to influenza vaccination, while rituximab has been seen to do so severely [16]. Moreover, a large meta-analysis revealed that the occurrence of adverse events following influenza vaccination was comparable in patients with autoimmune inflammatory rheumatic diseases (AIIRD) and in healthy controls [17]. On the basis of this evidence and expert opinions, in 2011 the Evidence-based European League Against Rheumatism (EULAR) formulated recommendations for annual influenza vaccination in patients with AIIRD.
It is well established that the immunological response to the seasonal TIV influenza vaccine is also attenuated in cancer patients. Rates of seroprotection and seroconversion vary by malignancy type and are higher in patients with solid tumors, unlike in those with hematologic malignancies or in allogeneic hematopoietic stem cell recipients. Recent literature has reported that the use of myeloablative chemotherapy regimens and biologics is correlated with decreased immunogenicity to influenza vaccines. Moreover, in cancer patients, influenza infections not only result in acute illness but can also lead to delay in vital treatments for the malignancy, such as subsequent dosing of chemotherapy or biologics. In order to avoid these complications, vaccination remains the principal way to boost immunity against seasonal influenza, and therefore prevent infection [18].
The use of systematic influenza vaccination in patients with coronary heart disease prevents cardiovascular morbidity and all-cause mortality, as reported in various cohort studies and randomized clinical trials [19]. On the basis of this evidence, since 2006 the American Heart Association and American College of Cardiology has recommended influenza immunization with inactivated vaccine as part of comprehensive secondary prevention in persons with coronary and other atherosclerotic vascular diseases (Class I, Level B) [20].

Recommendations for use of influenza vaccines in the US

In the US, recommendations for routine use of vaccines in children, adolescents and adults are issued by the Advisory Committee on Immunization Practices (ACIP) [21]. Routine annual influenza vaccination is currently recommended for all persons aged ≥ 6 months who do not have contraindications. No preference is expressed for LAIV or IIV for any person aged 2 through 49 years for whom either vaccine is appropriate, but some indications are given for LAIV, which should not be used in particular conditions: confirmed severe allergic reactions, asthma, long-term aspirin use and most forms of altered immunocompetence. In the case of specific immunocompromising conditions, the Infectious Diseases Society of America (IDSA) has published detailed guidance for the selection and timing of vaccines in persons with congenital immune disorders, stem-cell

and solid-organ transplantation, anatomic and functional asplenia, and cochlear implants [22].

Recommendations for use of influenza vaccines in Europe

In Europe, the European Centre for Disease Prevention and Control (ECDC) publishes periodic reports of national recommendations for the upcoming influenza season and of vaccination coverage rates in all 31 Member States [23]. At present, there is no consensus among European countries regarding the routine seasonal influenza vaccination of children, although this recommendation is now standard in the United States [24], and the WHO recommends vaccinating children aged from 6 to 59 months. The reluctance of some countries to adopt this measure may reflect a lack of evidence regarding cost-effectiveness and risk perception [25]. Live intranasal vaccines not requiring injection were licensed by the European Medicines Agency in 2010 and may, in the near future, increase the acceptance and delivery of annual vaccination among those EU/EEA countries recommending vaccination for children. As yet, however, the immunization rate in this age-group is still very low [26].

Since the 2010/11 pandemic season, the number of countries recommending seasonal influenza vaccination for pregnant women has increased, although there are some differences between countries with regard to the period in which vaccination is recommended. A body of literature has demonstrated the safety and effectiveness of vaccine in this group, including benefits for the fetus and the newborn child [27, 28].

In all 31 Member States, seasonal influenza vaccination is recommended for patients with immunosuppression due to disease or treatment and those with metabolic disorders or chronic pulmonary, cardiovascular and renal diseases. In other chronic conditions, such as hepatic disease, HIV/AIDS and morbid obesity, vaccination is recommended only in some countries [29-31].

Influenza vaccination is also offered to healthcare workers (HCWs) in most European countries. In some cases, recommendations also extend to other professional categories, such as military personnel, poultry industry workers, laboratory staff, police, firefighters, veterinary service workers and educational staff. However, vaccination coverage in these at-risk groups is still insufficient.

Member States are encouraged to adopt and implement national, regional or local action plans or policies, as appropriate, aimed at improving seasonal influenza vaccination coverage, with the aim of reaching a vaccination coverage rate of 75% in 'older age groups' as soon as possible, and, if possible, in all the other risk groups [32].

Recommendations for use of influenza vaccines in Italy

In Italy, representatives of the Ministry of Health, regional health authorities, the National Institute of Health and scientific societies constitute the National Committee on Immunizations, which annually updates a document indicating vaccine composition and recommendations for groups at risk.

The vaccination coverage target is established in each year at 75% for all subjects aged over 64 years. Influenza vaccination is also recommended for high-risk individuals < 65 years old, the target coverage rate being the same.

At-risk groups comprise pregnant women in the second and third trimesters, adults and children aged six months or more with chronic diseases, such as pulmonary, neurologic, cardiovascular, renal, or hepatic diseases, haematological disorders, metabolic disorders, immunosuppressed individuals, HIV/AIDS patients, the morbidly obese, long-term aspirin users (subjects < 18 years), healthcare workers and other at-risk occupational groups, residents of long-term care facilities, and household contacts of immunosuppressed individuals or individuals with chronic medical conditions [33, 34].

New quadrivalent influenza vaccines: strategies for use and cost-effectiveness studies

Since February 2012 in the US and since the 2014/2015 influenza season in the European Union/European Economic Area (EU/EEA), QIV influenza vaccines containing both B lineages for each season have been available. These offer the potential to improve protection by overcoming the drawbacks of wrongly predicting which B lineage will predominate in a given year.

TIV influenza vaccines contain antigens of the two A subtypes, A (H3N2) and A (H1N1), and of only one B lineage, which results in frequent mismatches between the circulating B strain and the vaccine B strain. QIV influenza vaccine has shown improved immunogenicity, compared with TIV, in children, adults and elderly people [35]. Moreover, QIV has proved to have an acceptable safety profile in comparison with TIVs, as reported in a phase III randomized controlled trial. In this trial, which enrolled a total of 3094 children, an inactivated QIV influenza vaccine proved non-inferior to the TIVs with regard to the shared strains, and superior with regard to the added B strains [36]. Block et al. obtained similar results in a study demonstrating the non-inferior immunogenicity of a Quadrivalent Live Attenuated Influenza Vaccine (Q/LAIV) to that of T/LAIV in children aged 2-17 years. The addition of a fourth vaccine strain did not result in clinically significant differences in the spectrum of safety events [37].

The safety and immunogenicity of a QIV inactivated influenza vaccine have also been investigated in adults. In a multicenter trial conducted in the 2011/2012 influenza season, Pepin et al. reported that antibody responses to the QIV were superior to the responses to TIV for the unmatched strains and non-inferior for the matched strains. Solicited reactions, unsolicited Aes and SAEs were comparable between the experimental QIV and the TIVs [38]. Moreover, QIV has the potential to substantially reduce the number of influenza infections, as reported in a ret-

rospective study by Crepey et al., in which QIV prevented 16% more B lineage cases in the United States [35].
On the basis of evidence and recent studies, QIV influenza vaccines are expected to provide a significant public health and economic benefit, and seem to be an innovative means of achieving universal influenza immunization, as recommended by some countries in which seasonal influenza vaccination has been extended to large numbers and diverse population subgroups not at high risk [39].
Several countries have adopted QIV vaccination for target populations. This choice has been based on cost-effectiveness analyses that take into account updated vaccine prices, reference costs, the circulation of influenza strains, and data on the burden of illness.
An economic evaluation of QIV influenza vaccination, as compared with TIV influenza vaccination, in elderly people and clinical risk groups was conducted in the UK over 10 years: from the 2002-2003 to the 2012-2013 influenza seasons. The main outcome measure was the number of quality-adjusted life-years (QALYs) gained and the incremental cost-effectiveness ratio (ICER) per QALY gained; the analysis reported that QIV vaccination would be expected to reduce influenza cases, hospitalizations and deaths to a greater degree than TIV vaccination, and the estimated ICER over a lifetime horizon was £ 14,645/QALY gained [40].
In the US, the cost-effectiveness of a policy of universal vaccination with QIV inactivated vaccine versus TIV inactivated vaccines was evaluated; the ICER was predicted to be $ 90,301/QALY gained. Influenza B vaccine-matched and -mismatched efficacies among adults aged > 65 years had the greatest impact on the ICER: for all these reasons, vaccination with QIV in the US is predicted to reduce morbidity and mortality [41].
In Europe, Eichner et al. obtained similar results on using an individual-based simulation tool to connect people in a dynamically evolving, age-dependent contact network based on the POLYMOD matrix [42].

Conclusions

In accordance with international recommendations, vaccination providers and immunization programs should work to achieve the target of 75% vaccine coverage in at-risk groups, with a view to reducing influenza-related morbidity and mortality. This goal can be reached by expanding access to immunization services and extending vaccination campaigns to other target populations, on the basis of the most recent scientific evidence available. While the introduction of new vaccines is desirable, their use must be supported by strong evidence, in terms not only of higher immunogenicity, but also of greater effectiveness, in order to combat the growing phenomenon of vaccine hesitancy. Indeed, public debate over vaccine effectiveness, which largely depends on matching between circulating influenza strains and vaccine strains, can negatively impact on vaccination coverage. For this reason, it is crucial to improve systems of surveillance of the most likely circulating strains and to ensure greater and broader vaccine effectiveness, which is expected to be achieved in the near future through the use of QIV vaccine. Moreover, switching from TIV to QIV is expected to be a cost-effective strategy that will further reduce the burden of influenza, as reported in several recent analyses worldwide.
The evolution of manufacturing processes will see the development of new technologies able to produce large quantities of vaccine rapidly in each influenza season, and new vaccines will be introduced. However, the production of a universal vaccine that is long-lasting and not subject to antigenic modifications still remains the ultimate goal.

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The old and the new: vaccine hesitancy in the era of the Web 2.0. Challenges and opportunities

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Keywords

Digital disintermediation • Vaccine hesitancy • Fast data-monitoring system

Summary

The phenomenon known as vaccine hesitancy (a term that includes the concepts of indecision, uncertainty, delay and reluctance) is complex, closely linked to social contexts, and has different determinants: historical period, geographical area, political situation, complacency, convenience and confidence in vaccines. The World Health Organization (WHO) recommends that vaccine hesitancy and any proxy of it should be constantly monitored. Given the growing importance and pervasiveness of information and communication technologies (ICTs), the new media could be exploited in order to track lay-people's perceptions of vaccination in real time, thereby enabling health-care workers to actively engage citizens and to plan ad hoc communication strategies. Analysis of so-called "sentiments" expressed through the new media (such as Twitter) and the real-time tracking of web-related activities enabled by Google Trends, combined with the administration of specific online "surveys" on well-defined themes to target groups (such as health-care workers), could constitute a "Fast data monitoring system" that yields a snapshot of perceptions of vaccination in a given place and at a specific time. This type of dashboard could be a strategic tool that enables public services to organize targeted communication actions aimed at containing vaccine hesitancy.

Vaccine hesitancy

A complex, multi-faceted phenomenon that dates back to the first vaccinations performed by Dr. Zabdiel Boylston (1721) and Edward Jenner (1796-1798), vaccine hesitancy constitutes a threat to the implementation of immunization programs [1-5]. Concerns and/or misconceptions regarding vaccines may prompt people to delay or refuse vaccination. Consequently, suboptimal vaccination coverage rates may jeopardize the attainment of herd immunity and result in pathogen recrudescence and disease outbreaks. It is therefore crucial to understand the determinants of compliance with vaccination. These have been grouped into the 5A taxonomy (Access, Affordability, Awareness, Acceptance, and Activation) [6] or the 3C model (Complacency, Convenience and Confidence) [7].

Vaccine hesitancy is a major, global issue. Being a very dynamic and heterogeneous phenomenon, it changes throughout space and time, varying according to the context and to geographic and demographic variables. Furthermore, as vaccine hesitancy is setting-dependent and vaccine-specific, it is highly unpredictable.

Today, vaccine hesitancy is closely connected with the increasing importance of the Internet and the new information and communication technologies (ICTs) [8].

The new media

The pervasive diffusion of the web is a characteristic feature of modern society. In 1962, Marshall McLuhan distinguished four different epochs of history: the first dominated by the oral tribe culture, the second by the manuscript culture, the third termed as the Gutenberg Galaxy, and the fourth defined as the electronic age [9]. Technological and information changes have contributed to the rise of the fluid postmodern society, which is characterized by uncertainty, nomadism, fragmentation, disintegration and relativization of the truth [10].

Digital media have dissolved reality into an infinite array of bits, an ocean, a fluctuating swarm, a chaotic magma, that can be navigated interactively by accessing the Internet. Indeed, the static heritage and the rigidly codified system of knowledge and hierarchies of the Gutenberg Galaxy have been broken down by the web.

Whilst the Web 1.0 was static, the Web 2.0 (and its further evolution, including the semantic web) has become a highly dynamic and interactive information reality, enabling users to share their content and to become consumers and producers at the same time (*prosumers*). Thus, the differences and the distance between webmasters and web surfers are becoming increasingly blurred.

This has led to a phenomenon known, in the field of electronic commerce, as "digital disintermediation"; consumers purchase products directly from producers *via* the Internet, thereby drastically shortening and modifying the product delivery chain and "disintermediating" the standard supply model. This direct-to-consumer model has its analogues in the medical field; in the emerging postmodern healthcare model, patients proactively search the Web for health-related information, thus bypassing clinicians. In this perspective, the legitimacy of science is questioned and expertise is redefined.
On the other hand, within e-health or health 2.0 – a term that indicates new modalities, strategies, and practices of healthcare delivery that exploit, and are supported by, electronic processes and communication – patients are at the center of healthcare processes, as they are more involved in and informed of the many steps of medical decision-making [11].

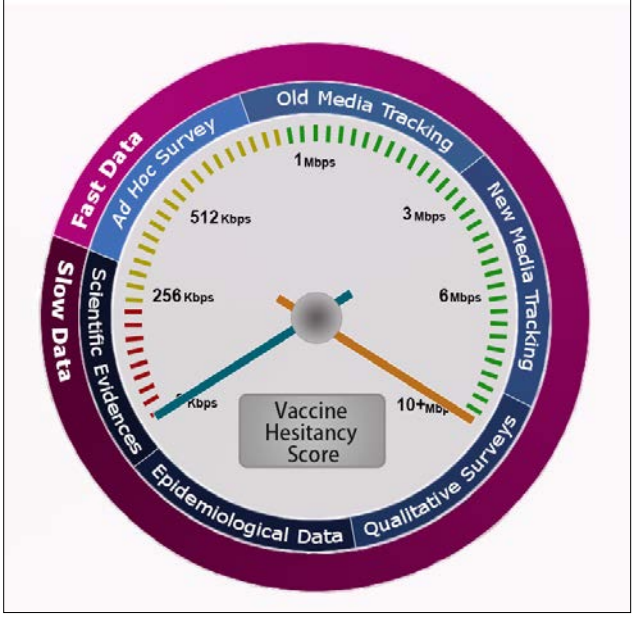
Vaccines and the web

Within the above-mentioned model, ICTs play a role in parents' decisions on whether or not to vaccinate their children. In Italy, according to the latest available data released by the National Institute of Statistics (ISTAT), 80% of parents use the Internet to search for vaccine-related information [12]. Moreover, a recent publication by CENSIS has shown that 48.6% and 42% of parents use social networks and the web, respectively, to obtain information on vaccines [13]. This implies that workers in the field of Public Health have to rethink their way of interacting with the media, especially the new media, in order to combat the unjustified alarmism and hoaxes regarding vaccination. Furthermore, they need to combine the accuracy and scientific rigor of information with a modality of communication that can be easily understood by lay-people. Targeted and authoritative information can be accompanied by awareness campaigns and school interventions. Indeed, while 91.1% of parents are aware that vaccines have eradicated diseases and constitute an important means of protecting themselves and the community, they still have doubts, uncertainties and concerns about vaccine safety. This highlights a specific information gap that needs to be properly addressed.
The Web 2.0 acts as a post-modern Pandora's box, which is difficult to control and to discipline. It can therefore spread disinformation, misleading news and falsehoods [14, 15]. Indeed, many critical websites or pages show anti-vaccination content. Despite being of low quality, these are highly ranked and are therefore frequently returned by search engines and consulted by users. Furthermore, they are more readable than websites containing information from reliable sources [16, 17]. Moreover, websites that are openly skeptical or even hostile to vaccinations are highly active on the Internet [18]. Since 2010, however, public institutions have increased the presence of sites in favor of vaccination. Consequently, in 2015, the use of such search terms as "immunization" or "vaccination" was seen to yield a predominance of pro-vaccination websites created by public institutions, scientific societies or individual health professionals [19].

Challenges and opportunities

The issue of vaccination is increasingly influencing political agendas.
Opportunities derive directly from the considerations that vaccine hesitancy is unpredictable and fluid and that anti-vaccination movements exploit the new ICTs. Workers in the field of Public Health can also exercise their role of advocacy on the Internet. An example of this is the website VaccinarSì (http://www.vaccinarsi.org/), which initially emerged from an idea by Mrs. Ulrike Schmidleithner (http://vaccinarsi.blogspot.it) [20]. Another example of bottom-up initiatives is that of an online pro-vaccination campaign started by an Italian mother, Miriam Maurantonio. Concerned about low vaccination coverage and the growing visibility of anti-vaccination movements, Mrs Maurantonio asked parents to take "selfies" and to post them by using the hashtag #iovaccino (#Ivaccine). This initiative has spread to other social networks, such as Facebook and Instagram, reaching thousands of followers and subscribers.
Further exploitation of ICTs involves applications for smart-phones, the popularity of which is rapidly increasing. In Italy, for example, the app "Pneumo Rischio" has been developed specifically to increase public awareness of invasive pneumococcal disease and its prevention [21].
All these instruments can be exploited in order to empower lay-people and increase their health literacy. Local Health Units (LHUs) can utilize the new media to establish a novel, interactive dialogue with residents in their territories. This model has been termed as "@ Prevention" [22]. However, in order to exploit the new media effectively, it is essential to improve the information skills of clinicians and pediatricians. To this end, the Italian Scientific Society of Pediatricians (FIMP) has launched the "Hermes project", named after the Greek god of communication, the protector and patron of oratory and wit, literature and poetry [23]. This project provides a step-by-step course that teaches pediatricians how to open a Twitter account and to dynamically interact and communicate with children's families, so that they can address their concerns or doubts about vaccination.
Another opportunity is constituted by "infodemiology" (a *port-manteau* of information and epidemiology) and "infoveillance" (a *port-manteau* of information and surveillance), which have been introduced by Gunther Eysenbach as new emerging concepts and approaches [24]. Public health and epidemiological research can be based on large-scale monitoring and data-mining.
Infodemiology and infoveillance take into consideration all the virtual activities carried out by lay-people while

Fig. 1. Vaccine hesitancy is a fluid and constantly changing phenomenon that needs to be monitored over time. As recommended by the Strategic Advisory Group of Experts (SAGE) on vaccine hesitancy, an integrated approach based on a combination of both slow and fast data collection (scientific evidence and, in particular, systematic reviews, epidemiological data, qualitative surveys, *ad hoc* surveys, old and new media tracking) can ensure proper tracking of the phenomenon.



surfing health-related sites and/or communicating and sharing their health status. These pieces of information are known as "fast" or "big" data, in that this incredible wealth of data is quickly available to researchers.

Analysis of the so-called "sentiments" expressed through the new media (i.e. Tweets) [25] and the real-time tracking and monitoring of web-related activities, enabled by Google Trends, can yield a snapshot of the "social climate"; this picture could also be combined with *ad hoc* online surveys on well-defined themes and topics, administered to specific target groups (i.e. health workers). The resulting "Fast data monitoring system" could provide a real-time representation of perceptions of vaccination. Moreover, the use of georeferentiation through sophisticated and advanced geographic information systems (GIS) could capture perception in a specific place and at a given time.

This type of dashboard could be a strategic tool for public services, which could then organize targeted communication actions aimed at containing vaccine hesitancy (Fig. 1).

Conclusions

The World Health Organization (WHO) recommends that vaccine hesitancy and any proxy of it should be constantly monitored [26]. Given the growing importance and pervasiveness of ICTs, the new media could be exploited in order to track lay-people's perceptions of vaccination in real time, thereby enabling health-care workers to actively engage citizens and to plan *ad hoc* communication strategies [27-29].

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