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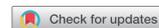


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REVIEW



Strategies in recommending influenza vaccination in Europe and US

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ABSTRACT

There is potential for influenza vaccine programmes to make a substantial impact on the disease burden. The World Health Organization (WHO) has identified young children, pregnant women, persons with chronic medical conditions, and the elderly as being at risk for severe influenza disease and therefore important groups to be considered for influenza vaccination. Applying the methodology of scoping review of grey and scientific literature we described the European and the US approach to influenza vaccine prevention. Although vaccination remains the most effective means of reducing the incidence and severity of influenza, vaccine uptake in many European countries remains suboptimal (i.e. 45.5% in the elderly, 24% in health care workers, from 49.8% in patients with chronic medical conditions, median 23.6% in pregnant women) and vaccine strategies are not harmonized in particular with regard to vaccinating healthy children. Whereas in the US the vaccine strategies are more standardized across states and vaccine coverage are higher than those reported in EU on average.

The integration of different strategies is crucial in order to increase influenza vaccine coverage: public health authorities should encourage healthcare workers to vaccinate themselves, as target category, and to recommend seasonal influenza vaccination to people in the target groups; there should also be structured communication campaigns on influenza and influenza vaccines, directed specifically at these target groups, and an adequate and sustainable funding is also an important factor to achieve higher vaccination coverage rates.

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Introduction

Influenza is a major public health problem. Influenza affects every third child and every tenth adult, about 60 of the 500 million inhabitants of the European Union every year.^{1–2} It is related to 5 million of mild clinical disease, 150 thousand hospital admissions and 15 to 40 thousand of excess deaths annually.^{3–6}

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 acute respiratory diseases, including influenza.^{7–8} However, vaccines are the cornerstone for preventing influenza and its consequences and influenza vaccination is still the main tool for preventing the spread of influenza.

The World Health Organization (WHO) has identified young children, pregnant women, persons with chronic medical conditions, and the elderly as being at risk for severe influenza disease and therefore important groups to be considered for influenza vaccination.⁹ Beginning in 2012, WHO recommended that pregnant women to be prioritized for influenza vaccination by countries initiating or expanding influenza vaccine programmes.¹⁰ Moreover, WHO recommended coverage targets of 75% (minimum achievable goal) and 95% (optimal goal in the target population) in elderly and at risk individuals by 2010.¹¹ In Europe, annual vaccination recommendations vary widely among Member States but are usually restricted to individuals with specific underlying conditions and to the

elderly¹² and even in these groups, vaccine coverage in the last decade has decreased and was below 50% in 2014. In the US, routine annual influenza vaccination is recommended for all persons aged ≥ 6 months who do not have contraindications.¹³

Twice yearly, the WHO Global Influenza Programme leads a consultation of experts to recommend the composition of influenza vaccines based on the antigenic characteristics of circulating influenza viruses tested within the WHO Global Influenza Surveillance and Response System (GISRS).¹⁴ The Northern Hemisphere influenza vaccine composition is recommended in February and the Southern Hemisphere influenza vaccine composition is recommended in September. Ensuring antigenic match of vaccine strains to circulating viruses is important to optimize vaccine effectiveness.

Many aspects of influenza disease and prevention have to be considered by countries when making decisions about immunization programmes, including disease burden, vaccine-specific issues such as vaccine performance and vaccine safety, programme impact, programmatic issues, country capacities, and political will. Hereby we present an overview of the European and the US approach to influenza vaccine prevention.

Methods

We applied the methodology of systematic scoping review of grey and scientific literature as described by Arksey et al.,¹⁵

taking into account the methodology for the conduction of systematic literature reviews proposed by Khan et al.,¹⁶ and search strategies as presented by Relevo et al.¹⁷ and by DeLuca et al.¹⁸ The scientific database PubMed was used, and selected web-sites were accessed for the grey literature search. The search encompassed four concepts, searched by Medical Subject Headings (MESH), including influenza (influenza, human [MESH] or influenza [MESH] and human [MESH]) and vaccination [MeSH] and recommendations [MESH] and EU [MESH]) and US [MESH]. Article/report selection and extraction of information was performed by one reviewer.

The search restrictions used were English language and publication date from 2010 to present. Descriptive/analytical studies/reports on the diseases of interest published in Europe and USA were considered. Documents for which abstracts/full texts were not retrievable from open source and journal subscriptions available to the team were excluded.

The burden of influenza

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.¹⁹ 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.²⁰ 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.^{21–22} In temperate countries in the northern hemisphere, the weekly number of deaths among the elderly (individuals aged ≥ 65 years) frequently exhibits sharp increases above normal expected levels of mortality during the winter season. This excess mortality in the elderly is often attributed to seasonal influenza, especially in seasons dominated by influenza A (H3N2), but factors other than influenza including other respiratory tract infections or environmental conditions (e.g. cold spells) can also play an important contributory role. From 1976 to 2007, individuals aged ≥ 65 years accounted for approximately 90% of all influenza-related deaths in the US and similar results were also obtained in Italy.²³

Available influenza vaccines

Two types of influenza vaccine are available: inactivated vaccine and live attenuated vaccine. Inactivated vaccines are mostly produced by means of propagation in embryonated hens' eggs. Since the end of the 1970s, when a new strain of influenza A with different HA and NA was identified, 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).²⁵ In Europe, inactivated vaccines are mainly used, the first

trivalent live attenuated influenza vaccine (LAIV) was licensed and used in Russia and in North America in 2003. Live intranasal vaccines not requiring injection were licensed by the European Medicines Agency in 2010 and its use is recommended in children aged at least 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 infection²⁶ and it may, in the near future, increase the acceptance and delivery of annual vaccination among those EU/EEA countries recommending vaccination for children.

The immunological mechanisms of action and correlates of protection of influenza vaccines remains largely unclear.²⁷ In recent years, improvements were obtained in technological advances and the use of adjuvants. However, innovative formulations were mainly based on two principles: the production of reassortant strains between wildtype viruses (for their antigenic properties) and culture adapted strains (for their replication properties).

Alternative routes of delivery, in particular intradermal (ID) administration, have been also investigated. 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.²⁸ 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).²⁸

Influenza vaccination recommendations

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.²⁹ At present, there is consensus among European countries regarding the routine seasonal influenza vaccination of elderly, however, for children few countries (Austria, Estonia, Finland, Latvia, Malta, Poland, Slovakia, Slovenia and the United Kingdom) have introduced the recommendation of routine influenza vaccination at different age groups and with different reimbursement methods,²⁹ although this recommendation is now standard in the United States,³⁰ and the WHO recommends vaccinating children aged from 6 to 59 months.³¹

Although vaccination of pregnant women has been recommended since 2005 by the World Health Organization (WHO),³¹ the utilization of the influenza vaccine during pregnancy is still limited because of concerns about its potential effect on the fetus development and possible teratogenic effects.³² 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. In Europe, 27 countries recommend vaccination of pregnant women: twenty-five countries recommend vaccination for all pregnant women; two countries recommend vaccination only for pregnant women with chronic medical conditions. Twenty Member States recommend vaccination at any stage of pregnancy and seven Member States recommend vaccination only for the second and third trimesters. Ten Member States indicated that women who did not receive seasonal influenza vaccination during pregnancy should still be immunised in the immediate postpartum period (within six weeks after delivery).²⁹ A body of literature has demonstrated the safety and effectiveness of vaccine in this group, including benefits for the fetus and the newborn child.³⁰

In all 31 Member States, seasonal influenza vaccination is recommended for patients with immunosuppression caused either by disease or treatment, and to 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 (Table 1).²⁹

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 and difficult to estimate. 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.²⁹

In Europe, the last vaccine coverage data available refers to the 2014–15 season, and on average is 45.5% (range from 1.0% to 76.3%) in the elderly, 24% (from 5% to 54.9%) in health care workers, 49.8% (from 21% to 71.8%) in patients with chronic medical conditions, and 23.6% (from 0.3% to 56.1%) in pregnant women.²⁹

Vaccination as a preparedness measure against cross-border threats in EU

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.³³ The Decision highlights that vaccines are an important component of emergency preparedness; and 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.

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).³⁰ Routine annual influenza vaccination is currently recommended for all persons aged ≥ 6 months who do not have contraindications (Table 1). Until 2015/2016 season no preference was expressed for LAIV or TIV for any person aged 2 through 49 years for whom either vaccine is appropriate, but some indications were 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. Since 2016/2017 season, ACIP release an interim recommendation that live attenuated influenza vaccine not be used, in light of low effectiveness against influenza A(H1N1)pdm09 in the United States during the 2013–14 and 2015–16 seasons.³⁰ 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 who are at increased risk for severe complications from influenza, or at higher risk for influenza-related outpatient, ED, or hospital visits. In particular with individuals aged ≥ 50 years, adults and children with chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus) persons who have immunosuppression (including immunosuppression caused by medications or by HIV infection); women who are or will be pregnant during the influenza season.

The influenza vaccination coverage during the 2014–15 in the US among all people ≥ 6 months, flu season was 66.7% in adults 65 years and older, 50.3% in pregnant women, 59.3% among children 6 months through 17, 47.6% in 18–64 years at high risk and 77.3% in health care workers.³⁰ In the US the vaccine coverage was higher compare to that reported on average in Europe.

Discussion

Although vaccination, nonetheless remains the most effective means of reducing the incidence and severity of influenza, vaccine uptake in many European countries remains suboptimal. This policy analysis indicates that a EU decision-making in the field of influenza prevention is not clearly established. Nevertheless, there is quite large room for collaboration, especially in the field of influenza vaccine effectiveness and safety monitoring. 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.

A major problem is represented by the fact that influenza viruses are the only vaccine preventable viruses that undergo frequent genetic and antigenic changes. As a consequence, the

Table 1. Member States recommending seasonal influenza vaccination by target groups in Europe and the USA.

Target group for vaccine program	EU Countries (age groups recommended)	USA (age groups recommended)
Recommended seasonal influenza vaccination to healthy children or adolescents vaccination to healthy children or adolescents	Austria ($\geq 6\text{mo}$ -18yo), Estonia ($\geq 6\text{mo}$ -18yo), Finland (≥ 6 -36mo), Latvia (≥ 6 -24mo), Malta (≥ 6 -59mo), Poland ($\geq 6\text{mo}$ -18yo), Slovakia ($\geq 6\text{mo}$ -12yo), Slovenia (≥ 6 -24mo) the UK -England (≥ 2 -4yo), UK -Northern Ireland (≥ 2 -11yo), UK -Scotland (≥ 2 -11yo), UK - Wales (≥ 2 -4yo and 11yo)	≥ 6 months
Adults	Austria (18-64 yo), Estonia (18-64 yo), Poland (18-64 yo)	
Elderly	Austria (≥ 50), Belgium (≥ 50), Ireland (≥ 50), Malta (≥ 55), Poland (≥ 55), Germany (≥ 60), Greece (≥ 60), Iceland (≥ 60), Netherlands (≥ 60), Portugal (≥ 60), all the others: (≥ 65)	
Chronic medical conditions (i.e. Respiratory (pulmonary) diseases, Cardiovascular diseases, Renal Disease, Immunosuppression, Metabolic disorders)	All	
Pregnant women:		
<i>Pregnant women with chronic conditions</i>	Croatia and the Netherlands	
<i>Pregnant women at any stage</i>	Czech Republic, Croatia, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Latvia, Liechtenstein, Lithuania, Malta, the Netherlands, Poland, Romania, Slovenia, Spain, Portugal, the United Kingdom	
<i>Pregnant women in the 2nd and 3rd trimester</i>	Austria, Belgium, Cyprus, Germany, Italy, Norway, Sweden, Denmark	
Health Care Workers**	All	

*UK-England and the UK-Wales, vaccination was recommended only for frontline HCWs or those HCWs who have direct contact with patients). In Sweden, vaccination was only recommended for staff caring for severely immunocompromised persons. In Slovakia, vaccination was recommended for HCWs in close contact with patients or foci of infection.

influenza vaccine is reformulated every year and annual revaccination is recommended. Moreover, vaccine induced immunity is not known to last beyond 6–12 months, perhaps less.³⁴

In accordance with international recommendations from WHO and European Commission,¹¹⁻¹² vaccination providers and immunization programs should work to achieve the target of 75% vaccine coverage in at-risk groups, with a view of 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, such as healthy children, on the basis of the most recent scientific evidence available.¹¹

Indeed, decisions regarding the best way to combat the threat posed by seasonal influenza epidemics are heavily influenced by the characteristics of the populations that are at risk, as these are key drivers of disease epidemiology. Europe is one of the most densely populated regions in the world,³⁵ although substantial intra and inter country variation exists. Although variations in density appear to have an impact on the frequency of contacts, a large scale study in a sample of European countries found the age and intensity of contact patterns to be highly consistent.³⁶

The European Commission has limited power to influence national vaccination policies, however, influenza prevention is perceived as a priority at the EU level because of the potential pandemic threat and its subsequent cross-border issues. Therefore, the EU has decided to support national vaccination programmes by providing evidence of the effectiveness and safety of influenza vaccination. However, the strategies in recommending influenza vaccine are different in each country, due to a different background and culture. and it is difficult to harmonize influenza vaccine strategies in Europe.

The perceived low effectiveness of influenza vaccines and the fear of suspected adverse events are considered the main obstacles to increase vaccine uptake. In Europe there was no established system to monitor vaccine effectiveness, while the

surveillance system for monitoring adverse events following immunizations (AEFI) is constituted by the statutory pharmacovigilance system – shared with all other drugs and is coordinated by the European Medicines Agency (EMA) through the Eudravigilance system.³⁷ This routine passive surveillance system is good to detect clear safety signals, but able to support public health authorities who deal with vaccine hesitancy or anti-vaccine lobbies. Therefore, the availability of reliable data on post marketing evaluation of influenza vaccines may constitute an evident added value for national and local Health authorities. To this end, the European Center for Disease Control (ECDC) has funded two different projects one on monitoring of influenza vaccine effectiveness (I-MOVE) and the other one on surveillance and communication of vaccine adverse events (VAESCO).^{38,39}

Since the 2008–9 influenza season, I-MOVE has provided estimates of vaccine effectiveness using standardised protocols for different methods (test negative design case control, cohort, and screening method studies), and a large number of participating EU countries, in order to reach a size large enough to yield robust estimates, with a good geographical representativeness.³⁹ As expected, influenza vaccine effectiveness is strongly dependent on the quality of matching between vaccine strains and circulating virus strains. Definitely, 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. With regard to safety, the VAESCO consortium composed of public health institutions using a multinational case-control study³⁸ followed by a prospective self-controlled case series study [ref] assessed

the risk of Guillain-Barré syndrome (GBS) in individuals vaccinated with the influenza vaccine. The conclusion of both studies was that the risk of GBS was not significantly associated with 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.⁴⁰ Moreover, the added value of such studies was clearly shown when an unexpected increase in narcolepsy cases was reported in Finland and Sweden in 2010, after vaccination with Pandemrix®.⁴¹

There are a lot of expectations coming from the recent scientific progresses in the development of new universal influenza vaccine that is long-lasting and not subject to antigenic modifications,⁴² however, the introduction and use must be supported by strong evidence, in terms of higher immunogenicity and 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.

In 2009, the European Council of Ministers recommended that all EU countries reach an influenza vaccination coverage of 75% in all risk groups by the winter season 2014–15, including individuals 60 or 65 years and older and people with a range underlying medical conditions. Member States are also encouraged to improve influenza vaccine coverage among healthcare workers and maternal immunisation as a measure to reduce the burden of disease among pregnant women and their infants. However, vaccine uptake in most of the EU countries remains low for influenza, the EU target of 75% was reached in only one Member State in the 2013–2014 season, and in the 2014–15 influenza season not a single Member State reached the target.²⁹ While, in the US, even if the target goal of WHO has not been reached in most of the states, on average higher vaccine coverage rates are reported in target groups especially in HCW, pregnant women, individuals with chronic conditions and elderly. Providing evidence-base data on the safety and effectiveness of vaccines, and improving communication may contribute to improve vaccine uptake and to reduce human and economic costs of influenza. But, also the different characteristics of the Health Systems across EU and US could explain differences in vaccine coverage rates.

There were some limitations in this review. Only few studies met inclusion criteria; all studies were observational, often pre-post in design, and the definition of target categories varied by study. However, documents collected through documents and reports (e.g. VENICE reports) retrieved from the gray literature had been very informative for the review.

Conclusions

The integration of different strategies is crucial in order to increase influenza vaccine coverage: public health authorities should encourage healthcare workers to vaccinate themselves, as target category, and to recommend seasonal influenza vaccination to people in the target groups. Moreover, there should also be structured communication campaigns on influenza and

influenza vaccines, directed specifically at these target groups, and an adequate and sustainable funding is an important factor to achieve higher vaccination coverage rates.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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