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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