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

C. COSTANTINO, F. VITALE
Department of Science Promotion and Mother to Child Care "G. D'Alessandro", Hygiene Section, University of Palermo, Italy

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®.

References

[1] Brammer TL, Murray EL, Fukuda K, Hall HE, Klimov A, Cox NJ. *Surveillance for influenza – United States, 1997-98, 1998-99, and 1999-00 seasons*. MMWR Surveill Summ 2002;51:1-10.

[2] Schanzer DL, McGeer A, Morris K. *Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada.* Influenza Other Respir Viruses 2013;7:799-808.

[3] ECDC Technical Report. *Seasonal influenza vaccination in Europe: overview of vaccination recommendations and coverage rates in the EU Member States for the 2012-13 influenza season.* Available online at: http://ecdc.europa.eu/en/publications/Publications/Seasonal-influenza-vaccination-Europe-2012-13.pdf [Accessed 08/02/2016].

[4] Bonmarin I, Belchior E, Lévy-Bruhl D. *Impact of influenza vaccination on mortality in the French elderly population during the 2000-2009 period*. Vaccine 2015;33:1099-101.

[5] Molbak K, Espenhain L, Nielsen J, Tersago K, Bossuyt N, Denissov G, Baburin A, Virtanen M, Fouillet A, Sideroglou T, Gkolfinopoulou K, Paldy A, Bobvos J, van Asten L, de Lange M, Nunes B, da Silva S, Larrauri A, Gomez IL, Tsoumanis A, Junker C, Green H, Pebody R, McMenamin J, Reynolds A, Mazick A. *Excess mortality among the elderly in European countries, December 2014 to February 2015.* Euro Surveill 2015;20.

[6] Office of National Statistics. *Excess Winter Mortality in England and Wales 2014/15 (Provisional) and 2013/14 (Final).* Available online at: http://www.ons.gov.uk/ons/dcp171778_425192.pdf [Accessed 08/02/2016].

[7] Michelozzi P, De Donato F, Scortichini M, De Sario M, Asta F, Agabiti N, Guerra R, de Martino A, Davoli M. *On the increase in mortality in Italy in 2015: analysis of seasonal mortality in the 32 municipalities included in the Surveillance system of daily mortality.* Epidemiol Prev 2016;40:22-8.

[8] Thiberville SD, Gaudart J, Raoult D, Charrel RN. *Influenza-attributable deaths in south-eastern France (1999 to 2010): mortality predictions were undependable*. BMC Public Health 2015;15:539.

[9] Nielsen J, Mazick A, Glismann S, Mølbak K. *Excess mortality related to seasonal influenza and extreme temperatures in Denmark, 1994-2010*. BMC Infect Dis 2011;11:350.

[10] Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. *Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status.* Influenza Other Respir Viruses 2014;8:507-15.

[11] *European monitoring of excess mortality for public health action network*. Available online at: http://www.euromomo.eu/ [Accessed 11/02/2016]

[12] Mazick A, Gergonne B, Nielsen J, Tersago K, Bossuyt N, Denissov G, Baburin A, Virtanen M, Fouillet A, Sideroglou T, Gkolfinopoulou K, Paldy A, Bobvos J, van Asten L, de Lange M, Nunes B, da Silva S, Larrauri A, Gomez IL, Tsoumanis A, Junker C, Green H, Pebody R, McMenamin J, Reynolds A, Mazick A. *Excess mortality among the elderly in 12 European countries, February and March 2012*. Euro Surveill 2012;17.

[13] ECDC/WHO. *FluNews Europe*. Joint ECDC/WHO Europe weekly influenza update bulletin. Available online from: http://www.flunewseurope.org/ (last accessed 11/02/2016)

[14] Signorelli C, Odone A, Conversano M, Bonanni P. *Deaths after Fluad flu vaccine and the epidemic of panic in Italy*. BMJ 2015;350:h116.

[15] van der Werf S, Levy-Bruhl D. *Influenza – the need to stay ahead of the virus*. Euro Surveill 2015;20:21030.

[16] Mosnier A, Caini S, Daviaud I, Bensoussan JL, Stoll-Keller F, Bui TT, Lina B, Van der Werf S, Cohen JM; GROG network. *Ten influenza seasons in France: distribution and timing of influenza A and B circulation, 2003-2013*. BMC Infect Dis 2015;15:357.

[17] Heikkinen T, Ikonen N, Ziegler T. *Impact of influenza B lineage-level mismatch between trivalent seasonal influenza vaccines and circulating viruses, 1999-2012*. Clin Infect Dis 2014;59:1519-24.

[18] Pebody R, Warburton F, Andrews N, Thompson C, von Wissmann B, Green HK, Cottrell S, Johnston J, de Lusignan S, Moore C, Gunson R, Robertson C, McMenamin J, Zambon M. *Low effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 mid-season results.* Euro Surveill 2015;20:21025.

[19] Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. *Prevention and control of Influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 Influenza Season.* MMWR Morb Mortal Wkly Rep 2015;64:818-25.

[20] ECDC. *Seasonal influenza vaccines. Influenza vaccination.* Available online from: http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/vaccines/Pages/influenza_vaccination.aspx#vaccinationstrategies [Accessed 11/02/2016].

[21] Ministero della Salute. *Piano Nazionale Prevenzione Vaccinale. Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2015-2016*. Available online from: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=2218 [Accessed 12/02/2016]

[22] European Centre for Disease Prevention and Control. *Seasonal influenza vaccination in Europe: overview of vaccination recommendations and coverage rates in the EU Member States for the 2012-13 influenza season.* (2015). Available online from: http://ecdc.europa.eu/en/publications/Publications/Seasonal-influenza-vaccination-Europe-2012-13.pdf [Accessed 12/02/2016].

[23] Fischer WA, Gongz M, Bhagwanjeex S, Sevransky J. *Global burden of influenza as a cause of cardiopulmonary morbidity and mortality.* Glob Heart 2014;9:325-36.

[24] Beck CR, McKenzie BC, Hashim AB. *Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology*. J Infect Dis 2012;206:1250-9.

[25] Sheridan PA, Paich HA, Handy J, Karlsson EA, Schultz-Cherry S, Hudgens M, Weir S, Noah T, Beck MA. *The antibody response to influenza vaccination is not impaired in type 2 diabetics.* Vaccine 2015;33:3306-13.

[26] Beck CR, McKenzie BC, Hashim AB, Harris RC, Zanuzdana A, Agboado G, Orton E, Béchard-Evans L, Morgan G, Stevenson C, Weston R, Mukaigawara M, Enstone J, Augustine G, Butt M, Kim S, Puleston R, Dabke G, Howard R, O'Boyle J, O'Brien M, Ahyow L, Denness H, Farmer S, Figureroa J, Fisher P, Greaves F, Haroon M, Haroon S, Hird C, Isba R, Ishola DA, Kerac M, Parish V, Roberts J, Rosser J, Theaker S, Wallace D, Wigglesworth N, Lingard L, Vinogradova Y, Horiuchi H, Peñalver J, Nguyen-Van-Tam JS. *Influenza vaccination for immunocompromised patients: summary of a systematic review and meta-analysis*. Influenza Other Respir Viruses 2013;7(Suppl 2):72-5.

[27] Vinograd I, Eliakim-Raz N, Farbman L, Baslo R, Taha A, Sakhnini A, Lador A, Stemmer SM, Gafter-Gvili A, Leibovici L, Paul M. *Clinical effectiveness of seasonal influenza vaccine among adult cancer patients.* Cancer 2013;119:4028-35.

[28] Sung LC, Chen CI, Fang YA, Lai CH, Hsu YP, Cheng TH, Miser JS, Liu JC. *Influenza vaccination reduces hospitalization for acute coronary syndrome in elderly patients with chronic obstructive pulmonary disease: a population-based cohort study.* Vaccine 2014;32:3843-9.

[29] Siriwardena AN, Asghar Z, Coupland CC. *Influenza and pneumococcal vaccination and risk of stroke or transient ischaemic attack-matched case control study.* Vaccine 2014;32:1354-61.

[30] Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. *Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women.* Am J Epidemiol 1998;148:1094-102.

[31] Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, MacDonald N. *Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women*. CMAJ 2007;176:463-8.

[32] Freeman DW, Barno A. *Deaths from Asian influenza associated with pregnancy*. Am J Obstet Gynecol 1959;78:1172-5.

[33] Rasmussen SA, Jamieson DJ, Bresee S. *Pandemic influenza and pregnant women*. Emerg Infect Dis 2008;14:95-100.

[34] Louie JK, Acosta M, Jamieson DJ, Honein MA; California Pandemic (H1N1) Working Group. *Severe 2009 H1N1 influenza in pregnant and postpartum women in California.* N Engl J Med 2010;362:27-35.

[35] Thompson MG, Li DK, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, Bozeman S, Reynolds SB, Odouli R, Henninger ML, Kauffman TL, Avalos LA, Ball S, Williams JL, Irving SA, Shay DK, Naleway AL; Pregnancy and Influenza Project Workgroup. *Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010-2011 and 2011-2012 influenza seasons.* Clin Inf Dis 2014;58:449-57.

[36] Kissling E, Valenciano M; Team IMC-CS. *Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case-control study, 2011/12*. Euro Surveill 2012;17.

[37] Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Adrian PV, van Niekerk N, Treurnicht F, Ortiz JR, Venter M, Violari A, Neuzil KM, Simões EA, Klugman KP, Nunes MC; Maternal Flu Trial (Matflu) Team. *Influenza vaccination of pregnant women and protection of their infants.* N Engl J Med 2014;371:918-31.

[38] Acs N, Bánhidy F, Puhó E, Czeizel AE. *Maternal influenza during pregnancy and risk of congenital abnormalities in offspring.* Birth Defects Res A Clin Mol Teratol 2005;73:989-96.

[39] Ludvigsson JF, Ström P, Lundholm C. *Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design*. BMJ 2015;351:h5 585.

[40] McMillan M, Porritt K, Kralik D, Costi L, Marshall H. *Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes.* Vaccine 2015;33:2108-17.

[41] Dolan GP, Harris RC, Clarkson M, Sokal R, Morgan G, Mukaigawara M, Horiuchi H, Hale R, Stormont L, Béchard-Evans L, Chao YS, Eremin S, Martins S, Tam JS, Peñalver J, Zanuzdana A, Nguyen-Van-Tam JS. *Vaccination of health care workers to protect patients at increased risk for acute respiratory disease.* Emerg Infect Dis 2012;18:1225e1234.

[42] Amodio E, Restivo V, Firenze A, Mammina C, Tramuto F, Vitale F. *Can influenza vaccination coverage among healthcare workers influence the risk of nosocomial influenza-like illness in hospitalized patients?* J Hosp Infect 2014;86:182-7.

[43] Elder AG, O'Donnell B, McCruden EAB, Symington IS, Carman WF. *Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993-4 epidemic: results of serum testing and questionnaire.* BMJ 1996;313:1241-2.

[44] Burls A, Jordan R, Barton P, Olowokure B, Wake B, Albon E, Hawker J. *Vaccinating healthcare workers against influenza to protect the vulnerable e is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation.* Vaccine 2006;24:4212e4221.

[45] Little KE, Goodridge S, Lewis H, Lingard SW, Din S, Tidley M, Roberts RJ, Williams NS, Hayes S. *Occupational vaccination of health care workers: uptake, attitudes and potential solutions.* Public Health 2015;129:755-62.

[46] Costantino C, Mazzucco W, Azzolini E, Baldini C, Bergomi M, Biafiore AD, Bianco M, Borsari L, Cacciari P, Cadeddu C, Camia P, Carluccio E, Conti A, De Waure C, Di Gregori V, Fabiani L, Fallico R, Filisetti B, Flacco ME, Franco E, Furnari R, Galis V, Gallea MR, Gallone MF, Gallone S, Gelatti U, Gilardi F, Giuliani AR, Grillo OC, Lanati N, Mascaretti S, Mattei A, Micò R, Morciano L, Nante N, Napoli G, Nobile CG, Palladino R, Parisi S, Passaro M, Pelissero G, Quarto M, Ricciardi W, Romano G, Rustico E, Saponari A, Schioppa FS, Signorelli C, Siliquini R, Trabacchi V, Triassi M, Varetta A, Ziglio A, Zoccali A, Vitale F, Amodio E. *Influenza vaccination coverage among medical residents: an Italian multicenter survey.* Hum Vaccin Immunother 2014;10:1204-10.

[47] Costantino C, Battaglia A, D'Asta M, Furnari R, Gimigliano A, Guaccero A, Mallamace N, Marcantoni C, Maringhini, Marsala MGL, Micò R, Biafore A, Papalia R, Pasqua C, Simone B, Franchino G. *Knowledge, attitudes and behaviors regarding influenza vaccination among hygiene and preventive medicine residents in Calabria and Sicily*. Euromed Biomed J 2012;7:77-83.

[48] Costantino C, Amodio E, Vitale F, Maida C, Meringhini G, Asciutto R, Tramuto F, Calamusa G. *Attitudes, behaviours and perceptions of Italian general practitioner trainees towards influenza vaccination in Western Sicily (Italy).* Ital J Public Health 2012;9:33-9.

[49] Pitts SI, Maruthur NM, Millar KR, Perl TM, Segal J. *A systematic review of mandatory influenza vaccination in healthcare personnel.* Am J Prev Med 2014;47:330-40.

[50] Isaacs D, Leask J. *Should influenza immunisation be mandatory for healthcare workers?* No. BMJ 2008;337:a2140.

[51] Di Gregori V, Franchino G, Marcantoni C, Simone B, Costantino C. *Logistic regression of attitudes and coverage for influenza vaccination among Italian Public Health medical residents.* J Prev Med Hyg 2014;55:152-7.

[52] Costantino C, Amodio E, Calamusa G, Vitale F, Mazzucco W. *Could university training and a proactive attitude of coworkers be associated with influenza vaccination compliance? A multicentre survey among Italian medical residents.* BMC Med Educ 2016;16:38.

[53] Gasparini R, Bonanni P, Amicizia D, Bella A, Donatelli I, Cristina ML, Panatto D, Lai PL. *Influenza epidemiology in Italy two years after the 2009-2010 pandemic: need to improve vaccination coverage*. Hum Vaccin Immunother 2013;9:561-7.

■ Received on January 25, 2016. Accepted on February 16, 2016.

■ Correspondence: Claudio Costantino, Department of Science Promotion and Mother to Child Care "G. D'Alessandro", Hygiene Section, University of Palermo, via del Vespro 133, 90127 Palermo, Italy - Tel. +39 091 6553635 - Fax +39 091 6553641 - E-mail: claudio.costantino01@unipa.it