

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

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## Keywords

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 evaluat-

ing 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 10<sup>th</sup> 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  $\geq 6$  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-

respective 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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## References

- [1] Parodi V, de Florentiis D, Martini M, Ansaldi F. *Inactivated influenza vaccines: recent progress and implication for the elderly*. *Drugs Aging* 2011;1;28:93-106.
- [2] Hannoun C. *The evolving history of influenza viruses and influenza vaccines*. *Expert Rev Vaccines* 2013;12:1085-94.
- [3] Wood JM, Williams MS. *History of Inactivated Influenza vaccines*. In: *Textbook of Influenza*. Oxford: Blackwell Science 1998, pp. 317-23.
- [4] de Florentiis D, Parodi V, Orsi, Rossi A, Altomonte F, Canepa P, Ceravolo A, Valle L, Zancolli M, Piccotti E, Renna S, Macrina G, Martini M, Durando P, Padrone D, Moscatelli P, Orengo G, Icardi G, Ansaldi F. *Impact of influenza during the post-pandemic season: epidemiological picture from syndromic and virological surveillance*. *J Prev Med Hyg* 2011;52:134-6.
- [5] Crovari P, Alberti M, Alicino C. *History and evolution of influenza vaccines*. *J Prev Med Hyg* 2011;52:91-4.
- [6] Haaheim LR, Madhun AS, Cox R. *Pandemic influenza vaccines – the challenges*. *Viruses* 2009;1:1089-109.
- [7] Treanor JJ. *Prospects for broadly protective influenza vaccines*. *Vaccine* 2015;33(Suppl 4):D39-45.
- [8] Gasparini R, Amicizia D, Lai PL, Panatto D. *Live attenuated influenza vaccine*. *J Prev Med Hyg* 2011;52:95-101.
- [9] Sridhar S, Brokstad KA, Cox RJ. *Influenza vaccination strategies: comparing inactivated and live attenuated influenza vaccines*. *Vaccines* 2015;3:373-89.
- [10] Ansaldi F, Bacilieri S, Durando P, Sticchi L, Valle L, Montomoli E, Icardi G, Gasparini R, Crovari P. *Cross-protection by MF59-adjuvanted influenza vaccine: neutralizing and haemagglutination-inhibiting antibody activity against A(H3N2) drifted influenza viruses*. *Vaccine* 2008;26:1525-9.
- [11] Minutello M, Senatore F, Cecchinelli G, Bianchi M, Andreani T, Podda A, Crovari P. *Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in helderly subjects, immunized for three consecutive influenza Seasons*. *Vaccine* 1999;17:99-104.
- [12] Del Giudice G, Hilbert AK, Bugarini R, Minutello A, Popova O, Toneatto D, Schoendorf I, Borkowski A, Rappuoli R, Podda A. *An MF59-adjuvanted inactivated vaccine containing A/Panama/1999 (H3N2) induced broader serological protection against heterovariant influenza strain A/Fujian/2002 than a subunit and a split influenza vaccine*. *Vaccine* 2006;24:3063-5.
- [13] Gasparini R, Pozzi T, Montomoli E, Frapapano E, Senatore F, Minutello M, Podda A. *Increased immunogenicity of the MF59-adjuvanted vaccine compared to a conventional vaccine in elderly subjects*. *Eur J Epidemiol* 2001;17:135-40.

- [14] Arakane R, Annaka R, Takahama A, Ishida K, Yoshiike M, Nakayama T, Takeshita F. *Superior immunogenicity profile of the new intradermal influenza vaccine compared to the standard subcutaneous vaccine in subjects 65 years and older: a randomized controlled phase III study*. *Vaccine* 2015;33:6650-8.
- [15] van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, Emery P, Geborek P, Ioannidis JP, Jayne DR, Kallenberg CG, Müller-Ladner U, Shoenfeld Y, Stojanovich L, Valesini G, Wulffraat NM, Bijl M. *EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases*. *Ann Rheum Dis* 2011;70:414-22.
- [16] Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Badour LM, Dunbar S, Krumholz HM; American Heart Association; American College of Cardiology; American Association of Cardiovascular and Pulmonary Rehabilitation; American Association of Critical Care Nurses; American Association of Heart Failure Nurses; American Diabetes Association; Association of Black Cardiologists, Inc; Heart Failure Society of America; Preventive Cardiovascular Nurses Association; American Academy of Nurse Practitioners; Centers for Disease Control and Prevention and the Advisory Committee on Immunization. *Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology*. *J Am Coll Cardiol* 2006;48:1498-502. Erratum in: *J Am Coll Cardiol* 2006 Dec.
- [17] Kobashigawa, T, Inoue E, Tanaka E, Momohara S, Yamanaka H. *Vaccination against seasonal influenza is effective in Japanese patients with rheumatoid arthritis enrolled in a large observational cohort*. *Scand J Rheumatol* 2013;42:445-50.
- [18] Westra J, Rondaan C, van Assen S, Bijl M. *Vaccination of patients with autoimmune inflammatory rheumatic diseases*. *Nat Rev Rheumatol* 2015;11:135-45.
- [19] Baluch A, Pasikhova Y. *Influenza vaccination in oncology patients*. *Curr Infect Dis Rep* 2013;15:486-90.
- [20] Caldeira D, Costa J, Vaz-Carneiro A. *Analysis of the Cochrane review: influenza Vaccines for preventing cardiovascular disease*. *Cochrane Database Syst Rev* 2015;5:CD00505. *Acta Med Port* 2015;28:424-6.
- [21] 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*. *Am J Transplant* 2015;15:2767-75.
- [22] Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, McGeer AJ, Neuzil KM, Pavia AT, Tapper ML, Uyeki TM, Zimmerman RK; Expert Panel of the Infectious Diseases Society of America. *Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America*. *Clin Infect Dis* 2009;48:1003-32.
- [23] *Seasonal influenza vaccination recommendations in Europe*. Available at: <http://ecdc.europa.eu/en/publications/Publications/Seasonal-influenza-vaccination-Europe-2012-13.pdf>. [Accessed 18/01/16].
- [24] Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, Iskander JK, Wortley PM, Shay DK, Bresee JS, Cox NJ; Centers for Disease Control and Prevention (CDC). *Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010*. *MMWR Recomm Rep* 2010;59:1-62.
- [25] European Centre for Disease Prevention and Control (ECDC). *ECDC scientific advice on seasonal influenza vaccination of children and pregnant women*. Stockholm: ECDC 2012. Available at: <http://www.ecdc.europa.eu/en/publications/Publications/Seasonal%20influenza%20vaccination%20of%20children%20and%20pregnant%20women.pdf>. [Accessed 18/01/16].
- [26] European Medicines Agency (EMA). *Fluenz influenza vaccine (live attenuated, nasal). Summary of opinion I (initial authorisation)*. 21 October 2010. London: EMA 2010. EMA/CHMP/503333/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Summary\\_of\\_opinion\\_-\\_Initial\\_authorisation/human/001101/WCS500098347.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/001101/WCS500098347.pdf) [Accessed 18/01/16].
- [27] Kissling E, Valenciano M, Cohen JM, Oroszi B, Barret AS, Rizzo C, Stefanoff P, Nunes B, Pitigoi D, Larrauri A, Daviaud I, Horvath JK, O'Donnell J, Seyler T, Paradowska-Stankiewicz IA, Pechirra P, Ivanciuc AE, Jiménez-Jorge S, Savulescu C, Ciancio BC, Moren A. *I-MOVE multi-centre case control study 2010-11: overall and stratified estimates of influenza vaccine effectiveness in Europe*. *PLoS One* 2011;6:e27622.
- [28] Kissling E, Valenciano M; I-MOVE case-control studies team. *Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case-control study*. *Euro Surveill* 2011;16:pii=19818.
- [29] Centers for Disease Control and Prevention (CDC). *Intensive-care patients with severe novel influenza A (H1N1) virus infection - Michigan, June 2009*. *MMWR Morb Mortal Wkly Rep* 2009;58:749-52.
- [30] Louie JK, Acosta M, Samuel MC, Schechter R, Vugia DJ, Harriman K, Matyas BT; California Pandemic (H1N1) Working Group. *A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1)*. *Clin Infect Dis* 2011;52:301-12.
- [31] Morgan OW, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P, Belay B, Jain S, Cox C, Kamimoto L, Fiore A, Finelli L, Olsen SJ, Fry AM. *Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A (H1N1) disease*. *PLoS One* 2010;5:e9694.
- [32] *Council Recommendation of 22 december 2009 on seasonal influenza vaccination*. Official journal of the European Union. Available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32009H1019>. [Accessed 18/01/16].
- [33] European Centers for Disease Control and Prevention (ECDC). *Seasonal Influenza Vaccination Programme in Italy*. Available at: <http://ecdc.europa.eu/en/publications/Report%20Assets/seasonal-vaccination-coverage-in-europe-2012-13/Seasonal-Influenza-Vaccination-Programme-Country-Profile-Italy.pdf>. [Accessed 18/01/16].
- [34] Bonanni P, Ferro A, Guerra R, Iannazzo S, Odone A, Pompa MG, Rizzuto E, Signorelli C. *Vaccine coverage in Italy and assessment of the 2012-2014 National Immunization Prevention Plan*. *Epidemiol Prev* 2015;39(4 Suppl 1):146-58.
- [35] Crépey P, de Boer PT, Postma MJ, Pitman R. *Retrospective public health impact of a quadrivalent influenza vaccine in the United States*. *Influenza Other Respir Viruses* 2015;9(Suppl 1):39-46.
- [36] Langley JM, Carmona Martinez A, Chatterjee A, Halperin SA, McNeil S, Reisinger KS, Aggarwal N, Huang LM, Peng CT, Garcia-Sicilia J, Salamanca de la Cueva I, Cabañas F, Treviño-Garza C, Rodríguez-Weber MA, de la O M, Chandrasekaran V, Dewé W, Liu A, Innis BL, Jain VK. *Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate: a phase III randomized controlled trial in children*. *J Infect Dis* 2013;208:544-53.
- [37] Block SL, Falloon J, Hirschfield JA, Halperin SA, McNeil S, Reisinger KS, Aggarwal N, Huang LM, Peng CT, Garcia-Sicilia J, Salamanca de la Cueva I, Cabañas F, Treviño-Garza C, Rodríguez-Weber MA, de la O M, Chandrasekaran V, Dewé W, Liu A, Innis BL, Jain VK. *Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children*. *Pediatr Infect Dis* 2013;31:745-51.
- [38] Pépin S, Donazzolo Y, Jambrecina A, Salamand C, Saville M. *Safety and immunogenicity of a quadrivalent inactivated influenza vaccine in adults*. *Vaccine* 2013;31:5572-8.
- [39] Thommes EW, Ismaila A, Chit A, Meier G, Bauch CT. *Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom*. *BMC Infect Dis* 2015;15:465.

- [40] Meier Gregg M, Poulsen Nautrup B. *Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the UK*. *J Med Econ* 2015;18:746-61.
- [41] Clements KM, Meier G, McGarry LJ, Pruttivarasin N, Misurski DA. *Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States*. *Hum Vaccin Immunother* 2014;10:1171-80.
- [42] Eichner M, Schwehm M, Hain J, Phoff H, Salzberger B, Knuf M, Schmidt-Ott R. *4Flu – an individual based simulation tool to study the effects of quadrivalent vaccination on seasonal influenza in Germany*. *BMC Infect Dis* 2014;14:365.

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