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Influenza vaccination recommended for all adults aged between 50 and 64 years: conceptual basis and methodological limitations

L. Manzoli*, C. De Vito**, M.E. Flacco *, C. Marzuillo**, A. Boccia**, P. Villari**

Key words: Influenza vaccine, vaccination schedule, vaccination for the adults, meta-analysis.
Parole chiave: Vaccino antinfluenzale, calendario vaccinale, vaccinazione negli adulti, meta-analisi.

Abstract

In the first half of this year, the experts of the Italian Society of Hygiene (SItI), along with those of other National Scientific Societies, agreed with the recommendations made by the USA CDC in 2009, and developed a proposal for a vaccination schedule (Vaccine Schedule for Life), in which influenza vaccination is recommended for all adults aged between 50 and 64 years. In the National Plan for Vaccinal Prevention 2012-2014, which was published just before the issue of the SitI Calendar but concluded earlier (end of 2011), influenza vaccination is recommended "only" for all persons ≥65 years or included in one of the many at-risk categories. The issue is controversial and has generated considerable debate at national and international level. This short note discusses the logical processes and the scientific evidence in support or against the decision to extend the influenza vaccination. The Authors conclude that the epidemiological approach used by SItI experts is appropriate. In any case, further studies on the topic are strongly needed, and their results should be taken into account in the drafting of future vaccination schedules.

In the first half of 2012, the experts of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI), along with those of other National Scientific Societies, wrote a proposal for a vaccination schedule (the "Vaccine Schedule for Life") in which influenza vaccination is recommended for all adults aged 50 to 64 years (1). In the National Plan for Vaccinal Prevention 2012-2014, which was published just before the issue of the SItI schedule but concluded at the end of 2011, influenza vaccination is recommended "only" for people ≥65 years, and for a large number of subjects at risk (Table 1) (2). The issue is controversial and has generated a large debate at a national and international level (3-7).

** Department of Medicine and Aging Sciences, Section of Hygiene, Epidemiology and Legal Medicine, University "G. d'Annunzio" - Chieti, Italy*
*** Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy*

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It should first be noted that, expanding the age-range of "healthy" subjects to be vaccinated, the SItI vaccination schedule aligned with the recommendations made by the USA CDC in 2009 (4), however the SItI Calendar still remains more restrictive than the current schedule issued by CDC, which recommends vaccination for all adults and in general for all individuals after 6 months of age (8).

On another hand, the decision to increase the number of persons to be vaccinated evokes strong resistances among some expert epidemiologists and, especially, among non-experts (5, 6). The formers claim for a greater body of evidence, which should be satisfactory both in quality and in quantity, in order to justify any change in health policies targeted at the general population. Non-experts are typically afraid of a huge increase in the number of people to be vaccinated, and some of them also distrust any choice that may in any way favor manufacturing companies. Indeed, it is indisputable that the recent controversy following the 2009 H1N1 pandemic has reduced the population trust on vaccines, and despite new studies suggest that the alarm was justified (9), immunization coverage declined in the last years in Italy and in several other countries (10-12).

So, why the experts of both CDC and SItI and decided otherwise?

Firstly, the alarm of a substantial increase in the number of subjects to be immunized is not justified because, as noted by CDC in 2009, according to the previous vaccination schedule (which is in line with the current National Plan for Vaccinal Prevention of the Italian Ministry of Health) 83% of the American population in that age range already presented one or more indications for vaccination (4). Therefore, the total number of people to be vaccinated would increase, at most, by 17%. If such extra number estimated by CDC may seem excessive, it is worth reminding the categories of adults for whom influenza vaccination is currently recommended by the Italian Ministry of Health (Table 1):

- Medical doctors, nurses, salaried and self-employed veterinarians, and all healthcare professionals;
- Policemen and Firemen;
- Breeders and all workers in farming activities;
- People in charge of transport of live animals, slaughterers and vaccinators;

All subjects with one of the following diseases: chronic respiratory diseases (including asthma, broncho-pulmonary dysplasia, cystic fibrosis and chronic obstructive pulmonary disease-COPD), cardiovascular diseases (including congenital and acquired heart diseases), diabetes mellitus and other metabolic diseases (including obese patients and severe underlying diseases), kidney disease with renal failure, blood disorders and hemoglobinopathies, cancer, congenital or acquired diseases involving defective antibody production, immunosuppression caused by drugs or HIV infection, chronic bowel inflammatory diseases and intestinal malabsorption syndromes, diseases requiring major surgery treatment, diseases associated with an increased risk of aspiration of respiratory secretions (e.g. neuromuscular diseases);

- In general, all the workers involved in public services of general interest, and all workers at high risk because of their activity;
- All family members and contacts of the above-listed individuals.

Since the categories for which the vaccine is already recommended are so many, and considering that the influenza vaccine has shown to be substantially safe for all adults (4, 8, 13), recommending vaccination for all adults over the age of 50 is first of all a choice of common sense,

Table 1 - List of the categories or adults for whom influenza vaccination is recommended by the Italian Ministry of Health [source: National Plan for Prevention Vaccination 2012-2014 (2)].

	Categories	Details
1	Subjects ≥65 years	
2	Children >6 months, adolescents and adults aged less than 65 years with diseases that increase the risk of complications from influenza	a) Chronic respiratory diseases (including asthma, bronchopulmonary dysplasia, cystic fibrosis and chronic obstructive pulmonary disease-COPD) b) Cardiovascular diseases (including congenital and acquired heart diseases) c) Diabetes mellitus and other metabolic diseases (including obese patients with BMI> 30 and severe underlying diseases) d) Chronic renal failure e) Blood disorders and hemoglobinopathies f) Cancer g) Congenital or acquired diseases involving defective antibody production, immunosuppression caused by drugs or HIV infection h) Chronic bowel inflammatory diseases and intestinal malabsorption syndromes i) Diseases requiring major surgery treatment j) Diseases associated with an increased risk of aspiration of respiratory secretions (e.g. neuromuscular diseases) k) Chronic liver diseases
3	Children and adolescents under long-term therapy with acetylsalicylic acid at risk of Reye's syndrome in case of influenza	
4	Women who are in the second or third trimester of pregnancy at the beginning of the epidemic season	
5	People of any age admitted in long-term care facilities	
6	Doctors, nurses, and all healthcare professionals	
7	All family members and contacts of people at high risk	
8	Workers involved in public services of general interest, and some specific categories of workers	a) Policemen b) Firemen c) Other types of socially useful workers could benefit from the vaccination, for reasons related to their activity: in this regard, it is up to the Regions and Autonomous Provinces to define the principles and methods of supply to these categories d) It is widespread and active practice among employers to offer a free vaccination to workers who are particularly exposed as a consequence of their activity and to limit the negative impact on productivity
9	Workers who are in contact with animals that may be a source of infection with influenza viruses of animal origin	a) Breeders b) Workers in farming activities c) Individuals who transport live animals d) Slaughterers and vaccinators e) Salaried and self-employed veterinarians

because it eliminates the need (and the related difficulty) to identify all patients at risk. In other words, this recommendation does not increase so much the theoretical number of subjects to be vaccinated, but in practice it may substantially contribute to protect the majority of at-risk subjects. In fact, the implementation of strategies aimed at identifying at-risk subjects is problematic and is one of the reasons

for the very low rates of immunization among adults in several countries (10-12). Interestingly, the same "pragmatic" logic was recently followed for the treatment of hypercholesterolemia by a panel of international experts, who proposed the administration of statins to all adults aged over 50 years (14, 15).

The above concepts may address the concerns of non-expert individuals, but it is also necessary to discuss the existing evidence in favor of a change in the vaccination strategy. Such an evidence was found through an extensive literature search described in detail elsewhere (13).

First of all, if during the decade 1990-99, in the United States, the death rate from influenza-related cardiovascular and respiratory diseases was very low among the subjects aged up to 49 years (0.5 per 100,000), the rate in those aged 50-64 years was 15 times greater (7.5), although the latter was still 13 times lower than the rate of the elderly (16). Moreover, during the recent 2009 H1N1 pandemic the mortality rate due to influenza complications was significantly higher among individuals aged less than 60 years, as compared with past seasonal epidemics (17). It is thus definitely likely that in the next years the influenza mortality and morbidity rates among adults aged between 50 and 64 years will be higher than in the past.

Secondly, and this appears more important, the only two cost-effectiveness analyses to date that have considered this specific age group, estimated a vaccine cost of 28,000 U.S.D. $ for each saved QALY ($ 7,200 if transportation costs and time lost by vaccinated subjects are excluded) (18), and of $ 34,610 per life saved (although such an estimate was exclusively focused on the Emergency Department setting) (7). Even if not sensational, these results lead the authors to conclude that influenza vaccination can be considered a cost-effective intervention also the for adults over 50 years of age.

Certainly, these findings are encouraging but not yet conclusive. However, it must be kept into account that the evaluation of the effectiveness and, even more, the cost-effectiveness of influenza vaccine is certainly an extremely complex issue (19). In order to evaluate the efficacy and safety of different vaccines, seasonal and pandemic, in diverse age groups, it was recently necessary to perform a re-analysis of 15 meta-analyses (13): 5 on seasonal vaccines for children/adolescents (20-24), 3 for the adults (22, 25, 26), 4 for the elderly (22, 27-29), and 2 for each emerging pandemic influenza virus [Avian (30, 31) and 2009 H1N1 (32, 33)]. These meta-analyses include hundreds of individual studies and adopted different inclusion criteria and statistical methods, and it was necessary to reassess the inclusion/exclusion criteria for each single study and to perform new analyses with all or some of the studies included in at least one meta-analysis to fully understand which (and whether) differences in the results were caused by methodological factors or by time, and to finally provide a reliable estimate of the real vaccine efficacy. In fact, despite the body of evidence and the complexity of the analysis, some qualitative (34), interpretative (35) and legal issues (36), and possible biases (37) still remain, in addition to a substantial lack of information on children under 2 years of age and on mild or moderate adverse events. For such reasons, at least in the short-term, it is not reasonable to believe that a large amount of scientific evidence will appear and rule out all the controversial aspects of vaccination (38), and it may paradoxically be more rational to plan and act on the basis of the available data, which in any way, in the specific case, are encouraging.

In conclusion, it can be deduced that the experts of the Italian Society of Hygiene, Preventive Medicine and Public Health adopted an appropriate epidemiological approach and properly followed the indications emerging from the existing literature. Because this literature is unfortunately limited, further studies on the topic are certainly to be warranted, and their results will most probably be taken into account in the drafting of future vaccination schedules.

Riassunto

Vaccinazione antinfluenzale raccomandata per tutti gli adulti tra i 50 ed i 64 anni: basi concettuali e limiti metodologici.

Nella prima metà dell'anno in corso, gli esperti della Società Italiana di Igiene (SItI), insieme a quelli di altre Società Scientifiche Nazionali, si sono allineati alle raccomandazioni formulate dal CDC di Atlanta nel corso del 2009, ed hanno sviluppato una proposta di calendario vaccinale (Il Calendario Vaccinale per la Vita), nella quale viene raccomandata la vaccinazione antinfluenzale per tutti gli adulti di età compresa tra i 50 ed i 64 anni. Nel Piano Nazionale Prevenzione Vaccinale 2012-2014, che è stato pubblicato poco prima del Calendario SItI ma concluso al termine del 2011, la vaccinazione antinfluenzale viene raccomandata "solamente" per tutti i soggetti di età ≥ 65 anni, e per un ampio numero di soggetti a rischio. La questione è controversa ed ha suscitato un notevole dibattito a livello nazionale ed internazionale. Nella presente nota sono discussi i passaggi logici e le evidenze scientifiche a supporto o contro la scelta di estendere la vaccinazione antinfluenzale. Gli autori concludono che l'approccio epidemiologico usato dagli esperti SItI sia appropriato. Si auspicano in ogni caso ulteriori studi sull'argomento, dei cui risultati dovrà essere tenuto in debito conto nella stesura dei futuri calendari vaccinali.

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Corresponding author: Dr.ssa Maria Elena Flacco, Department of Medicine and Aging Sciences, Section of Hygiene, Epidemiology and Legal Medicine, University "G. d'Annunzio", Palazzina Di Odontoiatria, Via dei Vestini 5, 66013 Chieti, Italy
e-mail: elena.flacco@gmail.com