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Influenza vaccine use to protect healthy children: A debated topic

Nicola Principi^a, Susanna Esposito^{b,*}^a Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy^b Pediatric Clinic, Department of Surgical and Biological Sciences, Università degli Studi di Perugia, Perugia, Italy

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ABSTRACT

At the beginning of this century, a number of studies suggested that in healthy children, particularly those <2 years of age, influenza could have a serious and complicated course, as it frequently led to hospitalization and sometimes, albeit rarely, to death. Moreover, pre-schoolers and school-age children were found to be among the most important causes of influenza transmission to the community, as they shed the virus for a longer time than adults and had frequent contact with greater numbers of individuals through day-care and school. These findings led a number of health authorities to modify the official recommendations regarding the use of influenza vaccine in healthy children. Several factors seem to indicate that vaccination against influenza in healthy children of any age and in pregnant women could be effective in preventing the disease in the entire paediatric population and in providing herd immunity in adults and old people as well. The direct advantages of the vaccine seem greater in younger subjects, particularly those <2–3 years of age. Vaccination of older children is considered effective by most experts, but high vaccination coverage of these subjects has been difficult to attain. Similar difficulties have been identified for the vaccination of pregnant women. These challenges can be overcome, at least in part, by appropriate information and accurate evaluations of available data. In addition, further studies specifically designed to clarify unresolved problems regarding vaccine use in paediatric and pregnant populations are needed to convince reluctant health authorities. More effective vaccines for younger children as well as improved availability of data regarding the optimal time period for vaccine administration in pregnant women appear relevant in this regard.

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1. Introduction

Influenza is a common disease that affects a substantial number of individuals of all ages every winter. Annual influenza epidemics cause relevant medical, social and economic problems [1–3], which is why prevention of the infection through the influenza vaccine has been recommended by health authorities worldwide for several decades [4–6]. For years, influenza vaccination policies have prioritized the elderly because of the greater number of severe and complicated cases frequently leading to death that occur in this population [7,8]. Children were not included in the list of groups for whom influenza vaccine was recommended unless they suffered from a severe chronic underlying disease that predisposed them to developing influenza-related complications [6–8].

At the beginning of this century, a number of studies suggested that influenza could have a serious and complicated course even in healthy children, particularly those <2 years of age, frequently leading to hospitalization and sometimes, albeit rarely, to death [9,10]. Moreover, pre-schoolers and school-age children were found to be among the most important causes of influenza transmission to the community, as they shed the virus for a longer time than adults [11,12] and had frequent contact with greater numbers of individuals at day-care and school [13]. These findings have led a number of health authorities to modify the official recommendations regarding the use of influenza vaccine in healthy children. In some cases, as in the USA, the age limit for vaccination of healthy children initially included only younger subjects and was progressively increased to presently include all subjects between 6 months and 17 years of age [4]. In other countries, only infants and pre-school children were considered for vaccination. However, in most countries, the suggestions arising from epidemiological studies have gone unheeded and healthy children have not been included in the list of subjects for whom influenza vaccination is strongly recommended. A good example of this situation is evident

* Corresponding author at: Pediatric Clinic, Department of Surgical and Biomedical Sciences, Università degli Studi di Perugia, Piazza Menghini 1, 06129 Perugia, Italy.

E-mail address: susanna.esposito@unimi.it (S. Esposito).

in the results of a survey regarding the 2014–2015 influenza season conducted by the European Centre for Disease Prevention and Control; in that study, a questionnaire was sent to health authorities of Member States of the European Union and the European Economic area (EEA) [14]. Of the 30 Member States that responded to the questionnaire, only Austria, Estonia and Poland recommended influenza vaccine for all paediatric population groups. Latvia and Slovenia recommended vaccination for children aged ≥ 6 –24 months, whereas Finland, Malta, and Slovakia extended the vaccination period to healthy subjects aged ≥ 6 –36 months, ≥ 6 –59 months, and ≥ 6 months–12 years, respectively. A unique situation was reported for the UK; England and Wales recommended the vaccine for children aged ≥ 2 –4 years and to those 11 years old in Wales only, whereas Northern Ireland and Scotland extended the recommendation to all children ≥ 2 –11 years old. In all the other 21 countries of the EU and EEA, influenza vaccination of healthy children was not considered a priority.

Differences were also observed in methods for protecting children <6 months old from influenza for whom an appropriate vaccine was not licensed. In this case, based on some studies, vaccination of pregnant women was considered a possible solution [15]. However, Bulgaria, Malta and Slovakia did not recommend vaccination for pregnant women, and Croatia and the Netherlands recommended the vaccine only for pregnant women with chronic medical conditions; all other countries indicated that the influenza vaccine had to be administered to pregnant women, although with differences regarding the best period for administration during pregnancy.

In this study, an attempt to evaluate the pros and cons of influenza vaccination in otherwise healthy children on the basis of available literature and personal experience will be performed.

2. Vaccination of healthy younger children

Health authorities that recommend influenza vaccination for younger children, although with differences in the defined age limit, have attached great importance to studies showing that influenza is extremely common among children in their first years of life; that it causes a significant increase in the number of medical visits, drug prescriptions, and hospital admissions for respiratory diseases; and that it can lead, although rarely, to death [4–6,9,10]. Further support for the implementation of vaccination programmes in younger children was provided by the finding that, with few exceptions, studies evaluating the influenza vaccine in clinical practice showed that the administration of both inactivated (IIV) and live attenuated (LAIV) vaccines in healthy children was effective in reducing the total burden of influenza, including preventing severe cases (i.e., those requiring admission to the intensive care unit), with an acceptable level of safety and tolerability in all cases [16–31]. Moreover, both IIV and LAIV were found to be significantly cost-saving or cost-effective, particularly when both direct and indirect costs due to productivity losses, especially in parents, were considered [32–40].

Many aspects of paediatric influenza that have led health authorities to plan influenza vaccination programmes for younger children have been supported by reliable data from well conducted studies. Approximately 15 years ago, studies found that the hospitalization rates and antibiotic consumption of younger healthy children significantly increased during periods when the circulation of influenza virus predominated over those of other respiratory viruses [9,10]. In particular, Neuzil et al. reported that in the USA, the number of hospitalizations in excess of the expected number per 10,000 children per year totalled 104, 50, and 19 for subjects aged <6 months, 6–12 months, and 13–35 months, respectively [9]. Moreover, an estimated annual average of 6–15

outpatient visits and 3–9 antibiotic courses for every 100 children were ascribable to influenza, with a 10–39% increase in the prescription of these drugs in comparison to periods with poor influenza virus circulation [9]. Similar data were collected by Izurieta et al., who found that the hospitalization rates among healthy children <2 years old were approximately 12 times higher than those of healthy school-age children and quite similar to those of children with chronic health conditions who were 5–17 years old [10].

Recently, more precise estimates of the total burden of influenza in healthy children were obtained using laboratory confirmed diagnoses. These figures showed that in full-term infants aged 1 year or younger, the annual incidence of symptomatic seasonal influenza could be significantly higher than 50 per 1000 children [41]. Moreover, it was shown that seasonal influenza plays a relevant role in the occurrence of lower respiratory tract infections requiring medical assistance among children ≤ 36 months of age, with an annual incidence of 1.1 per 100 children-years [42]. Similar data were reported when the impact of the 2009 pandemic on younger children was evaluated. A series of studies showed that infants and toddlers had either the highest risk of hospitalization or the highest proportion of severe respiratory cases ascribed to influenza [43–53]. Finally, several reports indicate that children with influenza can die [54–56]. For example, data collected in the USA for the four influenza seasons between 2012–2013 to 2015–2016 [56] indicate that during this period, a total of 517 influenza-associated paediatric deaths were reported to the Centers for Disease Control and Prevention (CDC), and of them, only approximately half occurred in at-risk children, thereby highlighting the risk of healthy subjects [56]. To support the relevance of influenza in healthy younger children, supporters of vaccination have highlighted that it is highly likely that the official data regarding the number of medical visits, drug prescriptions, hospitalization rates and deaths due to influenza underestimate the true importance of the disease. In clinical practice, laboratory tests for detecting influenza virus are not commonly performed. Moreover, even when they are conducted, many cases of patients actually infected by the influenza virus will test negative because the virus is no longer present in the respiratory secretions at the time they were collected. Finally, influenza as a cause of death is very rarely reported. This could explain why, in contrast to what was found in the USA [54], death due to influenza was never or only rarely reported in Europe during both pandemics and seasonal epidemics, even in children aged 0–4 years [57–61].

Some of the conclusions of the studies cited above have been criticized by experts, and these criticisms convinced some health authorities around the world to not recommend the influenza vaccine for younger children. The most relevant observations were raised in response to data regarding the true efficacy and effectiveness of the influenza vaccine in younger patients. As reported in a meta-analysis [62], the general methodological quality of a great number of studies that positively evaluated the impact of influenza vaccines in children was considered very poor. Moreover, even when studies with the lowest risk of bias such as randomized controlled studies, cohort studies and case-control studies were considered, a certain degree of efficacy and effectiveness could be demonstrated only for children ≥ 2 years of age, in whom the efficacy and effectiveness reached 80% and 33% for LAIVs and 59% and 36% for IIVs, respectively [62]. In contrast, both vaccines were found to be inadequate in providing even minimal protection to children <2 years old: LAIVs because they were not licensed for children in that age range, and IIVs because their efficacy and effectiveness did not differ from that of placebo. Further doubts regarding the use of influenza vaccines in younger children were raised when their efficacy and effectiveness were found to significantly vary from year to year and, in some years, to be even lower than that reported in the meta-analysis by Jefferson et al., even among

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