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Preventing influenza in younger children

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Abstract

Influenza is common in infants and children: attack rates vary from 23% to 48% each year during inter-pandemic periods, and are even higher during pandemics. Severe cases occur more frequently in children with underlying chronic diseases; however, epidemiological studies have clearly shown that influenza also causes an excess of medical examinations, drug prescriptions and hospitalizations in otherwise healthy children (particularly those aged <5 years), as well as a considerable number of paediatric deaths. Childhood influenza also has a number of social and economic consequences. However, many European health authorities are still reluctant to include influenza vaccinations in their national vaccination programmes for healthy children because, among other things, there are doubts concerning their real ability to evoke a protective immune response, especially in children in the first years of life. New hope for the solution of these problems has come from the introduction of vaccines containing more antigens and the possibility of intradermal administration. However, further studies are needed to establish whether universal influenza vaccination in the first years of life should be recommended, and with which vaccine.

Keywords: Adjuvanted influenza vaccine, children, influenza, influenza vaccine, live attenuated influenza vaccine
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Introduction

Influenza is common in infants and children: attack rates vary from 23% to 48% each year during inter-pandemic periods, and are even higher during pandemics [1]. Severe cases occur more frequently in children with underlying chronic diseases; however, epidemiological studies have clearly shown that otherwise healthy children (particularly those aged < 5 years) can experience significant clinical problems when infected by influenza viruses. Influenza causes a substantial excess of medical examinations, drug prescriptions and hospitalizations in healthy children, and a number of influenza-related deaths in paediatric subjects without any risk condition [2–6]. Children are the main cause of the spread of influenza in the community because they shed greater amounts of virus for a longer time than adults. This means that they frequently infect their own households and give rise to various clinical, social and economic problems, including parental absenteeism from work [7].

Yearly administration of influenza vaccine to children at risk has been recommended by health authorities worldwide for several years [8,9], but its use in healthy children is widely debated. The most favourable attitude is found in the USA, where healthy children aged 6–23 months have been included in the list of subjects for whom influenza vaccination should be recommended since 2003, and subsequent additions have led to universal vaccination being officially recommended for all subjects aged between 6 months and 18 years since 2008 [10]. This lead has been followed by a number of Asian and Latin American countries although, in most cases, vaccination is suggested only for healthy children in the first years of life. In contrast, despite repeated recommendations by multinational experts and advisory groups [11–13], only six European countries (Austria, Estonia, Slovakia, Latvia, Slovenia and Finland) have included influenza vaccine in the paediatric vaccination schedule (Table 1) [14]. Moreover, although Finland has implemented a fully reimbursed vaccination programme for

TABLE 1. Influenza vaccination recommendations

WHO/Europe
Recommend that member states vaccinate all individuals ≥6 months [1]
EU
Six member states currently recommend paediatric vaccination [2–4]; recommendations vary by country:
6 months to <18 years of age: Austria, Estonia and Slovakia
6–35 months: Finland
6–24 months: Slovenia, Latvia
USA, Canada and PAHO countries
USA: All individuals ≥6 months of age [5]
Canada: Children 6–24 months of age, and encourages all individuals ≥6 months of age to be vaccinated [6]
Currently, 27 PAHO countries and territories recommend paediatric seasonal influenza vaccination [7][a]

PAHO, Pan American Health Organization.
[a]PAHO recommendations vary by country or territory.

healthy children, this is limited to subjects aged 6–35 months [15].

There are two main reasons for the reluctance of many European health authorities to include influenza vaccination in their national vaccination programmes. The first is their widespread conviction that, although very common, influenza in healthy children is always very mild and therefore does not need to be prevented by vaccination. The second is that there are doubts concerning the real ability of the available vaccines to evoke a protective immune response in children, particularly those in the first years of life. Data regarding the total burden of childhood influenza collected over the last 10 years [1–7] indicate that the first assumption is probably wrong, and that influenza in healthy children (particularly the youngest) gives rise to a substantial medical and economic burden that largely justifies prevention. However, it is significantly more difficult to establish whether the available vaccines are effective enough to support their universal use in healthy children, and two recent meta-analyses have reached opposing conclusions [16,17].

As the course of influenza can be worst in children aged <5 years, the main aim of this review is to discuss whether the currently available data concerning the efficacy of influenza vaccines justifies their universal use in healthy children of this age.

Injectable influenza vaccines

Trivalent inactivated vaccines

Trivalent inactivated vaccines (TIVs; split-virus and subunit TIVs) are the only injectable preparations that are licensed for paediatric use throughout the world. Modern TIVs are very different from the monovalent products containing one whole killed virus (mainly type A) that were first prepared more than 40 years ago [18] because they usually contain fractions of three viruses, the most important of which in immunological terms are the haemagglutinin of each. The three viral strains are chosen every year on the basis of WHO indications of the most probable causes of seasonal influenza epidemics.

Throughout the world, TIVs are only licensed for children aged ≥6 months. Moreover, it is recommended that previously unvaccinated children until the age of 9 years in some countries and until the age of 3 years in other countries should be given two TIV doses 1 month apart [8,9]. However, antibody production after TIV administration increases with age: Walter *et al.* [19] studied children aged 6–23 months in two consecutive years, and found that significantly higher proportions of the older subjects achieved seroprotective antibody concentrations or a four-fold increase in geometric mean titres. Nevertheless, the majority of the youngest children had significantly high levels of antibodies against influenza antigens, which suggests that, although the correlate of protection for children has never been established, some protective efficacy is possible in younger subjects [19]. Unfortunately, there are very few data concerning the immunogenicity of TIVs in children <2 years of age and no definite conclusions can yet be drawn.

Evaluating the data from other studies of the efficacy and effectiveness of TIVs in children is more difficult because there are frequent differences in their endpoints (i.e. the prevention of infection or diseases), the methods used to evaluate them (i.e. seroconversion, seroprotection, culture or PCR), and the characteristics of the children themselves. However, when the few comparable studies are considered together, they clearly show that TIVs are efficacious in preventing influenza in children aged >3 years, although the reduction in the number of disease cases is less than that usually reported for other paediatric vaccinations. Using the pooled results of five studies [20–24] of children aged <9 years, Zangwill and Belshe [20] found that the efficacy of TIVs was 63%, which, together with the indirect advantages of preventing paediatric influenza, may justify the universal use of TIVs in healthy children aged >3 years [25].

However, the efficacy of TIVs is significantly less when the viral strains included in the vaccine do not perfectly match those circulating in the community during an epidemic. Heikkinen and Heinonen [26] examined the data collected in ten clinical trials [22,24,27–34] that evaluated the efficacy of TIVs in children aged <5 years using laboratory tests to confirm the diagnosis of influenza, and found that the protection offered by these vaccines strictly related to the degree of matching: when matching was very good, efficacy was always 60% or more (and in some cases higher than 80%); in the case of a poor match, it was always less than 60%, and sometimes near 0% [26]. The best example in this regard is