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Pediatric influenza immunization

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"Effective pediatric influenza vaccines will be of little use if parents lose confidence in vaccine programs. Immunization bodies need to embrace community consultation and be willing to publicly debate difficult scientific issues such as the safety and tolerability of particular adjuvants and vaccines."

The recent H1N1 2009 pandemic provided an opportunity to reflect on current influenza immunization practices in children and future directions in this field. While the elderly suffer the vast burden of seasonal influenza morbidity and mortality, there is also an increased disease burden in very young children, a population in which approximately 1–5% of influenza deaths occur [1]. An Australian study reported a mean hospital admission rate with influenza-associated illness in children 0–4 years of age of 49.5 per 100,000, comparable to the rate of 52 per 100,000 in people over 85 years [2]. Thus, although influenza mortality rates are much lower in children than the elderly, the converse is true of hospitalization rates. One reason for the increased disease burden of influenza in young children is that the frequency of influenza infection is much higher in children than in any other age group. Children, as a group, are more susceptible to infection as many are immunologically naive to influenza viruses. This, combined with their notoriously poor hygiene and their concentration in institutions such as daycare and schools, makes them an ideal vector for viral transmission. Serological data from Hong Kong early in the 2009 H1N1 pandemic showed that 43.4% of school children 5–14 years of age had seroconverted consistent with having been infected, compared with a seroconversion rate of just 4.6% in those 30–59 years of age [3]. When hospitalization or death was corrected for the higher infection rate in children, adults aged 50–59 years had a 9.5-times higher risk if infected of intensive care unit admission and 66-times higher risk of death than children [3].

Pediatric influenza vaccines

Prophylactic vaccination combined with good hygiene practices remains the best defense against influenza. The Advisory Committee on Immunization Practices of the CDC and the American Academy of Pediatrics have recommended that annual influenza vaccination be provided to all children over the age of 6 months [4]. To date, the largest experience with pediatric seasonal influenza immunization was in Japan, where, in response to the 1957 Asian influenza pandemic, from 1962 mandatory seasonal influenza immunization of all Japanese school age children was undertaken, with an estimated 50–85% vaccine uptake and 50–80% effectiveness in reducing influenza A in schoolchildren [5]. This program was abandoned in 1994 in response to community pressures following publicity of adverse reactions and questions about vaccine effectiveness. The initiation of the Japanese schoolchildren vaccination program corresponded with a major drop in excess community mortality rates from influenza-related illness [6]. The vaccination of Japanese children has been estimated to have prevented 37,000–49,000 deaths per year, representing approximately one death avoided for every 420 children vaccinated [6]. This data suggests that vaccination of schoolchildren not only protected the children

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themselves, but also reduced influenza and associated morbidity throughout the community. Mathematical models confirm that high rates of vaccination of schoolchildren can reduce the community-wide effects of influenza [7,8]. To prevent one hospitalization per year with 50% vaccine efficacy, the number of children needed to be vaccinated ranges from 1031–3050 for children 6–23 months of age to 4255–6897 for children 24–59 months of age [9]. A 2008 Cochrane review estimated the efficacy of trivalent inactivated influenza vaccine (TIV) at preventing confirmed influenza at 59% in children aged over 2 years of age [10]. The review noted only one study of TIV in children younger than 2 years of age, despite current recommendations to vaccinate healthy children over 6 months of age in the USA and Canada, and made the recommendation that if immunization in children is to be recommended as a public health policy, large-scale studies assessing important outcomes including efficacy and safety and directly comparing vaccine types are urgently required [10].

> "...the public's confidence in vaccines should not be taken for granted and old-style paternalistic public health responses to potential vaccine problems are no longer appropriate."

Traditional egg-derived TIVs have been the mainstay of adult and pediatric immunization campaigns for over 50 years. Because they are often naive to influenza, it is common practice to give children under 10 years of age receiving influenza vaccine for the first time two doses 1 month apart. Whole-cell TIVs are well recognized for their high reactogenicity and pyrogenicity, and as young children are sensitive to pyrogen-induced febrile convulsions, whole-cell TIVs are contraindicated in this population. More purified split and subunit TIVs exhibit less reactogenicity and pyrogenicity, albeit with reduced immunogenicity. Subunit vaccines represent the most highly purified vaccines and contain only the major protective proteins, hemagglutinin (HA) and neuraminidase (NA). Given the potential problems of egg allergy [11], recently developed egg-free alternatives include cell-culture grown and recombinant protein vaccines [12–14], which have comparable efficacy to egg-derived vaccines [15]. Competition to TIV is also coming from live-attenuated influenza vaccines (LAIVs). LAIVs have been successfully used in children in Russia for many decades [16] and more recently have been introduced to the USA and other markets [17]. LAIV have the potential advantage that they are administered by nasal spray rather than intramuscular injection, but, on the negative side, induce wheezing in young asthma-prone infants and are therefore not licensed for children less than 2 years of age [18]. Comparative efficacy studies of LAIV versus TIV suggest that LAIV may be slightly more effective at preventing influenza infection in children [19].

Other recent entrants to the pediatric influenza vaccine market are adjuvanted TIVs [20]. These include Grippol (Mikrogen), a Russian TIV containing polyoxidonium adjuvant [21], Inflexal® V (Crucell), a European TIV based on reconstituted influenza HA and NA proteins integrated into phosphatidylcholine liposome [22] and two European monovalent pandemic influenza vaccines Focetria® (Novartis) [23] and Pandemrix (GlaxoSmithKline) [24] that contain squalene oil emulsion adjuvants called MF59 and AS03, respectively. Unfortunately, the increased immunogenicity of squalene adjuvants comes at the expense of increased reactogenicity, particularly in young children, with increased injection-site pain, fatigue, headache, myalgia and fever [23,25,101]. The Pandemrix platform was granted marketing authorization in Europe in May 2008 for pandemic avian influenza, with use restricted to 18–60-year olds [101]. At the time of European release of the Pandemrix vaccine for H1N1 2009, there is no public record of any completed pediatric studies [102]. Subsequently, an open-label, randomized study reported on the comparative safety, reactogenicity and immunogenicity in 937 children aged 6 months–13 years of two doses 3 weeks apart of the AS03-adjuvanted Pandemrix vaccine containing 1.875 µg of HA with a nonadjuvanted whole-virion cell-culture vaccine containing 7.5 µg HA [26]. Seroconversion was higher with Pandemrix but at the expense of more frequent and more severe local and systemic reactogenicity including fever. A systemic review by the National Institute for Health and Welfare of Finland recently reported a nine-times higher risk of narcolepsy among children aged 4–19 years who had received Pandemrix, equating to a risk of one case of narcolepsy per 12,000 children vaccinated, creating considerable controversy [27,28,103]. Confirmation of causality requires further investigation, but this incident highlights the potential for differences between the responses of children and adults to the same vaccine. Conditions such as autoimmunity may be triggered in genetically susceptible subjects within a discrete age range, such that trial data in subjects outside this age range or in populations without the genetic susceptibility may not be informative as to the potential risks of a particular vaccine or adjuvant. As another example, a pediatric TIV (Fluvax, CSL, Australia) recently had to be withdrawn from the market after causing excessive pyrogenicity and febrile convulsions in young children [29]. It has been estimated that the CSL vaccine would cause three hospitalizations of children with febrile convulsions for every hospitalization with influenza prevented, an unacceptable risk–benefit relationship [30]. The problem with the CSL vaccine was only identified when an Australian state conducted an immunization campaign in large numbers of young children, with the vaccine previously predominantly used in adults. Local hospital clinicians raised the alert after seeing a high rate of post-vaccination febrile convulsions. This highlights that children can behave very differently to a vaccine previously well tolerated in adults. Clinical trials in several hundred children may not be sufficient to identify such problems, particularly when the frequency of such adverse events is taken into account. This reinforces the need for strong postlicensing vaccine adverse event surveillance systems. Unfortunately, adequate postregistration surveillance systems do not exist in many countries, including Australia, despite many recommendations for their implementation. Marketing approvals for vaccines to be used

in children should be based on substantive pediatric clinical trial data rather than simply extrapolated from adult data, a requirement that, in the authors' opinion, was clearly bypassed in the approval of Pandemrix for use in European children.

Five-year view

The benefits of influenza immunization of school-age children is striking, both in terms of preventing hospitalizations and time lost from school, but also in terms of reducing the burden of influenza across the whole community. It is desirable to increase the uptake of influenza vaccines in this population and this requires careful consideration of strategies to identify the safest and best tolerated influenza vaccines for children. Even rare or transient adverse reactions have the potential to damage community confidence in effective immunization campaigns, as was experienced in Japan. Pediatric clinical trials confirm that both TIVs and LAIVs are 50–80% effective in preventing influenza-like illness in children above 2 years of age, enabling both types of vaccine to lay claim to a share of the pediatric market. Within TIVs, newer cell-culture vaccines have few distinguishing features other than being egg-free. The big question is what will be the future of the new aspirants to the pediatric influenza market, namely the recombinant protein vaccines and the squalene oil-adjuvanted vaccines? The recombinant vaccines appear to have a bright future, with the US government recently investing more than US$0.5 billion in the manufacture of these vaccines. The issue of poor immunogenicity of recombinant proteins will need to be overcome through the use of appropriate adjuvants. Recent publicity of febrile convulsions caused by CSL's Fluvax vaccine and the ongoing question of the relationship between the AS03-adjuvanted Pandemrix vaccine and narcolepsy remind us that children are not just 'little adults'. The public's confidence in vaccines should not be taken for granted and old-style paternalistic public health responses to potential vaccine problems are no longer appropriate. Effective pediatric influenza vaccines will be of little use if parents lose confidence in vaccine programs. Immunization bodies need to embrace community consultation and be willing to publicly debate difficult scientific issues such as the safety and tolerability of particular adjuvants and vaccines. Policy makers need to appreciate the price of current underinvestment into research into the cause and prevention of vaccine adverse reactions. Any loss of community confidence in pediatric vaccine programs through perceived vaccine shortcomings could have far-reaching negative impacts on vaccine utilization that are extremely difficult to overturn. Prevention is always better than cure and hence the development of safer and better tolerated pediatric influenza vaccines should be a top priority.

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