Leading articles

Routine influenza vaccination for healthy children—old concept, new technologies

Annual vaccination against infection with influenza virus types A and B is strongly recommended for all adults over the age of 65 years and for persons of all ages, who are at risk for influenza induced mortality or the development of serious complications after influenza infection (chronic cardiac, pulmonary, metabolic, renal or immunological disorders, residence in institutional care facilities).[1] Vaccination is also recommended for children who receive long term salicylate therapy, to reduce the risk of Reye syndrome, which occasionally occurs during convalescence from influenza and varicella infection and shows a strong correlation with the use of salicylates.[2]

The absolute number of children at risk for complications of influenza is small. For them, inactivated purified surface antigen (subunit) or detergent disrupted (split) influenza vaccines are available to be administered every year. Whole virus vaccines, which can be used in adults, are not recommended for children because of a higher incidence of vaccine induced systemic reactions,[3] such as transient fever. Previously unvaccinated children less than 9 years of age should receive two doses of half the adult dose (currently 7.5 μg haemagglutinin per vaccine component) at least one month apart to guarantee a satisfactory antibody response.[4] Clinical trials such as the one by Gonzalez *et al* reported in this issue of the journal[5] and others[6–10] show that this policy is safe in those vulnerable young individuals.

Healthy children are currently not a target for routine influenza vaccination although there are at least two good reasons to support such a policy. Firstly, an infected child typically sheds high amounts of virus up to two weeks, while virus shedding in an adult lasts usually only a few days and produces low titres.[11] As a consequence, the epidemic curve in preschool and schoolchildren precedes the overall community peak, and children introduce influenza epidemics into households and the entire community.[12–14] One may expect, and it has even been shown,[15] that an effective mass vaccination in children would significantly reduce the overall impact of influenza on the community and particularly mortality and morbidity in the elderly. Secondly, influenza illness in children themselves, particularly in infants, is not as innocent as is usually perceived. The real impact of influenza is confounded by the co-circulation of viruses like respiratory syncytial virus (RSV), adenoviruses (AV), or parainfluenza viruses (PIV). Moreover, an influenza infection in young children can clinically manifest itself as lower respiratory tract infection, febrile convulsions, myositis, myocarditis, or pericarditis, and may be complicated by bacterial superinfections such as otitis media,[16 17] bacterial pneumonia, sepsis, or the toxic shock syndrome. Influenza is not often recognised as a cause of these serious clinical conditions.

Two recent studies involving large numbers of observations corrected for such confounders, revealed the surprisingly high influenza associated morbidity in healthy young children. Maletic-Neuzil *et al* showed that the rate of hospitalisations attributable to influenza in infants younger than 6 months of age was similar to that for adults at high risk for influenza (104 excess cases per 10 000).[18] The rate of hospitalisation decreased considerably with age but was increased in all age groups up to 15 years of age. For every 100 children, an annual average of six to 15 outpatient visits and three to nine courses of antibiotics were attributable to influenza. Izurieta *et al* found highly increased hospitalisation rates in previously healthy children younger than two years of age.[19] The authors conclude therefore that routine influenza vaccination should be considered for all infants and young children.

The concept of a general influenza vaccination programme in children meets important logistic, financial, and other obstacles. National health authorities may be reluctant to add another entity to the existing crowded childhood immunisation scheme against a variety of viral and bacterial diseases, which is certainly difficult enough to maintain. The use of the currently available inactivated vaccine types would mean no less than one or two additional intramuscular injections every year. In Japan, such a policy failed. In 1976, obligatory national annual influenza vaccination was introduced for children of 3 to 15 years. Concerns about serious vaccine reactions, inappropriate scientific evaluation and resulting doubts about vaccine efficacy, and public campaigns led to a weakening of the obligatory nature of the vaccination programme in 1987. Since then, parents have been allowed to refuse influenza immunisation for their children, and vaccination rates have decreased sharply in the target group.[20 21] Following the Japanese experience, most health authorities would agree that mass vaccination with the current influenza vaccine types is not a feasible option.

As a possible alternative, a live, attenuated, cold adapted vaccine has been developed, which can be administered intranasally by spray, thus avoiding parenteral injection and providing higher acceptability in children. It has been extensively studied in the USA for over 30 years but is not yet licensed. Its basic concept is the attenuation of the Ann Arbor master strains by repeated passage on chicken eggs under decreasing temperature conditions. The final variants can no longer replicate at human core body temperature and grow only in the mucous membrane of the upper respiratory tract where temperatures do not exceed 32–33°C. Many thousands of doses have been given in the USA under experimental conditions without serious concerns about adverse events: local and systemic reactions were mild and transitory, and regarded as acceptable. No vaccine induced inflammation of the lower respiratory tract was seen, and the vaccine appeared to be reproducibly attenuated, genetically stable, and non-transmissible.[22] A large placebo controlled study in children 15 to 71 months old showed a vaccine efficacy of 93% against culture confirmed influenza and, most interestingly, a 30% reduction of febrile otitis media.[23] A similar vaccine efficacy was found in another recent trial.[24] In comparative studies, efficacy of the live vaccine appeared to be similar to that of an inactivated vaccine in all age groups.[25 26]

There are also theoretical, though serious, concerns about the use of living influenza particles in humans. These include the possibility of co-infection with human or,

worse, non-human wild type virus and consecutive hazardous reassortment, and the transmission of vaccine virus to other species.[27 28]

Another alternative, which combines the safety of the inactivated vaccine and the convenience of intranasal administration, is liposomal influenza vaccine. A liposome is a small suspended sphere (diameter <200 nm) consisting of a lipid bilayer and serving as vehicle for solubilised viral proteins.[29] Liposomal influenza vaccine for intramuscular administration[30] has already been licensed in some European countries for adults, and it may also be used for children at risk.[31] Currently, an intranasal formulation is under study, which shows promising preliminary results in adults.[32] More data, in particular from efficacy studies, are needed for a sound clinical assessment. Other vaccine delivery systems, for example ISCOM,[33 34] are candidates for suitable mucosal influenza vaccines.

Another potential advantage of these vaccine delivery systems, in addition to their easier mode of administration (compared to current inactivated vaccines) and probable greater safety (compared to live vaccine), lies in the potential to include other immunogenic proteins from influenza C, respiratory syncytial virus, adenovirus, and parainfluenza virus as well, in order to create broad prophylaxis against the predominant viral causes of serious respiratory disease in childhood. The next decade will show whether such an option is feasible.

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