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Influenza vaccination in kids, are you kidding me?

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Summary Seasonal influenza infections cause a high burden of disease for the whole community every year. Effective vaccines are available and used worldwide in adults and children. Discussion is ongoing as to whether influenza vaccination for children should be implemented in the National Immunization Program (NIP). Is there enough evidence to support routine influenza vaccination in children? In this review we briefly discuss the influenza viruses and the available vaccines. Subsequently, the current data available on influenza vaccination is reviewed and weighed against the Dutch criteria for the introduction of new vaccines into the NIP.

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Introduction

Influenza virus is a RNA virus belonging to the *Orthomyxoviridae* which primarily infects the respiratory tract. Transmission mainly occurs through aerosols created after coughing. However, the virus can also be transmitted via direct contact with nasal secretions (daycare centers and siblings) or feces of animals (bird droppings and avian flu).¹

Influenza occurs worldwide in winter epidemics, resulting in three to five million cases of severe illness and 250,000 to 500,000 deaths yearly.² Some years, a new influenza A virus subtype emerges in which the hemagglutinin gene is not related to the circulating influenza strains. Influenza strains can acquire genes from influenza viruses

that infect birds or pigs. These new strains of influenza viruses can spread worldwide and cause a pandemic.^{3–5}

In late March 2009 such a novel influenza A (H1N1) virus was identified in Southern America which showed reassortment of swine avian and human strains.⁶ This virus was subsequently recognized as the cause of an outbreak of respiratory illness in Mexico.⁷ In June 2009 the WHO declared a pandemic. At the start of the pandemic the virus appeared to be very virulent with a high mortality rate, especially in young adults and children.⁸ This information resulted in the decision to vaccinate people in the Northern hemisphere to protect them against this severe disease. However, in the Northern hemisphere the virus behaved more like a seasonal influenza virus. H1N1 disease had the

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highest attack rate in young children causing relatively mild disease.⁹ The pandemic H1N1 replaced the seasonal flu so that, in the influenza season 2009–2010, over 99% of the influenza positive isolates in Europe and America were pandemic H1N1 influenza A.^{10,11}

There are three types of influenza viruses: types A, B and C, of which influenza A is the most virulent and causes more severe disease. Influenza A predominantly infects (aquatic) birds where extensive reassortment of genes can occur increasing the risk to form strains which can infect humans.¹² This has led to pandemics in the past (H1N1, Spanish Flu 1918 and Swine Flu 2009; H2N2, Asian Flu 1957; and H3N2 Hong Kong Flu 1968) and poses a continuous threat for new outbreaks. Due to the huge genetic variation of influenza A, different serotypes are known. Low cross protectiveness occurs throughout life and after vaccination.^{13,14} Influenza B is mostly restricted to humans and has a slow mutation rate leading to a low genetic diversity; only one serotype is known.¹³ Throughout life people acquire a certain degree of protection against influenza B, although antigenic drift of the virus prevents full protection.¹⁵ Influenza C is less common than the other types and can infect humans, pigs and dogs. It most often causes mild disease in children and rarely outbreaks of severe disease.¹⁶

Currently two types of influenza vaccines are available, the trivalent influenza vaccine (TIV) and the live attenuated influenza vaccine (LAIV), both registered in the US and Europe. Both vaccines contain two type A influenza strains (H1N1 and H3N2) and one type B influenza strain.^{17,18} Due to the high mutation rate of the virus, the vaccine composition has to be adjusted every year based on the prediction from the World Health Organization about which strains of the virus are most likely to be circulating in the next year.¹⁹ Both vaccines have been shown to be effective and are used in many national immunization programmes (NIP), although large differences in protection have been reported.^{20,21} LAIV has only been registered for vaccination of children older than 2 years and adults younger than 50 years.^{22,23} Currently no vaccine for children younger than 6 months is available. Vaccination of pregnant women in 3rd trimester with TIV may protect young infants.²⁴ There is the tendency to advise LAIV for pandemic influenza because it induces better protection if there is no pre-existing immunity in the community against these strains.²⁵

Influenza in children

Influenza infections lead to symptoms including fever, cough, nasal congestion, general malaise and muscle pain, also referred to as 'the flu' (Table 1).²⁶ In children, the disease is often accompanied by gastrointestinal complaints such as vomiting and diarrhea.²⁷ In comparison to other respiratory viruses, influenza infection appears to have a more severe course of disease in children over 1 year of age, in whom infection may lead to viral pneumonia or secondary bacterial super infection.^{28–30} Further, influenza infection is associated with the development of otitis media in children.³¹

The annual incidence of seasonal influenza infection is 2–10% worldwide.² Attack rates are highest in young

children (20–30%). Before the age of 6 years most children have been infected at least once with influenza A.^{32–34} The annual burden of disease in children is difficult to establish and often underestimated. This is partly due to seasonal overlap with epidemics caused by other respiratory viruses,³⁵ and the diverse spectrum of clinical manifestations in children.^{27,36} The average annual hospitalization rate in children is 9/10,000 and higher in young infants (up to 100/10,000). The overall mortality due to influenza is very low, and is the highest in children below the age of 6 months (0.9/100,000). Pre-existing medical conditions, such as chronic diseases and the use of immunosuppression, increases the risk of a complicated influenza infection.²⁷

Most children with an uncomplicated influenza infection are seen by the general practitioner, demanding high healthcare capacity during the respiratory season.^{37–39} Further, children with flu have to stay at home resulting in absence at work of their parents. In this way influenza infection in children also affects the community indirectly. Influenza is rapidly disseminated in school children and children play an important role in transmission cycle during an epidemic.^{40,41} Vaccination of children therefore also prevents morbidity and mortality in the elderly.⁴²

The Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) publishes yearly the recommendations for the prevention and treatment of influenza in children.⁴³ Regarding vaccination, they recommend annual TIV for: (i) All children, both healthy and with conditions that increase the risk of complications from flu, aged 6 months to 18 years, (ii) household contacts and out-of-home care providers of children with conditions that place them at high risk or healthy children younger than 5 years, (iii) all healthcare professionals and (iv) pregnant women.

According to these recommendations, 85% of the US population should be vaccinated.⁴⁴ In practise, only 50% of high risk patients are vaccinated and 27% of all children in the US are completely vaccinated. Most of the children between the ages of 2 and 18 years are vaccinated with TIV (90%) and 10% with LAIV.⁴⁵ In previous recommendations of the AAP only the youngest children should be vaccinated (TIV for children 6–23 months in 2004 and 6–59 months in 2006).⁴⁶ The evidence base to vaccinate older children up to 18 years is poor.⁴⁷

The European Centre of Disease Prevention and Control (ECDC) does not recommend routine seasonal flu vaccination in healthy children.^{18,48} Since 2007 TIV has been included in the NIP of Finland for children 6–35 months.⁴⁹ During the 2009 H1N1 pandemic, many countries in Europe decided to vaccinate young children, pregnant women, the elderly and high-risk patient groups (Fig. 1).²⁹ In The Netherlands, the policies regarding routine vaccination of the elderly led in 2012 to media commotion initiated by an article in the *Lancet Infectious Diseases* by Osterholm et al. and opinion articles by a general practitioner based on this article in the *Geneesmiddelen Bulletin*.^{50,51} As a result of this commotion, uptake of influenza vaccines by the elderly, hospital employees and high-risk patient groups decreased, policy makers were taken to court and public concern about vaccination grew. The main arguments against vaccination were: (i) there are no randomized controlled trials with appropriate end-points in many high

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