

Safety of a Virosomal Adjuvanted Influenza Vaccine in Children Suffering from Chronic Disease

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Abstract: Children suffering from chronic disease are at increased risk for complications and mortality caused by influenza. Influenza can be most effectively prevented by vaccination. Although recommended for children with chronic disease, vaccination rates remain low in this population. One possible explanation is the parents' concern that the child's underlying disease may worsen or that adverse events following influenza vaccination may be more severe than in healthy children. Data demonstrating the safety of influenza vaccination in this population are therefore crucial and may help to increase future vaccination rates in children suffering from chronic disease. The present review summarises published data on safety following vaccination with a virosomal adjuvanted influenza vaccine in children suffering from chronic disease compared with healthy children. The vaccine was shown to be immunogenic and safe in four particularly vulnerable populations: children suffering from asthma, cystic fibrosis, diabetes, or HIV infection. No changes in the course of the underlying diseases were observed after vaccination.

Keywords: Influenza vaccine, virosomes, asthma, cystic fibrosis, HIV, diabetes.

INTRODUCTION

Influenza is one of the most common respiratory diseases in humans. Young children, including infants and toddlers, are especially at risk because they have not yet developed immunological memory to influenza viruses [1, 2]. Influenza may become life-threatening in individuals with an underlying chronic disease that likely impairs the immune response to upper respiratory tract infections [3-5]. During winter months, patients younger than 18 years with underlying conditions undergo up to 21 times more hospitalisations for an acute respiratory disease than healthy individuals of a comparable background [4]. More than half of the hospitalisations for influenza and associated costs in the United States in 2003 occurred among children and young patients (≤ 18 years) [6]. Vaccination remains the cornerstone of prevention and control of influenza and it was shown that the use of influenza vaccine in children at high risk could prevent hospitalisations and cases of influenza-related diseases [7].

National recommendations for influenza vaccination vary, particularly for children. In the United States, annual influenza immunisation is recommended for all healthy children aged 6 months or above [8, 9]. In Europe, only a few countries recommend annual influenza vaccination of healthy children, while the advice of the WHO to vaccinate all children aged 6 months or above with chronic conditions is widely implemented in national guidelines [10, 11].

Despite these recommendations, influenza vaccination rates remain low in children with underlying diseases. The paediatricians' knowledge and their ability to inform parents about the importance and benefits of influenza vaccination in children at risk seem to be critical. In a survey among parents of chronically ill children, 85.6% answered that lack of awareness was the main reason for not having their child vaccinated against influenza. Among parents of vaccinated children 87.5% stated that they had followed the paediatrician's advice [12]. In addition, the parents' concern that the child's disease may worsen, or that adverse events following vaccination might be more severe than in healthy children, may contribute to the low vaccination coverage [13]. According to a recent survey, most parents believed that influenza vaccination was safe in 1-year-old children (65%) and in older children or adults ($>80\%$). In contrast, influenza vaccination was perceived as less safe for 1-year-olds with a chronic health condition compared to healthy counterparts of the same age (39%) [14]. These findings are remarkable, because individuals with chronic illnesses are likely to experience complications if they contract the disease and would benefit significantly from vaccination [8, 15]. To increase the parents' confidence in the safety of influenza vaccination it is therefore crucial to gather data in particularly vulnerable subjects. Access to such data may reduce some reservations against vaccination among parents of children at risk.

SAFETY OF INFLEXAL[®] V

Inflexal[®] V is a virosomal adjuvanted influenza vaccine that was shown to be highly immunogenic and safe in all age groups, including the paediatric population [16-19]. The efficacy of the virosomal delivery system derives from the natural presentation of antigens mimicking natural infection [20-22]. In contrast to some split or subunit influenza

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vaccines on the market, Inflexal[®] V contains no thiomersal or formaldehyde and very low levels of ovalbumin, thus reducing the rate of unwanted side effects [19, 23].

Inflexal[®] V was introduced to the Swiss market in 1997, and since then more than 41 million doses have been sold worldwide [19]. During this period, 695 adverse drug reactions (ADRs) were spontaneously reported in 364 subjects. Based on the 41.1 million doses distributed, this results in a spontaneous reporting rate of 0.89 cases per 100,000 immunisations. Of the 364 subjects reporting spontaneous ADRs 36 were children (<15 years) and 8 were adolescents (15 to <18 years). Further post-marketing data are available from a recent surveillance study conducted in 405 children (≥6 months to ≤6 years), in which the vaccine was demonstrated to be safe, well tolerated, and widely accepted by parents [18].

Data assessing the safety of trivalent inactivated influenza vaccines in children are limited. Between 1990 and 2003 relatively few adverse events were reported to the Vaccine Adverse Event Reporting System (VAERS) after vaccination of children aged <2 years with trivalent inactivated influenza vaccine, alone or in combination with other vaccines [24]. The authors of a study designed to identify vaccine-related adverse events in children aged 6 to 24 months concluded that adverse events possibly linked to influenza vaccination among healthy young children are unusual [25].

INFLEXAL[®] V IN CHILDREN WITH CHRONIC DISEASE

The greatest clinical problems caused by influenza occur in children during their first 2 years of life, but also older children may suffer from severe complications [26]. This suggests that adequate vaccination should be implemented for all children, regardless of their age. In the following sections safety data after administration of Inflexal[®] V to children with asthma, cystic fibrosis (CF), diabetes, and HIV are reviewed in light of corresponding data in healthy children. In all groups the local and systemic adverse reactions have been considered. Table 1 summarises the local adverse

reactions in healthy children versus children with chronic diseases.

ASTHMA

Viral respiratory tract infections may exacerbate asthma, particularly in children [27]. Asthmatic children usually suffer from more severe wheezing episodes during the influenza season, leading to increased hospitalisation rates, out-patient visits, and drug prescriptions [28, 29]. Several studies have investigated the impact of influenza vaccination on children with asthma [8, 30]; among these Kramarz *et al.* extrapolated that influenza vaccination of all children with asthma could prevent 59 to 78% of asthma hospitalisations and Emergency Department visits during influenza season [31]. Yet, vaccination rates in asthmatic children are constantly low and more awareness of data supporting the safety in this vulnerable population is needed.

A recent publication compared safety data collected in a clinical study in 103 children with chronic asthma aged 3 to 9 years [32, 33] with corresponding data from an active post-marketing surveillance study in 269 healthy children aged 0.5 to 6 years [18]. Children in both studies were vaccinated with a single dose (0.5 mL) of Inflexal[®] V. Asthmatic children and healthy children tolerated influenza vaccination equally well [33]. Local adverse events were less frequently reported by asthmatic children than by healthy children. This was true for pain/tenderness at the injection site (4.9% asthmatic children vs. 16% healthy children), injection site erythema (6.8% asthmatic children vs. 11.5% healthy children), and swelling/induration (3.9% asthmatic children vs. 7.4% healthy children). By contrast, the systemic adverse events malaise/irritability and fever were slightly more frequent among asthmatic children (3.9% and 5.8%, respectively) compared with healthy children (0.4% and 1.5%, respectively). Local and systemic adverse events were generally mild to moderate and no serious adverse events were reported in any of the studies. As stated by the authors, no clinically relevant difference in the adverse event profile in healthy and asthmatic children was observed.

Table 1. Local Adverse Reactions After Vaccination with Inflexal[®] V

	Number of Subjects	Dose	Pain/Tenderness	Redness	Swelling/Induration
Healthy children [18]	269	0.5 mL – single dose	16%	11.5%	7.4%
Healthy children [18]	17	0.25 mL – two doses	5.9%	0	0
Asthma [32]	103	0.5 mL – single dose	4.9%	6.8%	3.9%
Asthma [37]	44	0.5 mL – single dose	15.9%	2.25%	6.8%
Asthma and egg allergy [37]	44	0.5 mL – single dose	13.6%	0	6.8%
Cystic fibrosis [41]	19	0.5 mL – single dose	5.3%	0	0
Cystic fibrosis [41]	24	0.25 mL – two doses	0	0	0
Type I diabetes mellitus [52]	52	0.5 mL – single dose	26.9%	7.7%	7.7%
HIV infection [58]	24	0.5 mL – single dose	12.5%	0	0
HIV infection [60]	23	0.5 mL – single dose	4.3%	0	0

The perception that influenza vaccination might worsen the disease may discourage vaccination, however, evidence from a recently published review indicates that there is no significant increase in asthma exacerbations immediately after vaccination, at least when the vaccination is with an inactivated influenza vaccine [34]. The results with virosomal adjuvanted influenza vaccine are consistent with these findings, as no episode of asthma exacerbation was reported after its administration [32].

Children with asthma might additionally suffer from allergies. Egg allergy is one of the most common food allergies in infants and young children [35]. It declines with age, but the prevalence is higher in asthmatic children [36]. Since inactivated influenza vaccines are produced on eggs, parent's concern of vaccinating their child may be enhanced. The residual amount of egg protein - reflected in the ovalbumin content of the vaccine - varies among influenza vaccines. Inflexal[®] V contains less than 10 ng of ovalbumin per dose [23], which makes it 100 times lower than the 1 µg permitted by the European Pharmacopoeia for conventional influenza vaccines. Recently, a study to evaluate whether Inflexal[®] V could be safely administered to asthmatic children with egg allergy was conducted. Asthmatic children (44 with and 44 without egg allergy) underwent epicutaneous skin testing with the undiluted vaccine and none of the children was tested positive. Subsequently, the children were vaccinated with a single dose (0.5 mL) of Inflexal[®] V. The vaccine was well tolerated by children with or without egg allergy; no significant difference in adverse event pattern between the groups was observed. The authors concluded that Inflexal[®] V can be safely administered to children with egg allergy without prior skin-testing [37].

In a recent review on the recommendations for the administration of influenza vaccine in children allergic to egg, the authors conclude that if a mammalian cell culture vaccine is not available the virosomal adjuvanted influenza vaccine should be used as it has the lowest egg content of any vaccine derived from eggs and there is clinical data to support its use [38].

CYSTIC FIBROSIS

Viral respiratory tract infections have a deteriorating effect on the lung function and on disease progression in patients with chronic respiratory diseases, such as CF. Influenza impairs the natural defence system of the respiratory tract and a secondary bacterial pneumonia may develop. It is expected that influenza vaccination of children with CF will result in a reduction of exacerbations, hospitalisations, and subsequent use of antibiotics, as has been shown for children with different types of chronic respiratory diseases [29]. Annual influenza vaccination is therefore commonly recommended for individuals suffering from CF.

The incidence of CF is generally low with a mean prevalence of 0.737 per 10,000 people in 27 European Union countries in 2004 [39] and 0.797 CF patients per 10,000 people in the United States in 2005 [40]. Furthermore, influenza vaccination of patients with CF was not common practice until recently. In Italy, only 8.3% of children with CF were vaccinated against influenza in the 2000/2001 season. Vaccination rates increased to 41.7% in 2002/2003 [12], and

the amount of data after immunisation in this population will progressively increase.

Data from clinical studies on influenza vaccination in children with CF are rare. In a small pilot study, Inflexal[®] V (1 dose of 0.5 mL or 2 doses of 0.25 mL 28 days apart) was administered to 43 subjects with CF (9 young children ≤6 years and 34 ≥6 years) [41]. Local and systemic adverse reactions observed in this study were compared with those spontaneously reported for healthy children (286 children aged 0.5 to ≤6 years) in the scope of an active post-marketing surveillance study [18,42]. Both dose regimens were well tolerated in children with CF and in healthy children. No serious adverse events were reported. Systemic adverse reactions reported by children with CF ≤6 years of age included fatigue in 3 (33.3%) subjects, cough in 5 (55.6%) subjects, and rhinitis in 5 (55.6%) subjects. Age-matched healthy children reported fatigue (18 [6.3%] subjects) and cough (5 [1.7%] subjects) but not rhinitis. Fever was not observed in young children with CF but was experienced by 5 (1.7%) healthy young children. The only local adverse reaction reported in children with CF ≤6 years was 1 case of pain at the vaccine injection site after administration of 0.5 mL. Age-matched healthy children reported pain (44 [15.4%] subjects), erythema (31 [10.8%] subjects), induration (2 [0.7%] subjects), and swelling (18 [6.3%] subjects) at the vaccine injection site.

Although safety data in children with CF are limited, the results indicate that, most likely, there are no clinically relevant differences in the adverse event profile following influenza vaccination in children with CF compared with healthy children. In conclusion, Inflexal[®] V was well tolerated and safe in children with CF.

Studies with influenza vaccines in children with CF are rare. One review considered 179 people (80% were children 1-16 years old) with CF who received different types of influenza vaccines (including virosomal adjuvanted influenza vaccine). The incidence of reported adverse events was dependent on the vaccine type. None of the adverse events was life threatening or persistent. The highest total adverse event rate was reported for the split virus vaccine. Although available data are very limited, there was no statistical difference the vaccines tested in this study [43].

TYPE I DIABETES MELLITUS

Diabetes may be connected with an impaired immune function, which may lead to increased morbidity and mortality from influenza [44]. Influenza infection may also interfere with blood glucose management and put patients at risk of diabetic coma [45]. Despite the recommendation for annual influenza vaccination of persons with diabetes aged 6 months or older, the vaccination rates remain alarmingly low in this population [2, 46-48]. In Italy the vaccination rate in 2002/2003 was only 35.7% [12]. Influenza vaccination has been shown to reduce hospital admissions in adult and elderly subjects with diabetes [49,50] but no data exists for children with diabetes, and this information is urgently needed [51].

A recent randomised, double-blind study assessed immunogenicity and safety of influenza vaccination in children and young adults (age range 9 to 30 years) with type I diabe-

tes [52]. A single 0.5 mL dose of virosomal (Inflexal[®] V, 52 subjects) or standard subunit influenza vaccine (Influvac[®], 53 subjects) was administered. No serious adverse events occurred. Influenza-like illness was reported by 3 and 2 subjects after administration of the virosomal or subunit vaccine, respectively. In total, 39 (37.1%) subjects (20 in the virosomal group; 19 in the subunit group) reported local or systemic reactions; all were mild to moderate and resolved within 1 to 3 days. The most common symptom was pain/tenderness experienced by 14 and 13 subjects at the virosomal and at the subunit vaccine injection site, respectively. Redness, swelling, and induration were observed in 1 to 4 subjects in both groups. The systemic reactions headache, malaise, nausea, and myalgia were reported by up to 4 subjects in both groups. There were no significant differences in number or severity of any local or systemic reaction between the groups. Overall, both vaccines were equally well tolerated by children and young adults. The results indicate that influenza vaccination is safe with type I diabetes.

HIV INFECTION

Children infected with HIV are particularly susceptible to influenza-related complications which often require admission to hospital and antibiotic treatment [53-55]. In addition, HIV infection prolongs the duration of disease and patients with a low CD4 cell count discharge influenza virus for several weeks [56,57]. Success rates of antiretroviral treatment are higher in children than in adults, but it is unknown whether the ability to respond to vaccines is restored after the therapy. In addition, the use of vaccines in HIV-infected subjects is debated as there is concern that vaccination may enhance HIV replication, activate T-lymphocytes, and accelerate disease progression. The immune response to influenza vaccination following antiretroviral treatment was addressed in a recent observational study in 24 HIV-infected children (mean age 12.6 years) undergoing highly active antiretroviral treatment (HAART) and 14 healthy children (mean age 9.7 years) [58]. The results showed that although the humoral and cellular immune responses were reduced in these children, one injection of 0.5 mL Inflexal[®] V elicited good immune responses, the EMEA criteria for seroconversion and seroprotection were fulfilled 1 month after immunisation for all 3 influenza strains. No serious vaccine-related adverse events occurred. Pain/tenderness at the vaccine injection site was experienced by 3 HIV-infected children and by 2 healthy children; 2 children in each group reported an axillary body temperature >38 °C.

Another study investigated the immunogenicity and the impact of Inflexal[®] V vaccination on viral replication and T-lymphocyte activation in 29 HIV-infected children (mean age 10.3 years) receiving HAART [59]. The children (10 unprimed and 19 primed with a previous influenza vaccination) received 1 (primed) or 2 doses (unprimed) of 0.5 mL Inflexal[®] V. Although the interpretation of the immunogenicity results is limited by the small subject number, the findings indicate that Inflexal[®] V is immunogenic in the majority of children and does not lead to viral replication or T-lymphocyte activation. These results are in line with those from a similar study, in which 23 HIV-infected children (mean age 7.2 years) were vaccinated with a single

dose (0.5 mL) of Inflexal[®] V [60]. The children had not received previous influenza vaccination; 18 of the children were taking antiretroviral drugs. In this study, the children responded to vaccination with Inflexal[®] V with high seroconversion rates for all three influenza strains. No significant changes in viral load or CD4 lymphocyte count were observed. Vaccination was well tolerated; 3 of the children reported adverse events (pain at the injection site, mild headache, and fever).

This data is consistent with what has been observed with other types of influenza vaccines and supports the claim that influenza vaccination does not alter HIV RNA viral load or median CD4% [61].

Taken together, these study results support the use of Inflexal[®] V in HIV-infected children receiving antiretroviral treatment.

CONCLUSION

Individuals with chronic diseases are susceptible to complications if they contract influenza and may thus particularly benefit from influenza vaccination. Published data on the virosomal adjuvanted influenza vaccine Inflexal[®] V show that the vaccine is safe in children suffering from asthma, CF, diabetes, or HIV infection. In addition, no changes in the course of the underlying diseases were observed after vaccination. This further supports the excellent safety and tolerability of Inflexal[®] V in vulnerable patient populations.

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