

REVIEW

Is influenza vaccination in asthmatic children helpful?

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Summary

The rationale for influenza vaccination in asthmatic children theoretically lies in prevention of exacerbations and serious complications like pneumonia. Solid evidence from randomized clinical trials of its preventive effects on these clinical endpoints is, however, lacking. Nevertheless, most Western guidelines advise to vaccinate these children. In the real life situation this advice isn't very well followed: vaccine coverage for this indication is low. To assess the usefulness of influenza vaccination in children with asthma a set of fundamental questions regarding this activity is presented and answered. This leads to the conclusion that, given the evidence, influenza vaccination in children with mild to moderate disease should be reconsidered.

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Is influenza vaccination in asthmatic children helpful?

Asthma nowadays is seen as a disease of chronic inflammation of varying degrees of severity, instead of solely a disease of reversible airway obstruction. Treatment has progressed along with the growing knowledge of the underlying pathophysiological mechanisms [1]. With adequate treatment, consisting of a combination of maintenance and rescue medication, patients nowadays can lead a normal life and suppress the asthmatic symptoms following common airway infections [2]. This treatment is at direct disposal of patients and their caretakers and there is no indication that its efficacy is influenced by the antigenic characteristics of the influenza virus.

In children, asthma is in absolute and relative numbers the most important chronic disease. The reason to vaccinate asthmatic children against influenza is the prevention of exacerbations of upper respiratory tract (URT) and lower respiratory tract (LRT) symptoms, i.e. asthma symptoms, and the prevention of more rare complications, such as pneumonia. A diagnosis of asthma is the most common reason for which children should receive influenza vaccination [3].

Most western guidelines advise to vaccinate patients with asthma against influenza [4, 5], although we lack solid evidence from randomized trials for the preventive effect on clinical endpoints, i.e. based on symptoms of asthma [6].

When advocating a preventive activity, like influenza vaccination in children with asthma, a set of fundamental questions has to be answered. For this purpose, I adapted Demicheli's questions with respect to mass vaccination for influenza [7], which obviously derive from the criteria used for mass screening (Table 1) [8].

I will reflect on these questions in the light of the evidence that is now available and finally I will make suggestions for altering the guidelines and future research to be done.

How important is the disease?

Influenza is one of the common respiratory tract infections in children [9, 10] and, according to the World Health Organisation, a yearly public health problem in children as well as in the community at large [11]. Every season, after the virus has appeared and a rise in influenza-like illnesses (ILIs) has been assessed, influenza centres worldwide provide information on influenza activity and its presumed impact [12]. Many viruses, however, can be responsible for ILIs [13–15] and the true incidence of influenza proper and its associated illness is still unclear.

Because of different subtypes of the virus and its constant antigenic drift, acquired immunity is usually only partial and therefore the population will always to a greater or lesser extent be susceptible. Thus, to gain an

Table 1. Criteria used for mass screening

Is the condition or the disease to be prevented important?
Do we know enough about the incidence, the natural history and the burden of this disease to reasonably forecast the likely impact of immunization?
Does the vaccine work? (That is, is it effective in preventing clinical cases of influenza-related asthma exacerbations?)
Is the vaccine safe and acceptable? (That is, does it have adverse effects in children with asthma and, if so, are they localized or systemic and of short or long duration?)
Does the vaccine make the best use of resources available compared with doing nothing or other preventive or therapeutic options?

accurate view on the overall impact of influenza, one obviously should take several seasons into consideration.

Preferably, for influenza, laboratory proof for the presence of influenza virus should coincide with symptomatic disease [16]. Yet, in reports on the impact of influenza outbreaks these data are often lacking. Instead, isolated serologic incidence rates, rates of ILIs [9, 12, 17–20] and the occurrence of complications are used as a proxy [21–24]. In these studies, hard confirmation of 'influenza illness' on the individual level is not possible.

Besides, reports on the burden of disease for influenza (e.g. hospitalizations) are often not related to a properly described population at risk. Nevertheless, the clinical, societal and economic impact of non-pandemic influenza seems to be taken for granted and there is hardly any discussion on these basic assumptions.

Children with asthma are reported to be at a higher risk for complications than adults, although no mortality was reported [21–23, 25]. Because these studies were retrospective in design or the population at risk was not well defined, assumptions on complications of influenza infections in asthmatics are based on indirect evidence. Therefore, the information reported in these studies is mostly presented in general terms like 'excess health-care use' in influenza seasons, regarding for instance hospitalizations or prescriptions for asthma.

In children with asthma, influenza may cause URT infections that often precede exacerbations. Furthermore, it is the only respiratory disease for which vaccines are widely available.

However, because far more asthma exacerbations and complications of asthma in children are caused by other viruses, mostly rhinoviruses, the relative impact of influenza on disease in asthmatic children is limited [26, 27].

I conclude that, although the importance of influenza in asthmatic children is frequently stressed, one can question the reliability of the hitherto reported evidence for that belief. Apart from that, the believed importance of influenza obviously relies on the history of pandemics and fear of a new pandemic [28].

What is the burden of disease?

Incidence of influenza and related illness

Although incidences in specific seasons can peak up to 46%, we found [29], looking at studies which measured

the occurrence of influenza and its related illness over a prolonged time period, the average seasonal incidence of influenza A and B to be 4.6% in children 0–19 years and 9.5% in children < 5 years [19, 30]. In most of the studies, symptoms that triggered laboratory measurements as well as symptoms assessed in the course of episodes usually were characterized as mild. Convalescence was reported to be rapid [31] or within a school absence of 2 days [32], whereas the duration of the illness was reported to be between 3 days [33] and 10–13 days [19]. Mortality as an outcome of influenza illness in children was not found in these studies although case reports sometimes link cases of death in children to influenza infection [34]. Hospitalization rates for influenza widely differ in the long-term studies included and range from 29 per 100 000 children < 16 years of age [35] to 230 per 100 000 children < 5 years of age [30].

Incidence of respiratory symptoms because of influenza in children with asthma

We found only two studies that assessed the incidence of influenza-related respiratory illness in asthmatic children while confirming the presence of influenza by culture. This 'hard' incidence was found to be 11.5% for both influenza A and B in 48 unvaccinated children (aged 2–14 years) under surveillance of an asthma clinic in Japan [36]. Three children (6%) were hospitalized for pneumonia. In another, community-based, study 18% of schoolchildren (aged 9–11 years) had influenza-related asthma exacerbations but no serious complications occurred [26]. Asthma exacerbations as well as episodes of URT symptoms lasted about 7 days and did not differ between viruses detected. In the placebo arm of our trial in asthmatic children the incidence of laboratory-confirmed influenza-related asthma exacerbations was found to be 5%, again no serious complications occurred [37]. Influenza-related URT episodes lasted 8 days whereas influenza-related asthma exacerbations lasted 11 days.

In conclusion, the incidence of influenza-related asthma exacerbations in children and its complications have not been extensively investigated. Incidences for children with asthma as reported here were between 5% and 18%. Although one small study, with children under the surveillance of an asthma clinic, found a hospitalization rate of 6%, no complications were found in the above-mentioned community-based study on asthmatic children nor

in our study that recruited patients in general practice. Regarding the long-term overall incidence for influenza-related illness in children of 4.6% (0–19 years) and 9.5% (0–5 years) and the mild clinical picture of the disease in healthy and asthmatic children one can question the likely impact of immunisation in asthmatic children.

Does the vaccine work?

Is influenza vaccine effective in preventing clinical cases of influenza-related asthma exacerbations? A systematic review of randomized trials of the effects of influenza vaccine in healthy adults showed that inactivated parenteral vaccines indeed had an efficacy of 70% (95% confidence interval (CI) 56–80%) in reducing serologically confirmed cases of influenza. But when using symptom-based outcomes, i.e. clinical cases of influenza, the vaccine had only an effectiveness of 25% (95% CI 13–35%) [38]. These figures on efficacy were recently confirmed in another meta-analysis [39]. A systematic review of randomized trials in asthmatics, children as well as adults, asserted that uncertainty remains about the degree of protection vaccination affords against influenza-related asthma exacerbations [6]. In our randomized trial on the effectiveness of influenza vaccination in asthmatic children 6–18 years, in which we aimed to detect a 50% reduction in the number of asthma exacerbations, no effect on the number, duration and severity of influenza-related asthma exacerbations was found [38]. The results from our study (95% CI –34% to 161%), exclude a protective effectiveness of influenza vaccination of 35% or more. Nonetheless an effect on the duration of all asthma exacerbations, irrespective of cause, of 0.8 days [40] as well as discrete effects on health-related quality of life in influenza-related weeks of illness favouring the vaccine group were found [40]. However, in influenza positive weeks of illness no differences were found between the vaccine group and the placebo group for mean URT or LRT symptoms or spirometry values. Regarding all weeks of illness, irrespective of their cause, no differences were found for mean URT or LRT symptoms or for spirometric parameters. For respiratory symptoms throughout the seasons, influenza vaccination did not reduce URT and LRT symptoms in asthmatic children.

Recapitulating, the vaccine works but the degree of protection against clinical outcomes is meagre for healthy subjects and asthmatics.

Is the vaccine safe and acceptable?

Recent studies did not confirm that influenza vaccination exacerbates asthma defined as complications such as hospitalizations and emergency department visits [41, 42].

In our study we considered local and systemic symptoms, including URT and LRT symptoms, in the first week

after influenza vaccination, as adverse effects. Except for one LRT symptom (frequency of cough at daytime) favouring placebo in the first season, we did not find an indication that influenza vaccination provokes asthma exacerbations or other complications [43].

It is clear that influenza vaccination can be given safely to children with asthma.

Does the vaccine make the best use of resources available?

Role of influenza incidence and clinical effectiveness of parenteral influenza vaccine

When determining cost-effectiveness of influenza vaccination several seasons should be considered and included in a cost-effectiveness analysis. However, an overall incidence of influenza-related illness between 4.6% and 9.5% [19, 29, 30] as found before or 5% as found in the placebo arm of our study [37] is a difficult starting point. Using this incidence, regardless of clinical relevance and assuming protective effectiveness of vaccination to be 100%, 22 children (0–19 years), 11 children (0–5 years), and 20 children (6–18 years) with asthma have to be vaccinated in order to prevent influenza-related illness in one child. Because the effectiveness of influenza vaccination is lower than 100% and clinical relevance has to be taken into account, the numbers needed to treat will be higher than calculated here. For instance, in healthy subjects, a clinical effectiveness of the vaccine of just 25% was found [38]. When extrapolating, this quadruples the above-mentioned numbers needed to treat.

In asthmatics there is no evidence about the degree of protection vaccination provides against influenza-related asthma exacerbations [6]. When assuming a maximum protection rate of 34%, as can be derived from our study, vaccinating 59 children with asthma could prevent only one influenza-related asthma exacerbation.

Other preventive options

Intranasal vaccines. In the past years, intranasal influenza cold adapted live attenuated vaccines have been developed and tested. Besides the less invasive route of administration, the triggering of the mucosal Ig A defence system may prove to be a potential benefit. However, serologically as well as clinically, intranasal vaccines have been reported to be less effective than parenterally administered vaccines [38].

Although intranasal vaccines are generally well tolerated in children and adolescents with asthma no evidence in randomized trials was found for its clinical effectiveness in asthmatics [6].

Antiviral agents. Apart from influenza vaccination as preventive treatment for influenza there are antiviral agents that can be used for this purpose.

Amantadine and rimantadine are effective in the treatment and prophylaxis of influenza A, but these drugs are not widely used because of a lack of knowledge of their potential value and concerns about possible adverse effects [44].

The more recently developed neuraminidase inhibitors zanamivir and oseltamivir are safe and were clinically effective in healthy children with a clinical or laboratory diagnosis of influenza A and B. However, efficacy in 'at risk' children, such as asthma, remains to be proven and its role in the prevention of influenza-related illness in asthmatic children is currently not established [45].

Regarding cost effectiveness, the balance for antivirals in comparison with vaccination is rather unfavourable [46].

Inevitably one must conclude that for children with asthma cost-effectiveness for vaccination will be difficult to attain. Other preventive options, which could be used for children with asthma, lack the necessary evidence on clinical endpoints.

Conclusion and options for future research

In summary, I conclude that, given the available information on the effectiveness of airway medication; the low overall incidence of influenza; the absence of direct evidence for serious complications of influenza infection in asthmatic children; the absence of evidence for the clinical effectiveness of influenza vaccination in asthmatic children; the absence of adverse effects of influenza vaccination and the doubts about cost-effectiveness of this preventive intervention in asthmatic children, guidelines on influenza vaccination should be revised and, despite the safety of vaccination, should reconsider the advice to vaccinate children with mild-to-moderate asthma.

Future research should first of all focus on long-term observational research, spanning more seasons, to determine the real impact of influenza in children with and without asthma.

In this way, the update of recommendations can be guided by medicine-based evidence [47], which in turn will improve the effectiveness of recommendations [48].

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