

What Is the Role of Virus Vaccination in Patients with Asthma?

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It is estimated that viruses play a role in 30% to 80% of asthma exacerbations. Thus, virus vaccination in patients with asthma could play an important role in preventing asthma exacerbations and other complications. Influenza is the only agent for which a routine vaccine is currently available. This article discusses whether influenza vaccination in patients with asthma, based on the available evidence, is justified. Cost-effectiveness of (influenza) vaccination for patients with asthma is questionable. For the other major viruses involved, the present state of affairs is described. Although progress is being made, a vaccine may be available in the near future only for respiratory syncytial virus (RSV). Meanwhile, clinicians and patients should aim for an optimal treatment with the currently available asthma medication.

Introduction

Worldwide, asthma is one of the major chronic diseases and there is evidence its incidence and prevalence is still growing [1]. Today asthma is regarded as a chronic inflammatory disease of the airways instead of solely a reversible airway obstruction. The use of rescue and anti-inflammatory medication has altered the prospects of asthma patients and has improved their quality of life. Thus, most asthma patients can lead a normal life without restrictions. The degree of asthma control achieved by patients is an important predictor of the likelihood of complications of the disease [2•].

However, upper and lower respiratory infections can trigger exacerbations of acute asthma. Most infections have a viral origin. They play an important role in clinical complications of asthma such as dyspnea, pneumonia, and respiratory insufficiency, which result

in loss of quality of life, absenteeism, use of rescue medication, use of antibiotics, physician consultation, emergency department visits, hospitalization, and sometimes death.

The best way to prevent exacerbations caused by infection is vaccination. This review summarizes the current evidence on the role of viral vaccination in the protection of asthma patients. We searched Medline and Google Scholar for relevant articles and reports published between 1999 and July 2006 on the current status of vaccination in patients with asthma.

The Role of Viruses in Asthma Exacerbations

Viral infections have long been associated with asthma exacerbations. Studies in children report varying incidences, suggesting that between 30% and 80% of exacerbations are due to a virus [3–6]. For adults data on this issue are scarcer, but adults are believed to have as many asthma exacerbations linked with viral infections as children [7,8]. The spectrum of viruses found consists of rhinovirus, coronavirus, respiratory syncytial virus (RSV), influenza virus, and an assortment of other viruses. Of these, RSV and influenza affect primarily the lower respiratory tract, whereas rhinovirus and coronavirus replicate in the upper respiratory tract. The mechanism by which these viruses cause asthma exacerbations is not yet known precisely. Postulations vary from direct infection to indirect induction of inflammatory responses [9].

Clinical Impact

In case of complications in patients with asthma, laboratory proof for the presence of virus should preferably coincide with symptomatic disease. However, evidence for the rate of complications mostly comes from large observational studies. In these reports on the impact of viruses, laboratory proof is often lacking. Instead, extrapolated, partly population-based, incidence rates of influenza or influenza-like illness and the occurrence of complications are used as a proxy. In these studies, hard confirmation of the responsible agent on the individual level is not possible [10–13].

Other studies are often based on selected populations with existing symptoms or complications, reflecting only the worst of the spectrum of disease caused by acute respiratory infections [9,14–17] and thus disregarding their often self-limiting nature.

Prevention and Treatment

Although asthma control achieved by asthmatics is an important predictor of the likelihood of complications of the disease [2•], asthma exacerbations do not respond to inhaled steroids nor can they substantially be prevented in this way [18,19]. Only the use of oral corticosteroids seems to be unmistakably effective [20,21].

The availability of effective vaccines against the key viruses involved in asthma exacerbations thus could play an important role in its prevention. Below, we will discuss the vaccines that are available or may become available in the near future [22].

Human rhinoviruses

This species consists of about 100 serotypes and is responsible for the majority of “common colds.” In asthmatics human rhinoviruses are responsible for the majority of asthma exacerbations and complications of asthma [23].

Prevalent serotypes change from year to year. When prevalent, the relative predominance from any serotype is not higher than 40%. Due to these circumstances and the large number of serotypes, an effective vaccine is not expected in the near future [22,24•].

Coronavirus

Coronaviruses have recently been highlighted because of a disease outbreak caused by the so-called severe acute respiratory syndrome (SARS) coronavirus. In adults with asthma, coronaviruses are the second most important cause of virally induced exacerbations [7,8].

Animal vaccines are being tested. Despite this a vaccine for human use will probably not be available in the near future [22].

Respiratory syncytial virus

RSV is especially predominant in young childhood and causes wheezing in children. In elderly people with asthma, RSV also may play an important role [25]. A connection has been suggested between bronchiolitis caused by RSV infection in childhood and the development of asthma [26].

Against this background, a vaccine for RSV may not only prevent exacerbations but may also prevent the development of asthma later on. However, in the 1960s an experimental vaccine unfortunately had serious adverse effects by increasing the clinical symptoms of naturally acquired RSV infections. Several other vaccines are being tested [27], and despite the initial problems it is believed that a vaccine for routine immunization may be available within the next decade [22].

Human influenza

The influenza viruses are classified in three genera, labeled A, B, and C. Only types A and B cause considerable epidemics. Every year influenza viruses change their genome partially, which is called an antigenic drift. Because of different subtypes and antigenic drift, formerly built-up natural immunity or vaccine-initiated immunity will not provide protection throughout successive seasons.

There are three types of influenza A virus known to have infected humans and to have transmitted from human to human: H1N1, H2N2, and H3N2. However, water birds carry and are infected with about 15 different H-types. Infections can spread from these birds to poultry, swine, and other animals living more closely to humans. By mixing infections, new subtypes can develop (antigenic shift). If a new subtype has the ability to infect humans and disseminate, a pandemic could occur. This is an often expressed fear in the case of the H5N1 influenza virus.

Influenza is the only lower respiratory tract infection in humans for which a vaccine has existed for decades. Inactivated vaccines, delivered by subcutaneous or intramuscular injection, are widely used for the prevention of influenza. The guidelines of most Western countries advise to vaccinate patients with asthma [28].

Influenza is one of the common respiratory tract infections in humans [29] and according to the World Health Organization a yearly public health problem [30]. Every year, influenza centers worldwide report influenza activity and the occurrence of influenza-like illnesses (ILI) as well as data on subsequent health care use. But, many viruses can cause ILI and thus a direct relation between influenza virus and symptomatic disease is difficult to determine. In published articles isolated serologic incidence rates, rates of ILI, and the occurrence of complications are often used as proxy measures for influenza-related clinical illness. Confirmation of influenza at an individual level is not provided in these large observational studies [11,12,31,32]. However, when influenza infection is confirmed by laboratory tests as in trials or smaller observational studies, the clinical impact of influenza seems to be limited [4,6,33,34•,35].

Incidence of influenza varies from place to place and from season to season. National and international influenza centers and organizations worldwide report incidence figures. Usually, these figures are measured in an indirect way and relate to excess hospitalizations or mortality due to pneumonia and influenza or excess health care use. Seasonal incidence figures for ILI of 20% to 30% are not uncommon. However, symptomatic disease should preferably be corroborated by a positive laboratory test [36]. Only in children do such figures seem to be available for a considerable number of years [37]. Based on these data, the average incidence, depending on age category, is between 5% and 9.5%. The clinical picture is usually described as mild [37]. Regarding the fluctuating incidence of ILI reported,

Table 1. Availability of vaccines and challenges

Virus	Availability of vaccine in time	Challenges facing future development
Rhinovirus	Unknown	High number of serotypes, low prevalence of dominant serotype
Coronavirus	Unknown	Development of experimental human vaccines
Respiratory syncytial virus	Expected in 5–10 years	Serious side effects of first experimental vaccines used in children
Influenza virus	Available	Direct proof of effectiveness in preventing complications of current vaccines in patients with asthma unknown

it is likely that in adults, the average incidence does not exceed these figures. Comparable figures on the incidence in asthmatics are even scarcer. The proportion of asthma exacerbations due to influenza reported in asthmatic children were 18% and 5% [4,34•]. No severe complications (eg, hospitalizations) were found in these two studies.

The effect of influenza vaccination in preventing clinical symptoms is a much-debated item. A number of reviews indicate that (inactivated) vaccines can have an efficacy of 70% in reducing serologically confirmed cases of influenza. However, when using symptom-based outcomes the vaccines showed an efficacy of only about 25% [38–40]. Moreover, in case of a mismatch between the vaccine composition and the natural virus, efficacy will be much lower or absent.

Over the past years, live attenuated vaccines have been developed, tested, and used for intranasal administration. The less invasive route, of course, is a benefit in administering the vaccine. Besides, the extra local immune response that is activated is a potential benefit. Yet, even then there still remains a striking difference between efficacy and clinical effectiveness [39]. Currently, animal research is being done into the development of vaccines that induce broad-spectrum and long-lasting immune response, which, if successful, would alter the prospects of the current influenza vaccination programs.

In asthmatics, observational studies report varying and sometimes even contradictory outcomes [41–43]. But clinical efficacy has not been established yet at the highest level of evidence. Uncertainty still remains about the degree of protection vaccination affords against influenza-related symptoms such as asthma exacerbations [44••]. In a recent study in children with asthma, no positive effect of vaccination was found [34•]. However, a distinct effect on quality of life in influenza-related episodes in asthmatic children was reported [6].

As for side effects and complications, the evidence that influenza vaccination is safe and well tolerated is extensive [44••].

Cost-effectiveness of Vaccination

Several studies have addressed the cost-effectiveness of influenza vaccination. We also identified one cost-effectiveness study that addressed a hypothetical RSV

vaccine in elderly people [45]. All cost-effectiveness studies are based on a population-wide use of the vaccines, for example, in preschool children or elderly persons. In all of these studies, the cost-effectiveness of influenza vaccination is based on several premises. Often the incidence of influenza is approximated by that of ILI in epidemic seasons. These figures certainly exceed the average incidence of influenza when taking into account the seasons with low or no influenza activity. Other biases may be the target populations and the definition used for influenza [46]. In the elderly cost-effectiveness is globally accepted [47]. In either case, population-wide cost-effectiveness preventive options against influenza for healthy adults 14 to 60 years old do not seem to be easily achieved, and therefore some authors have suggested that the most cost-effective option is not to take any action [48]. For high-risk patients with chronic respiratory conditions, again, in the elderly cost-effectiveness was achieved; however, this was not the case for the 18 to 65 years age category [49,50]. In children with high-risk conditions the use of influenza vaccination was calculated to be cost-effective. However, this study assumed a much higher incidence and a far more favorable effectiveness of influenza vaccination than described above [50].

Conclusions

The role of virus vaccination in patients with asthma at this moment and in the near future seems to be limited (Table 1).

Currently, vaccines are available for routine use only for influenza. However, because of a lack of clinical effectiveness, the natural antigenic variations of the influenza virus, and the low average incidence of influenza, cost-effectiveness in children and adults with asthma will not be easily achieved if vaccination has to be delivered annually.

As for the other viruses that play an important role in the complications of patients with asthma, many hurdles remain to be overcome.

For RSV, the first experiences with vaccines were a major disappointment. In the case of coronaviruses, attention is understandably focused on a vaccine for the prevention of SARS. As for rhinoviruses, the major cause of asthma exacerbations, because of the amount of subspecies a vaccine will not be available in the near future.

Of course other therapies, such as antiviral medication or immunoglobulin, are used and are sometimes effective in reducing complications. But, the therapeutic use of these treatments is limited because they are often expensive and should be used only when there is proof of the agent that is causing the patient's symptoms. For prophylactic use their cost is a major problem.

Yet, the role of the clinician in patients with asthma experiencing the threat of an exacerbation with its complications is clear. An oral corticosteroid can be provided and kept on hand by the patient. This permits initiation of more prompt and effective treatment than is likely to occur when a patient must first go to a physician's office or emergency department, because it can be taken as soon as the response to bronchodilator therapy is incomplete [21]. Moreover, patients with asthma should be treated according to national and international standards. Access to and compliance with inhaled corticosteroid treatment is an important predictor of the likelihood of asthma exacerbations occurring, including those that occur during respiratory viral infections [2•].

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