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Review

Paediatric asthma and pneumococcal vaccination

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ABSTRACT

Asthma is a clinical condition that has only recently been considered a risk factor for the development of pneumococcal infections. In the most recent guidelines concerning the use of pneumococcal vaccines, the Advisory Committee on Immunisation Practices recommends pneumococcal vaccination only when children with asthma aged <71 months are treated with high-dose corticosteroids, whereas the same Committee clearly indicates that asthma (without any definition of severity or treatment) is a reason for systematic pneumococcal vaccination in adults. It is also unclear which pneumococcal vaccine should be used and how to face the problem of booster doses. The main aim of this paper is to describe what is known about the real risk of pneumococcal infections in children with asthma, and discuss the unsolved problems regarding the paediatric use of pneumococcal vaccines. There are few published data regarding pneumococcal colonisation and the burden of pneumococcal disease in asthmatic children and adolescents, and none at all concerning the relationship between paediatric asthma and immune responses to pneumococcal vaccines. Further studies are therefore essential to assure that children and adolescents with asthma receive the best protection against pneumococcal diseases.

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1. Introduction

Over the last 15 years, new and effective vaccines capable of evoking protective immune responses against *Streptococcus pneumoniae* in children have been developed and marketed. They have been widely administered to young children throughout the world, and this had led to a substantial reduction in the incidence of all pneumococcal diseases in vaccinated children and non-vaccinated households [1]. Despite this, *S. pneumoniae* is still one of the most frequent causes of invasive disease such as sepsis and meningitis, and most frequent cause of bacterial pneumonia, acute otitis media and rhinosinusitis [2]. These diseases are all diagnosed in both otherwise healthy children and patients with chronic underlying disease (CUD), but their incidence, severity and rate of recurrence are significantly greater in children with CUD.

It has been reported that 11–44% of children with invasive pneumococcal disease (IPD) have CUD [3–9], that IPD in children with CUD leads to death four times more frequently than in children without CUD [10], and that recurrent IPD is almost always diagnosed in children with CUD. Mason et al. studied 108 cases of recurrent IPD in 90 children, and found that 14 out of the 15 patients who had experienced more than two episodes of IPD had CUD [11]. This explains why the official recommendations for the use of pneumococcal vaccines worldwide include a list of patients at risk for whom vaccine prevention is strongly recommended [12–14]. However, these lists vary from country to country, and between children and adults, because not all of the clinical conditions accompanied by an increased risk of pneumococcal infections are clearly defined. The conditions for which specific risk rates have been precisely

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Table 1
Underlying medical conditions that are indications for pneumococcal vaccination among children by risk group.

Risk group	Condition
Immunocompetent children	Chronic heart disease Chronic lung disease Diabetes mellitus Cochlear implant Cerebrospinal fluid leaks
Children with immunocompromising conditions	Congenital immunodeficiency HIV infection Chronic renal failure and nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction

Adapted from Centers for Disease Control and Prevention [12].

calculated are anatomical or functional asplenia, HIV infection and cochlear implants, but there are many others that are presumed to be high-risk conditions: congenital immune deficiency (i.e. B or T lymphocyte deficiencies, complement deficiencies, or phagocytic disorders excluding chronic granulomatous disease); diseases associated with immunosuppressive or radiation therapy (including malignancies) and solid organ transplantations; chronic cardiac diseases (particularly cyanotic congenital heart disease and heart failure); chronic pulmonary disease; chronic renal insufficiency including nephrotic syndrome; cerebrospinal leaks due to congenital malformations, skull fractures or neurological procedures, and diabetes mellitus [6,9,15–19]. Table 1 summarises CUDs that are indications for pneumococcal vaccination among children by risk group according to the Advisory Committee on Immunisation Practices (ACIP) in United States. There are insufficient data to calculate specific risk rates for the conditions that are only presumed to be at high risk, and only the demonstrated presence of defects favouring infections, such as defective phagocyte function in diabetes [20] and hypogammaglobulinemia in nephrotic syndrome [21], justifies including them among those whose prevention is strongly recommended.

Asthma has only recently been considered a risk factor for the development of pneumococcal infections because it is only recently that studies specifically designed to evaluate their incidence in asthmatic patients have been carried out [22–24]. However, there are still few data (particularly paediatric data), which may explain why the official recommendations consider children differently from adults. In its most recent guidelines for the use of pneumococcal vaccines, the ACIP recommends pneumococcal vaccination only when children with asthma aged <71 months are treated with high-dose corticosteroids [12], whereas the same Committee clearly indicates that asthma (without any definition of severity or treatment) is a reason for systematic pneumococcal vaccination in adults [25]. It is also unclear which pneumococcal vaccine should be used and how to face the problem of booster doses.

The main aim of this paper is to describe what is known about the real risk of pneumococcal infections in children with asthma, and discuss the unsolved problems regarding the paediatric use of pneumococcal vaccines.

2. Pneumococcal diseases in patients with asthma

For many years, asthma was not considered a possible risk factor for the development of pneumococcal infections in adults or children, which is why the administration of pneumococcal vaccines was not included in the USA guidelines for the management of asthma published in 2002 [26]. It also explains why the ACIP recommendations for the prevention of pneumococcal diseases in adults and children, which were respectively published in 1997 [27] and 2000 [28], claimed that asthma was not associated with an increased risk of pneumococcal disease unless it occurs as a result of chronic bronchitis, emphysema or the long-term use of corticosteroids, and asthmatic subjects were explicitly excluded from those considered for vaccination.

The first study specifically planned to evaluate the possible relationship between asthma and the incidence of pneumococcal infections was the fundamental study by Talbot et al. published in 2005 [22]. This demonstrated for the first time that both children and adults with asthma were at higher risk of IPD, and that this risk was greater when the respiratory disease was severe and corticosteroid therapy was used to control it. Patients aged 5–17 years were at highest risk, which was four times higher than that of controls, and about twice as high as that of younger children and subjects aged 18–49 years.

Unfortunately, further studies did not enrol children or enrolled only very few paediatric patients with asthma, and so conclusions could only be drawn for adult patients. The results of two of these were quite similar to those published by Talbot et al. [22], but a population-based, retrospective, case-control study by Juhn et al., which involved 174 cases of pneumococcal infection and 348 age- and gender-matched controls, showed that asthma was not only associated with an increased risk of IPD, but also with radiologically confirmed pneumonia and sputum positive for *S. pneumonia* [23]. After adjusting for the other risk factors for pneumococcal infection, it was found that the adults with asthma had a more than six times higher risk of developing IPD and pneumococcal pneumonia than those without (odds ratio [OR], 6.7; 95% confidence interval [CI], 1.6–27.3; $p = 0.01$). The population attributable risk percentage (PAR%) was 17%, whereas the PAR% for all of the combined ACIP vaccine-eligible conditions was 24%, thus clearly highlighting the importance of asthma in increasing the burden of pneumococcal disease at population level. Klemets et al. carried out a retrospective, case control study of a Finnish population aged 18–49 years relating to the period 1995–2002, and the results were substantially similar [24]. They enrolled 1282 patients with IPD and 12,785 controls matched for age, gender and health district, and found that asthma was an independent risk factor for IPD. Overall, 7.1% of the subjects with IPD and 2.5% of the controls had asthma: respectively, 6.0% and 2.4% low-risk asthma, and 1.1% and 0.1% high-risk asthma. After adjusting for other independent risk factors in a conditional logistic regression model, IPD was associated with both low-risk (OR 2.8; 95% CI 2.1–3.6) and high-risk asthma (OR 12.3; 95% CI 5.4–28.0).

Although there are very few epidemiological data regarding children, the importance of repeated episodes of bronchial obstruction and the development of pneumococcal infections in paediatric patients has been highlighted by two recent studies that generally analysed pneumococcal infections in children with CUD. Hjuler et al. compared 1655 infected children (including 60 asthmatic children) with 282 controls [9]. In comparison with the controls, the adjusted risk rate ratio of IPD in the asthmatic children was 1.1 (95% CI, 0.7–1.6), thus suggesting an albeit slight effect of the CUD. However, the study of 578 children with IPD by Hsu et al. found that that the patients with asthma not receiving corticosteroid therapy developed pneumonia more often than those with no known risk (65% vs 31%; $p < 0.05$) [7].

Although limited in the number of examined paediatric cases, these studies seem to confirm that children with asthma are also at increased risk of developing pneumococcal infections. Furthermore, and in apparent contrast with the current official recommendations [7], it is interesting to note that the problem also involves patients not requiring corticosteroid administration.