

Received Date : 08-May-2016
Accepted Date : 10-May-2016
Article type : Review

Vaccines: Could asthma in young children be a preventable disease?

Varpu Elenius, MD; Tuomas Jartti, MD

Department of Pediatrics, Turku University Hospital, Turku, Finland

Running title: asthma prevention by vaccines

Corresponding author:

Tuomas Jartti

Department of Pediatrics

Turku University Hospital

Kiinamyyllynkatu 2-4

20520 Turku, FINLAND

email: tuomas.jartti@utu.fi

Elenius V., Jartti T.

Vaccines: Could asthma in young children be a preventable disease?

Abstract

The long battle with asthma is far from over in developed countries. Its incidence, prevalence and severity have been increasing for decades. By reducing the risk for asthma, significant health care costs can be saved. The desire to create a vaccine that might prevent asthma in young children is attractive and widely considered one of the main goals in translational asthma research. Several vaccination strategies have been tested. These include allergen-specific immunotherapy, vaccination against infectious pathogens, and modification of cell and cytokine responses. The lack of success in the prevention of asthma in young children lies on the complexity of the disease, which involves many genetic, epigenetic and environmental interactions. This review provides a summary of current literature and aims to address key questions how to develop vaccines to prevent asthma in young children.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12598

This article is protected by copyright. All rights reserved.

Key words: allergy, immunotherapy, asthma, bacteria, cytokine, immunomodulation, prevention, rhinovirus, vaccine, virus

Corresponding author:

Tuomas Jartti

Department of Pediatrics

Turku University Hospital

Kiinamyllynkatu 2-4

20520 Turku, FINLAND

Email: tuomas.jartti@utu.fi

Abbreviations

AIT	allergen immunotherapy
DC	dendritic cell
IgE	immunoglobulin E
PPSV-23	pneumococcal polysaccharide 23-valent vaccine
RSV	respiratory syncytial virus
Th	T helper
TLR	toll-like receptor
Treg	T regulatory cell

Introduction

Asthma and allergy have become an epidemic on the 21st century in developed world. Thus, much effort is placed to prevent allergy and asthma in children (1). However, not all symptoms seen in a child predisposed to asthma have an allergic cause. Only a relatively small proportion of infants who wheeze will develop asthma later in life. Recognition and accurate diagnosis of asthma in early life can be difficult. There is a great need to identify target populations, involved mechanisms and interactions for the best interventions.

Prevention strategies targeting asthma can be primary (e.g. infants at high risk for asthma), or secondary, aiming children who already have developed allergic sensitization or the first manifestations of allergic diseases (e.g. eczema or wheezing).

A vaccine is a biological preparation that provides active acquired immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often prophylactic to prevent an infection. However, vaccine can also

be therapeutic e.g. vaccines against cancer (human papilloma vaccines) or allergy (subcutaneous or intralymphatic immunotherapy). A concept of vaccine that might prevent asthma in young children is irresistibly attractive. It is possible to imagine a single injection that may make our current therapies for asthma seem as historical as clean air sanatorium treatments for tuberculosis. Reality is unfortunately a bit harder.

Allergy vaccines

Allergic rhinitis is a major risk factor for the development of asthma (2, 3). Allergen-specific immunotherapy (AIT) might effectively induce long-term remission of allergic rhinitis and might also prevent the onset of new sensitizations and development of asthma (4-6). Two open-label trials have indicated that AIT prevents asthma in children aged 5-14 years with allergic rhinitis (7, 8). AIT involves the repeated administration of allergen in order to induce clinical and immunological tolerance to the offending allergen. AIT is usually differentiated into subcutaneous and sublingual immunotherapy. The rationale of reducing vaccine allergenicity to increase safety while improving immunogenicity has led to investigation of T-cell epitope-based peptides and recombinant allergen derivatives (9, 10). Additionally, different routes of administration (e.g. intralymphatic, epicutaneous and intradermal) and adjuvants and adjunct therapies are being explored (11). By choosing a tissue for administration that contains high density of allergen-presenting cells but a low density of mast cells could enhance immunological effects of allergen and reduce side effects (12). Alternatively, standard subcutaneous immunotherapy can be combined with biological treatment to make it safer and more effective. Randomized controlled trials have shown that pretreatment with omalizumab increases the safety of immunotherapy (13). The asthma preventive effect is typically the strongest in products containing native allergens and it should be initiated early in the allergic disease. It might be that our attempts to prevent asthma by immunotherapy is actually too late, and asthma prevention should start earlier, even before the first sensitization against perennial and seasonal allergens exist (14-16).

Vaccines targeting common infectious pathogens to reduce asthma exacerbations

Vaccines against viruses

Early wheezing episodes are almost exclusively associated with virus infections (17). Both respiratory syncytial virus (RSV) and rhinovirus-induced episodes have been associated with increased risk of subsequent asthma (18-20). Of the asthma exacerbations in children, at least 80% have been associated with virus infections, mainly with rhinovirus (21). Moreover,

it has been shown that asthmatic persons appear to have a defect in producing interferons, which help to promote effective antiviral defense (22, 23). Thus, vaccinating young children against viral triggers of wheezing and asthma is an attractive strategy to prevent asthma (24).

Candidate vaccines, currently in clinical trials, against RSV can be divided in four types: live attenuated viruses (cold passaged, Δ M2-2), gene based vector (adenoviral, MVA, chimeric bovine/human PIV3 vector expressing RSV-F), RSV-F-nanoparticle, and RSV-F subunit vaccines. To date, results of these vaccines have not been published. Interestingly, monoclonal antibody treatment, palivizumab, has decreased not only RSV, but also other virus induced recurrent wheezing episodes during the first year of life (25).

Over 160 circulating rhinovirus genotypes have constituted a challenge for vaccine development. However, progress has been made and preclinical studies of potential rhinovirus vaccines have identified a highly conserved rhinovirus capsid protein (VP0 and VP1) that induces cross-reactive cellular and humoral immune responses (26, 27). Thus, capsid domains may allow the development of a broadly cross-reactive subunit rhinovirus vaccine (28). Although, none of these agents are currently on market, many have been or are in clinical trials. Effective rhinovirus vaccination is expected to have huge impact on prevention of asthma in children.

Influenza is the only respiratory virus for which a routine vaccine is currently available. Influenza infections can precipitate acute asthma exacerbations (29-32) and may be more severe among asthma patients (31). Therefore, annual vaccination against seasonal influenza is recommended for children and adults with asthma (33). Recent strategies in vaccine development aims to develop a universal influenza vaccine. Stimulating immune responses towards the conserved stalk rather than the head domains of influenza hemagglutinin, at least in theory, would allow cross-immunization against several influenza virus subtypes (34).

Vaccines against bacteria

Streptococcus pneumoniae colonization in children has been linked to increased risk of wheezing, asthma and asthma exacerbations (35, 36). Also, subjects with asthma have an increase risk of invasive pneumococcal infections (37, 38). Thus, pneumococcal vaccination is recommended for asthma patients over 6 years of age if they have not received routine

childhood pneumococcal immunization (39). The pneumococcal polysaccharide 23-valent vaccine (PPSV-23) offers protection against the most common invasive serotypes from 6 years of age, while pneumococcal conjugated vaccines are effective against early childhood invasive pneumococcal disease and antibiotic resistant strains, and can prevent nasopharyngeal carriage. Studies addressing pneumococcal colonization, the burden of pneumococcal disease and immune response to pneumococcal vaccination among asthmatics are currently missing (39). One study involving PPSV-23 vaccination of asthmatic patients reported fewer asthma exacerbations following vaccination (40).

Although patients with chronic respiratory diseases are commonly described as an at-risk population for pneumococcal infections, studies on pneumococcal vaccination efficacy in such patients are very limited and vaccination effectiveness remains controversial (41).

Other childhood vaccines

Significant evidence suggests anti-asthmatic effects of routine childhood vaccinations. Inverse associations have been found between childhood asthma prevalence and high cumulative vaccine doses (42), whole cell pertussis (43) and measles, mumps, and rubella vaccination (44, 45). Based on animal models, an anti-asthmatic effect of Bacillus Calmette–Guérin immunization has been of particular interest. However, it has shown no or only very weak protective effects on asthma prevalence in children in several large population studies and meta-analyses (46).

Vaccines designed for immunomodulation

Damaging cells or cytokines involved in asthma

A large number of cytokines and chemokine, as well as immunoglobulin E (IgE) are reasonable targets of neutralization in order to prevent asthma. Such vaccines would neutralize cytokines and damaging cells involved in asthma. Omalizumab, the anti-IgE therapy, has already proved to be beneficial in treatment of severe asthma (47). The main risk in this strategy is that these cascades are difficult to control, because the targets are endogenous. There is also a risk of overcoming tolerance and triggering a harmful autoimmune response (48).

Modification of antigen-presenting cells or regulatory T cells

In *in vitro* and mouse model studies it has been possible to induce so-called tolerogenic dendritic cells (DC) that are able to present allergenic peptides but in so doing induce a deactivated state (49). In the future, we might be able to genetically reprogramme autologous stem cells and derive tolerogenic or therapeutic DC.

Vaccines that specifically induce immunomodulatory beneficial Treg cells are another attractive idea. The idea is to fine tune the immune response away from asthma to another form of benign protective immunity. In theory, triggering T helper (Th) 1 cell –type immune response through activation of toll-like receptors (TLRs) could also do this (50). Several TLR agonists, including CRX-675 (a TLR4 agonist), AZD8848 (a TLR7 agonist), VTX-1463 (a TLR8 agonist) and 1018 ISS and QbG10 (TLR9 agonists), are currently in clinical development for allergic rhinitis and asthma (50). Both Th1 and T regulatory (Treg) cells can suppress Th2 cells and their mediators involved in asthma. However, to date, preclinical data of these approaches have failed to achieve the primary end-point.

Vaccines with microbes, pathogens and their products to promote tolerance

Growing up on a dairy farm protects children from allergy, hay fever, and asthma (51, 52). The hygiene hypothesis suggests that early life exposure to microbes, pathogens and their products promote innate immune system and induce protection against asthma and atopic inflammation (53). TLRs recognize structurally conserved molecular motifs of microbial pathogens and elicit appropriate defense mechanisms. Pathogens interactions with Toll-like receptors (TLRs) on innate immune cells, including DCs, alveolar macrophages, B cells, and others are known to lead enhance Th1 and suppressed Th2 cells and induced Treg cell responses. For example, many *Helicobacter pylori* factors, such as the neutrophil-activating factor of *Helicobacter pylori*, are able to drive Th1 cell polarization and to display a powerful inhibition of allergic Th2 cell responses (54). Intestinal helminths can regulate immune responses and hookworm infection has been constantly linked with a reduced prevalence of asthma (55). Recently, it was shown that farming environment protects from allergy and asthma by modifying the communication between barrier epithelial cells and DCs through A20 induction, implicating A20 as a potential therapeutic target (56). However, there seems to be a limited time for window of opportunity after birth for this reprogramming of immune system. For example, in mice neonatal exposure but not adult exposure to bacterial vaccines

induces antibodies that dampen the allergic airway response to fungal and insect allergies (53).

Future aspects

After understanding and defining better different asthma endotypes, it seems certain that prophylactic and therapeutic vaccines will eventually be added to asthma therapeutics, at least for some subpopulations of asthma. The use of vaccine strategies in early life to prevent asthma is attractive. Although, a vaccine to prevent asthma in children is not currently on market, many are in preclinical or clinical trials. It is likely that in the next decades we will see a novel biotherapeutic strategy to prevent asthma and atopic disorders.

References

1. Nieto A, Wahn U, Bufe A, *et al.* Allergy and asthma prevention 2014. *Pediatr Allergy Immunol.* 2014; **25**: 516-33.
2. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med.* 2015; **372**: 456-63.
3. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet.* 2011; **378**: 2112-22.
4. Passalacqua G, Durham SR, Network GAaAE. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol.* 2007; **119**: 881-91.
5. Bousquet J, Schünemann HJ, Samolinski B, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol.* 2012; **130**: 1049-62.
6. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: Results from a large retrospective cohort study. *J Allergy Clin Immunol.* 2015; **136**: 1511-6.
7. Möller C, Dreborg S, Ferdousi HA, *et al.* Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol.* 2002; **109**: 251-6.
8. Novembre E, Galli E, Landi F, *et al.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* 2004; **114**: 851-7.
9. Sandrini A, Rolland JM, O'Hehir RE. Current developments for improving efficacy of allergy vaccines. *Expert Rev Vaccines.* 2015; **14**: 1073-87.
10. Jutel M, Akdis CA. Novel immunotherapy vaccine development. *Curr Opin Allergy Clin Immunol.* 2014; **14**: 557-63.
11. Senti G, Prinz Vavricka BM, Erdmann I, *et al.* Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc Natl Acad Sci U S A.* 2008; **105**: 17908-12.
12. Senti G, Kündig TM. Novel Delivery Routes for Allergy Immunotherapy: Intralymphatic, Epicutaneous, and Intradermal. *Immunol Allergy Clin North Am.* 2016; **36**: 25-37.

13. Massanari M, Nelson H, Casale T, *et al.* Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol.* 2010; **125**: 383-9.
14. Jacobsen L, Wahn U, Bilo MB. Allergen-specific immunotherapy provides immediate, long-term and preventive clinical effects in children and adults: the effects of immunotherapy can be categorised by level of benefit -the centenary of allergen specific subcutaneous immunotherapy. *Clin Transl Allergy.* 2012; **2**: 8.
15. Calderon MA, Demoly P, Gerth van Wijk R, *et al.* EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy. *Clin Transl Allergy.* 2012; **2**: 20.
16. Jutel M, Agache I, Bonini S, *et al.* International consensus on allergy immunotherapy. *J Allergy Clin Immunol.* 2015; **136**: 556-68.
17. Turunen R, Koistinen A, Vuorinen T, *et al.* The first wheezing episode: respiratory virus etiology, atopic characteristics, and illness severity. *Pediatr Allergy Immunol.* 2014; **25**: 796-803.
18. Meissner HC. Viral Bronchiolitis in Children. *N Engl J Med.* 2016; **374**: 62-72.
19. Bacharier LB, Cohen R, Schweiger T, *et al.* Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol.* 2012; **130**: 91-100.e3.
20. Sigurs N, Aljassim F, Kjellman B, *et al.* Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax.* 2010; **65**: 1045-52.
21. Johnston SL, Pattemore PK, Sanderson G, *et al.* Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ.* 1995; **310**: 1225-9.
22. Subrata LS, Bizzintino J, Mamessier E, *et al.* Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children. *J Immunol.* 2009; **183**: 2793-800.
23. Semic-Jusufagic A, Belgrave D, Pickles A, *et al.* Assessing the association of early life antibiotic prescription with asthma exacerbations, impaired antiviral immunity, and genetic variants in 17q21: a population-based birth cohort study. *Lancet Respir Med.* 2014; **2**: 621-30.
24. Bardin PG. Vaccination for asthma exacerbations. *Intern Med J.* 2004; **34**: 358-60.
25. Blanken MO, Rovers MM, Molenaar JM, *et al.* Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med.* 2013; **368**: 1791-9.
26. Glanville N, McLean GR, Guy B, *et al.* Cross-serotype immunity induced by immunization with a conserved rhinovirus capsid protein. *PLoS Pathog.* 2013; **9**: e1003669.
27. McLean GR, Walton RP, Shetty S, *et al.* Rhinovirus infections and immunisation induce cross-serotype reactive antibodies to VP1. *Antiviral Res.* 2012; **95**: 193-201.
28. Glanville N, Johnston SL. Challenges in developing a cross-serotype rhinovirus vaccine. *Curr Opin Virol.* 2015; **11**: 83-8.
29. Khetsuriani N, Kazerouni NN, Erdman DD, *et al.* Prevalence of viral respiratory tract infections in children with asthma. *J Allergy Clin Immunol.* 2007; **119**: 314-21.
30. Jain S, Kamimoto L, Bramley AM, *et al.* Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med.* 2009; **361**: 1935-44.
31. Miller EK, Griffin MR, Edwards KM, *et al.* Influenza burden for children with asthma. *Pediatrics.* 2008; **121**: 1-8.
32. Tan WC, Xiang X, Qiu D, Ng TP, Lam SF, Hegele RG. Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. *Am J Med.* 2003; **115**: 272-7.
33. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec.* 2012; **87**: 461-76.

34. Fiers W, De Filette M, El Bakkouri K, *et al.* M2e-based universal influenza A vaccine. *Vaccine*. 2009; **27**: 6280-3.
35. Kraft M. The role of bacterial infections in asthma. *Clin Chest Med*. 2000; **21**: 301-13.
36. Bisgaard H, Hermansen MN, Buchvald F, *et al.* Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med*. 2007; **357**: 1487-95.
37. Juhn YJ, Kita H, Yawn BP, *et al.* Increased risk of serious pneumococcal disease in patients with asthma. *J Allergy Clin Immunol*. 2008; **122**: 719-23.
38. Boikos C, Quach C. Risk of invasive pneumococcal disease in children and adults with asthma: a systematic review. *Vaccine*. 2013; **31**: 4820-6.
39. Esposito S, Musio A, Principi N. Paediatric asthma and pneumococcal vaccination. *Vaccine*. 2013; **31**: 5015-9.
40. Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma. *Cochrane Database Syst Rev*. 2002: CD002165.
41. Vila-Corcoles A, Ochoa-Gondar O. Pneumococcal vaccination among adults with chronic respiratory diseases: a historical overview. *Expert Rev Vaccines*. 2012; **11**: 221-36.
42. Grüber C, Illi S, Lau S, *et al.* Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics*. 2003; **111**: e282-8.
43. Möhrenschrager M, Haberl VM, Krämer U, Behrendt H, Ring J. Early BCG and pertussis vaccination and atopic diseases in 5- to 7-year-old preschool children from Augsburg, Germany: results from the MIRIAM study. *Pediatr Allergy Immunol*. 2007; **18**: 5-9.
44. Timmermann CA, Osuna CE, Steuerwald U, Weihe P, Poulsen LK, Grandjean P. Asthma and allergy in children with and without prior measles, mumps, and rubella vaccination. *Pediatr Allergy Immunol*. 2015; **26**: 742-9.
45. Hviid A, Melbye M. Measles-mumps-rubella vaccination and asthma-like disease in early childhood. *Am J Epidemiol*. 2008; **168**: 1277-83.
46. Linehan MF, Nurmatov U, Frank TL, Niven RM, Baxter DN, Sheikh A. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. *J Allergy Clin Immunol*. 2014; **133**: 688-95.e14.
47. Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med*. 2006; **354**: 2689-95.
48. Kucüksezer UC, Palomares O, Rückert B, *et al.* Triggering of specific Toll-like receptors and proinflammatory cytokines breaks allergen-specific T-cell tolerance in human tonsils and peripheral blood. *J Allergy Clin Immunol*. 2013; **131**: 875-85.
49. Li X, Yang A, Huang H, *et al.* Induction of type 2 T helper cell allergen tolerance by IL-10-differentiated regulatory dendritic cells. *Am J Respir Cell Mol Biol*. 2010; **42**: 190-9.
50. Aryan Z, Rezaei N. Toll-like receptors as targets for allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2015; **15**: 568-74.
51. Holt PG, Sly PD. Environmental Microbial Exposure and Protection against Asthma. *N Engl J Med*. 2015; **373**: 2576-8.
52. Ege MJ, Mayer M, Normand AC, *et al.* Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*. 2011; **364**: 701-9.
53. Kearney JF, Patel P, Stefanov EK, King RG. Natural antibody repertoires: development and functional role in inhibiting allergic airway disease. *Annu Rev Immunol*. 2015; **33**: 475-504.
54. Amedei A, Codolo G, Del Prete G, de Bernard M, D'Elis MM. The effect of *Helicobacter pylori* on asthma and allergy. *J Asthma Allergy*. 2010; **3**: 139-47.
55. Leonardi-Bee J, Pritchard D, Britton J. Asthma and current intestinal parasite infection: systematic review and meta-analysis. *Am J Respir Crit Care Med*. 2006; **174**: 514-23.
56. Schuijs MJ, Willart MA, Vergote K, *et al.* Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. *Science*. 2015; **349**: 1106-10.

Table 1

Vaccination strategies against asthma

- Allergen specific immunotherapy
 - Perennial
 - Seasonal
- Vaccines targeting common infectious pathogens to reduce asthma exacerbations
 - Viruses
 - Bacteria
- Vaccines designed for immunomodulation
 - Cells and cytokines involved in asthma
 - Antigen presenting cells
 - Regulatory T cells
 - Microbes, pathogens and their products to promote tolerance