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New Insights into the Natural History of Asthma: Primary Prevention on the Horizon

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Abstract

Recent studies of the natural history of asthma have shifted attention towards viral respiratory illness in early life as a major risk factor associated with the development of the most persistent forms of the disease. Although early aeroallergen sensitization is strongly associated with chronic asthma, several trials in which single aeroallergen exposure in pregnancy and early childhood was successfully accomplished and compared with sham avoidance have failed to show any decrease in asthma incidence. New evidence suggests that complex interactions occur between viral infection and aeroallergen sensitization in genetically susceptible subjects, which trigger the immune responses and airway changes that are characteristic of persistent asthma. The finding that exposure to bacterial products among children raised on farms is associated with diminished asthma prevalence during the school years has now been replicated, and experimental studies have suggested that these effects are mediated by the activation of T-regulatory cells in the airway. It is thus plausible to hypothesize that primary prevention of asthma could be attained through surrogate therapeutic interventions that activate similar mechanisms in young children at high risk for asthma.

The last few years have seen a steady increase in information about the natural history of asthma and asthma-like symptoms, starting with the potential effects of exposures and events occurring during the mother's pregnancy. In addition, the short- and long-term results of important clinical trials attempting to prevent the development of the disease with different interventions have also become available. The purpose of this review, which continues a series on the current status of asthma[1], is not to provide an exhaustive account of this plethora of information, but to identify what appear to be the most important indications that emerge from these studies, judged in the framework of the development of potential strategies for the primary prevention of the disease.

Heterogeneity of asthma-like symptoms

Asthma is now widely acknowledged as a heterogeneous condition, with different clinical expressions of the disease occurring within the population at any point in time and at different ages. Recently, particular attention has been paid to the preschool years, because there is now convincing evidence that, in a majority of cases of chronic, persistent asthma, symptoms develop in the first years of life[2, 3]. Hypothesis-based studies in the 1990's first suggested that preschool children presenting with wheezing illnesses could be separated into 2 larger groups, depending on if their wheezing episodes are present or have remitted by the

beginning of the school years[4, 5]. Among the former, a further subdivision was proposed between those whose episodes of airway obstruction begin very early in life (called persistent wheezers) and those in whom episodes initiate after that time (called late-onset wheezers)[5]. More recently, and using large birth cohorts and unbiased statistical methods, several groups have extended these findings[6-8]. The existence of a group of transient wheezers was confirmed, but this subtype was further divided into those whose symptoms persist into the fifth year of life ("prolonged early wheeze") and those who remit by age 3. Late onset wheeze was also subdivided into that starting before or after age 2-3 years[6]. Careful assessment of the outcome of these different phenotypes reveals that, during the school years, children with transient forms of preschool wheezing have lower levels of lung function and mildly increased bronchial hyperresponsiveness (BHR), but are not more likely to be atopic and are only at limited, if any, risk of developing asthma as compared with children who do not wheeze during the preschool years[5, 9]. In contrast, both persistent and late onset wheezers are at high risk of having asthma, BHR and of being atopic by the school years, while the greatest deficits in lung function growth are observed in persistent wheezers and in late onset wheezers whose symptoms start before age 3[7].

Taken together, these data suggest that, for any strategy of primary prevention to target the population at true risk of developing chronic asthma, it would be essential to identify early biomarkers for the chronic forms of the disease. Unfortunately, no such reliable biomarkers are available, and therefore, longitudinal data from birth cohorts has been used to develop indices of risk based mainly on clinical signs, family history, and laboratory findings[10-15]. These indices are useful, albeit imperfect[15], to assess prognosis, and have been used for studies of secondary prevention of asthma[16]. They have been criticized as inappropriate if the purpose is to identify children who could be responsive to different asthma therapies, and alternatives based on the main triggers of wheezing episodes have been proposed[17, 18]. If these alternatives will be better suited to identify children at high risk for asthma given the variable and often unpredictable clinical expression of the disease is unknown[19-21].

Viral illness in early life and subsequent asthma

Significant advances have been made in the understanding of the nature of the association between wheezing lower respiratory illnesses (LRI) in the preschool years and the subsequent development of asthma. The availability of advanced technologies for the assessment of the etiology of these illnesses has confirmed that children who have LRIs caused by respiratory syncytial virus (RSV) are at a 3-4-fold risk of subsequent wheezing during the early school years[22-25]. Most importantly, however, the strongest predictor of subsequent asthma is the occurrence of episodes of wheezing during which evidence of rhinovirus (RV) infection was found in the upper airway[26, 27], and this has also been observed for children hospitalized with bronchiolitis during the first year of life[28, 29]. Strikingly, in at least one study these associations were only observed among children who showed positive skin tests to a battery of allergens before the age of 2 years but not among those who were skin test negative or were sensitized after that age[26]. This finding has suggested the hypothesis that immunologic interaction between viral infections and Th2 immunity predisposes to more severe acute responses to the virus and to the development of asthma. Specifically, activation of type 1 interferon (IFN) anti-viral responses would also upregulate the expression of high affinity receptor for IgE (FcεRI) on local airway dendritic cells[30]. In sensitized subjects, the local presence of IgE and allergen would cross-link the receptors, initiating a cascade which would enhance aearoallergen specific Th2 memory cells. These mechanisms would be further boosted by the diminished Th1-type responses that have been observed in infants before the development of persistent wheezing and up to the school years[31]. It is also plausible to surmise that the diminished innate immune responses against infectious agents, which has been reported during asthma exacerbations in

older children[32], may be present in early stages of the disease, and may also explain the increased risk of colonization with pathogenic bacteria of the upper airway of young children who will go on to develop asthma-like symptoms[33].

The hypothesis that virus-allergen interactions play a role at the origins of asthma has been recently supported by experimental studies. Al-Garawi et al[34] infected neonatal mice with influenza virus and subsequently exposed them to house dust mite (HDM). Unlike adults, neonatal mice exhibited negligible immune responsiveness to HDM in the absence of influenza infection. However, this HDM hyporesponsiveness was overcome when exposure to allergen occurred concurrently with an acute influenza infection; young mice now displayed robust allergen-specific immunity, allergic inflammation, and lung remodeling. Remodeling persisted into early adulthood, even after prolonged discontinuation of allergen exposure and was associated with marked impairment of lung function. Taken together, these data suggest that asthma may be the result of an initial viral insult, which would enhance local and eventually systemic responses to allergens in subjects predisposed to Th2-type responses. The presence of a virus-allergen interactive mechanism at the beginnings of asthma may explain the dissociation between genetic determinants of total serum IgE and asthma[35]; why children with parental history of asthma are more prone to develop early sensitization to allergens independent of the atopic status of parents[36]; and why subjects with asthma have higher serum IgE levels than would be expected, given the levels of IgE in their parents[37].

Natural history of asthma symptoms, airway function, and airway structural changes in asthma

A major feature of chronic asthma is the presence of varying degrees of airflow limitation. As a group, asthma patients have lower levels of spirometric indices such as the ratio between the Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC)[38]. A diminished FEV1/FVC ratio is a strong predictor of asthma exacerbations[39] and persistence of childhood asthma into adult life[40, 41].

Longitudinal studies have suggested that airflow limitation in asthma may have congenital and acquired components. As compared with children without asthma, those who would go on to develop asthma by age 10 yrs were found to have decreased respiratory system compliance measured shortly after birth[42]. Similarly, children who wheezed persistently between ages 4 and 11 had lower maximal expiratory flows at functional residual capacity (VmaxFRC) shortly after birth when compared with those with no history of wheezing[43]. In the Tucson Children's Respiratory Study, we found that, although persistent wheezers up to age 6 had slightly lower size-adjusted VmaxFRC at birth compared to those who never wheezed, the differences between these two groups increased with age up to age 6 and remained relatively stable thereafter up to age 16[9]. These observations from general population samples were corroborated and extended by a thorough analysis of lung function data from the Childhood Asthma Management Program (CAMP) study[44]. Children with mild-moderate asthma aged 6-12 years were initially randomized to 4-6 years of treatment with budesonide, nedocromil, or placebo and subsequently followed for another 4 years. When compared with children from a general population sample, the mean FEV1/FEV ratio of CAMP participants was lower at the beginning of the study, and decreased further during the follow-up. Interestingly, two-thirds of the deficits in lung function growth observed at the end of follow-up in CAMP participants were already present at age 6, with the remaining third occurring between ages 6 and 18 years.

The early deficits in lung function growth that are characteristic of persistent childhood asthma occur in concomitance with a gradual change in the clinical expression of the disease

during the preschool years. In the Prevention of early Asthma in Kids (PEAK) trial[16], 2-3 year old children with a positive modified asthma predictive index, who thus had a history of >3 episodes of wheezing during the previous year, were treated with either fluticasone or placebo by inhalation for 2 years, and then followed for a third year while off study medicines. Episodes-free days (EFDs), i.e., those in which the child had no asthma-like symptoms and did not use asthma treatment apart from study medicines, were assessed using diaries compiled by parents. Children enrolled in the placebo arm had >95% EFDs at the beginning of the trial, but EFDs decreased steadily and progressively during the 3 years of follow-up, reaching approximately 85% of days at the end of the trial. These results clearly suggest that asthma is predominantly an intermittent disease with very few symptomatic days at its beginnings, and slowly becomes more chronic during the preschool years. Remarkably, proportion of EFDs was significantly lower in children treated with fluticasone that in those treated with placebo during the treatment period, but EFDs rapidly converged for the two groups during the observation period, as did frequency of exacerbations and lung functions. These results suggested that current anti-inflammatory therapy, while effective in preventing symptoms, does not change either the natural history of asthma[45] or the progression of the structural changes occurring in the asthmatic airway. At least 2 other major studies in preschool children reached similar conclusions[46, 47]

Data on structural airway changes suggest a similar progression of structural airway changes. Saglani et al[48] assessed whether epithelial reticular basement membrane (RBM) thickening and eosinophilic inflammation characteristic of asthma was present in symptomatic infants aged 3.4-26 months with reversible airflow obstruction. They found that these two parameters were not significantly different between 16 wheezing infants with decreased specific airway conductance (sGaw) and bronchodilator reversibility, 22 wheezing infants with decreased sGaw but without bronchodilator reversibility and 15 wheezing infants with normal sGaw. Moreover, RBM thickness was not significantly different in these 3 groups as compared with normal school age children, but was significantly lower than that of school age children with asthma. When these same authors subsequently assessed RBM thickness in wheezy children at a median age of 29 months[49], it was found to be significantly increased when compared with controls subjects of the same age. These data thus suggest that the characteristic pathologic features of asthma in adults and school-aged children develop in preschool children with confirmed wheeze between the ages of 1 and 3 years, the same age during which deficits in lung function growth and development of more persistent symptoms seems to occur in asthma.

What determines these concomitant functional, clinical and pathological changes in early asthma is unknown. Illi et al[50] reported that incidence of sensitization to perennial allergens (e.g., HDM, cat, dog) during the first 3 years of life was associated with loss of lung function at school age. Moreover, FEV1/FVC ratio was lowest in children who were both sensitized and exposed to perennial allergens but not to seasonal allergens. No concomitant assessment was made of incidence viral illness in early life, but in a different publication from the same cohort[51], early allergic sensitization was most strongly associated with asthma at the age of 11-13 years in children with a history of wheezing during the first 3 years of life. More recently, Guilbert et al[52] studied longitudinally children at high risk for asthma, half of whom had evidence of sensitization to aeroallergens by age 6. They found that those with a history of wheezing during rhinovirus infection during the first 3 years of life had significantly lower pre- and post-bronchodilator FEV1 and FEV1/FVC ratio than those without such a history. The authors found no association between early allergic sensitization and lung function, but did not test for a rhinovirussensitization interaction.

These findings suggest that airway remodeling and deficits in lung function growth may occur both as the result of allergen-virus interaction and as direct consequence of

inappropriate responses to viruses. The latter scenario is supported by the observation by Turato et al[53] that all pathological features were very similar in wheezy young children (median age 5 years) with and without atopy: both groups had similarly thickened RBM and increased number of blood vessels. Moreover, both groups also had significantly increased local eosinophilia, and increased expression of IL-4 and IL-5. More recently, the same group of investigators found similarly thickened RBM, increased epithelial loss and higher number of vessels in children with and without eosinophilic infiltration in the airway epithelium, and results were very similar for those aged ≥6 yrs as for those aged <6 yrs[54]. Both eosinophilic and non-eosinophilic cases had increased numbers of cells expressing IL-4 and IL-5 in the airways as compared with control.

Taken together, these results suggest that the complex, heterogeneous mechanisms associated with inception of childhood asthma have two major factors in common: incidence of early sensitization to local aeroallergens; and incidence of viral respiratory infection, especially due to rhinovirus, during the first 3 years of life. It is thus plausible to surmise that approaches that could decrease contact with or inappropriate immune responses to either of these environmental exposures at critical windows of opportunity in early life could prevent the development of asthma.

Avoidance of aeroallergen exposure and asthma prevention

It is not surprising that only one of these approaches, namely aeroallergen avoidance, has been tested in randomized clinical trials, because the potential for exposure to these allergens to cause asthma was first proposed almost two decades ago[55, 56]. The first such study was that of the Isle of Wight[57]. Starting in 1990, pregnant mothers of high risk infants, that is, those with 2 or more members of the immediate family affected with an allergic disease (asthma, eczema, or allergic rhinitis) or either parent or a sibling affected with an allergic disease plus cord serum IgE > 0.5 kU/L, were recruited and randomly assigned to prophylactic (n=58) or control (n=62) arms. Participants in the prophylactic group were either breast-fed with mother on a low allergen diet or given an extensively hydrolyzed formula for 12 months. Exposure to HDM was also reduced by the use of an acaricide and mattress covers. The control group followed standard advice. Asthma, assessed by repeated measurement analysis at 1, 2, 4, and 8 years was markedly lower (Odds Ratio=0.24, p=0.005) in the treated group than in the control group. The protective effect was primarily observed in the subgroup of children with persistent disease, i.e., asthma symptoms at all visits: 1 (1.7%) child in the prophylactic group had persistent asthma, compared with 7 (11.3%) children in the control group (p=0.04). This study shows than in a highly selected population, reduction of asthma incidence is indeed possible; but limitations were the small numbers of subjects and the unblinded nature of the intervention. Moreover, the intervention is expensive and highly burdensome for the family, and it is not possible to know which of the two interventions (i.e., on feeding regimen or allergen exposure) were responsible for the results obtained. A similar approach was adopted in larger study in Winnipeg and Vancouver, starting in 1995: 545 high-risk infants with an immediate family history of asthma and allergies were prospectively randomized into intervention or control groups prenatally[58]. The intervention during the first year of life consisted of: extensive HDM control measures; pet avoidance measures; avoidance of environmental tobacco smoke; and encouragement of mothers to breast-feed for at least 4 months and for the first year if possible and to delay introduction of other foods until 6 months of age. Partially hydrolyzed whey formula was supplied for supplementation if necessary and after weaning until 12 months of age. Families were also encouraged to avoid use of daycare facilities until after the first year of life, and 3 times fewer children in the intervention group were in daycare by 1 year compared with control infants. At age 7, the prevalence of asthma (defined as wheeze without colds and the presence of BHR) was significantly lower in the intervention group

compared with the control group (risk ratio, 0.39). Here too, there were multiple prophylactic measures, it was not possible to mask all interventions, and losses to follow-up were substantial: only 350 children (64%) were assessed for BHR at age 7. A different approach was taken in the Childhood Asthma Prevention Study in Sydney, Australia[59]: newborns with a family history of asthma were recruited antenatally and randomized, separately, to HDM avoidance or control and to dietary fatty acid modification or control[60] during the first 5 years of life. Both interventions were highly successful in decreasing exposure to HDM and in decreasing the ratio of ω-6 to ω-3 fatty acids in plasma in the active diet group, but neither intervention was significantly effective in decreasing the prevalence of asthma at age 5 years[59] or that of either asthma or BHR at 8 years[60]. Similarly, in the prevention and incidence of asthma and mite allergy (PIAMA) cohort[61], 810 allergic mothers were enrolled during pregnancy and randomized to either mite-allergen avoidance measures or sham intervention. There was no significant difference between groups in prevalence of wheezing or sensitization to HDM at age 4. In the Study of Prevention of Allergy in Children in Europe [62], 696 newborns at high risk of developing allergies were enrolled in three European countries (Germany, Austria, UK). Children were randomly assigned to an intervention arm, which used mite-impermeable mattress encasings for the child's bed and an educational package on allergen avoidance, and a control arm, which received basic information about allergies. Children were followed up at age 6, 12, 18 and 24 month. No significant difference in the prevalence of sensitization to HDM (control vs. intervention group: 8.4% vs. 6.1%, P=0.33) or the development of symptoms (recurrent wheezing 10.3% vs. 10.7%, nocturnal cough 12.5% vs. 12.5%) or asthma (3.5% vs. 5.1%) could be found between the control and intervention group. Finally, in the Manchester Asthma and Allergy Study, 291 high risk families expecting a child were randomized to either extensive mite allergen avoidance or a sham intervention[63]. The intervention was highly effective in decreasing HDM exposure in the home. Unexpectedly, children in the active arm were significantly more frequently sensitized by age 3 compared with control subjects (at least one allergen by skin tests: risk ratio, 1.6; p =0.04; mite: risk ratio, 2.9; p=0.05). At that age, there was no difference in prevalence of any respiratory symptom between groups.

Taken together, these results suggest that interventions directed at reduction of exposure to single aeroallergens known to be strongly associated with the development of asthma in early life are not effective in the primary prevention of the disease[64]. Multifaceted interventions, in which aeroallergen avoidance is paired with other interventions such as dietary manipulation in high risk children has been shown to be potentially more effective, but a thorough analysis of these interventions[64] concluded that there remains uncertainty as to whether multiple interventions are more effective than mono-component interventions. These conclusions are supported by the results of epidemiologic studies showing that in locales where the allergens most strongly associated with asthma in template, coastal regions such as HDM are not prevalent, others seem to be take their place. In Tucson, Arizona[65] and Los Alamos, New Mexico[66], for example, *Alternaria alternata* is the allergen most strongly associated with asthma. In Northern Sweden, where mites and airborne molds appear to be rare, allergens from domestic animals were found to be most strongly associated with asthma in 7-8 year old children[67], and the subsequent, significant increase in prevalence of sensitization to these allergens 10 years later had no effect on the prevalence of wheezing in children of the same age[68]. These results thus suggest that the relation between asthma and early sensitization to aeroallergens is complex, and the reduction or even elimination of exposure to one aeroallergen may not prevent the development of asthma and sensitization to other aeroallergens.

Reduction of RSV and RV infection and asthma prevention

As explained earlier, both RSV and RV LRI during the first years of life are associated with increased risk of asthma and wheezing during the school years. The availability of effective therapies for RSV-LRI based on antibodies against RSV[69] has suggested the hypothesis that prevention of lower airway involvement during RSV infection could be associated with a subsequent reduction in the prevalence of asthma-like symptoms during the school years. No randomized trial with the pre-specified goal of assessing this hypothesis has been published. Wenzel et al[70] recruited 8-11 year old children who had had a physician diagnosis of chronic lung disease or bronchopulmonary dysplasia as infants and who had participated in earlier studies of monthly prophylaxis with RSV immune globulin obtained from pooled human blood samples. Controls were selected from children who had a history of physician diagnosed bronchopulmonary dysplasia or chronic lung disease but who were not treated with active medicine. At follow up, the number of asthma attacks was significantly smaller in children who had been treated with RSV immune globulin than in controls. There were no significant differences in the prevalence of BHR, diagnosis of asthma, use of inhaled bronchodilators or corticosteroids, or use of any asthma medication between the two groups, although rates were consistently lower in the treated children. Simoes et al [71] enrolled 101 children <36 months of age who had received a monoclonal antibody against RSV, palivizumab, in a previous respiratory season and were not hospitalized for RSV and matched them to control children who had never received palivizumab. There were 2 control groups: approximately one third had documented RSV hospitalization in the first year before enrollment (n=76), and the second group (n=154) was not hospitalized. The relative protective effect of palivizumab on physician-diagnosed recurrent wheezing through the ages of 2 to 5 years was 68% in those with no family history of asthma and 80% in those with no family history of atopy or food allergies. In contrast, there was no effect of palivizumab on subsequent recurrent wheezing in the 90 children with a family history of atopy or food allergies compared to 130 untreated infants with atopic families. Although no definitive conclusions can be reached from these 2 studies that are applicable to term children, the results suggest that prophylaxis with anti-RSV antibodies could reduce the subsequent development of wheezing in children who do not have an atopic background.

There are currently no strategies available for the successful prevention of respiratory illnesses due to RV[72]. The fact that respiratory illnesses caused by RV are highly frequent in young children attending daycares[73] has suggested the possibility that avoidance of daycare in early life could be used as a prevention strategy for asthma[58]. However, several studies have suggested that, although daycare attendance is associated with increased incidence of WLRI in early life[74], it is either unrelated to asthma risk[75] or may be associated with protection against the development of asthma[74, 76].

Oral bacterial extract and asthma prevention

Recent experimental and clinical studies have suggested an interesting new approach to asthma prevention that may straddle both responses to both respiratory viruses and allergens. Oral lyophilized extracts of respiratory bacteria have been used empirically for decades in European countries for the prevention of respiratory tract illnesses (RTI) in both children and adults[77], and have also been shown to decrease the severity of acute exacerbations in patients with chronic obstructive pulmonary disease[78]. A recent meta-analysis of randomized trials using these products suggested that, although there is some indication that they may indeed decrease the incidence of RTI, most studies evaluated were of low quality and there was only moderate evidence of efficacy[77]. Two recent reports assessed efficacy of these products in modulating airway inflammation and BHR in established animal models of allergic airway disease. Navarro et al[79] showed that oral treatment with bacterial extracts

suppressed airway inflammation and BHR through interleukin-10 (IL-10)-dependent and MyD88 -dependent mechanisms, and induced the conversion of FoxP3 negative T cells into FoxP3 positive regulatory T cells. These FoxP3 positive T-cells found in the airways expressed CCR9, suggesting that they were likely of intestinal origins, since only denditric cells from mesenteric lymph nodes and Peyer's patches have been shown to confer a CCR9 phenotype to T-cells[79]. Furthermore, CD4 + T cells purified from the trachea of extract-treated mice conferred protection against airway inflammation when adoptively transferred into sensitized mice. Strickland et al[80] showed prevention of T-cell activation and of the development of BHR during chronic allergen exposure of sensitized rats exposed to oral bacterial extracts, and demonstrated that these effects were mediated by T-regulatory cells localized in the airway mucosa. These findings complement those of Razi et al, who studied 75 1-6 yr old children with recurrent wheezing[81]. Participants were randomly assigned to groups given either and oral bacterial extract or a placebo (1 capsule per day for 10 days each month for 3 consecutive months). After 12 months of follow-up, there was a 37.9% reduction in WLRI in the group given oral bacterial extracts compared with the group given placebo ($p< 0.001$). The duration of each wheezing attack was also 2 days shorter in the group given active drug than in the group given placebo ($p=0.001$). These results thus suggest that exposure to bacterial products by an oral route may modulate allergy-mediated airway inflammatory responses in experimental animals and may also decrease inflammatory responses presumably to viruses in preschool children with a history of WLRI. Interestingly, consumption of raw milk is associated with protection against the development of asthma[82], and it is possible that the presence of bacterial products in these unpasteurized milk products may explain at least in part these protective effects. Further studies are needed to determine if oral bacterial products could be used to prevent WLRI, and potentially to prevent the development of asthma, in susceptible children.

Conclusions

The epidemiologic and experimental evidence presented above strongly suggests that persistent asthma may result from complex interactions between immune responses to allergens and respiratory viruses. The aeroallergens most strongly associated with asthma vary widely in different locales and aeroallergen avoidance prevention trials have not been successful in preventing subsequent asthma. On the other hand, RV- and RSV-WLRI have been found to consistently predict the subsequent development of asthma. It is thus reasonable to hypothesize that viral infection occurring in susceptible individuals at a critical window of opportunity during airway and immune development enhances allergic sensitization and the chronic changes in airway function and structure that are characteristic of asthma. Although more studies are needed to better understand the mechanisms that are at work at the beginnings of asthma, a major unmet challenge for the asthma community today is to design and conduct primary prevention studies that specifically test this hypothesis.

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What we know.

- A high proportion of cases of chronic asthma begins during the preschool years
- Structural and functional changes characteristic of the asthmatic airway are often detected at or before age 3
- In chronic persistent asthma, the first clinical manifestations of the disease are triggered by viruses, most often rhinovirus, and are associated with early aeroallergen sensitization
- Single allergen environmental avoidance is not effective in preventive asthma onset
- Current inhaled anti-inflammatory therapy does not change the natural course of asthma

What we do not know

- Could oral exposure to bacterial products activate immune regulatory mechanisms in the airway, and by this mechanism prevent the development of asthma?
- Could therapeutic approaches that activate innate immune responses prevent acute lower respiratory viral illnesses and be used to prevent asthma?
- Which are the biological mechanisms that underlie the interaction between virus infection and aeroallergen sensitization at the beginnings of asthma?