

PRO/CON DEBATE

Allergy is an important factor in asthma exacerbation: A Pro/Con Debate

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ABSTRACT

Allergy and allergens have been implicated in asthma and it has historically been assumed that deteriorating asthma is related to allergen exposure. In the current pro/con debate some leading academics and researchers in the field consider this notion in the light of recent evidence. They conclude that allergy does not directly cause exacerbations but suggest that it may contribute to acute asthma in a different fashion. Possibilities that are proposed by the authors include specific allergy phenotypes acting as risk factors for virus-associated exacerbations or alternatively that allergy may be implicated in the blunted innate immune responses detected in asthma.

Key words: acute asthma, allergy, asthma exacerbation, respiratory virus, rhinovirus.

INTRODUCTION

Phil Bardin

The history of asthma exacerbations provides a salutary lesson of how established dogmas can hold sway for extended periods and prevent generation of new ideas. Allergy and allergens have been implicated in asthma for most of the previous century and a logical assumption was that deteriorating asthma must be related to increased allergen exposure.^{1,2} This idea was upheld in spite of patients presenting with acute severe asthma experiencing (and reporting to their doctor) preceding symptoms of a 'cold' that was then followed by symptoms of asthma instability within a few days. However, in the 1990s a landmark study was conducted in Southampton, UK that finally provided unequivocal and persuasive evidence that 'allergy' is not the principal cause of exacerbations.³ This advance was largely attributable to the use of novel (at that time) PCR techniques. Numerous subsequent studies have confirmed these findings and today it is widely acknowledged that upper respiratory virus infections are the likely cause of most asthma exacerbations⁴—but where does this leave allergy? We

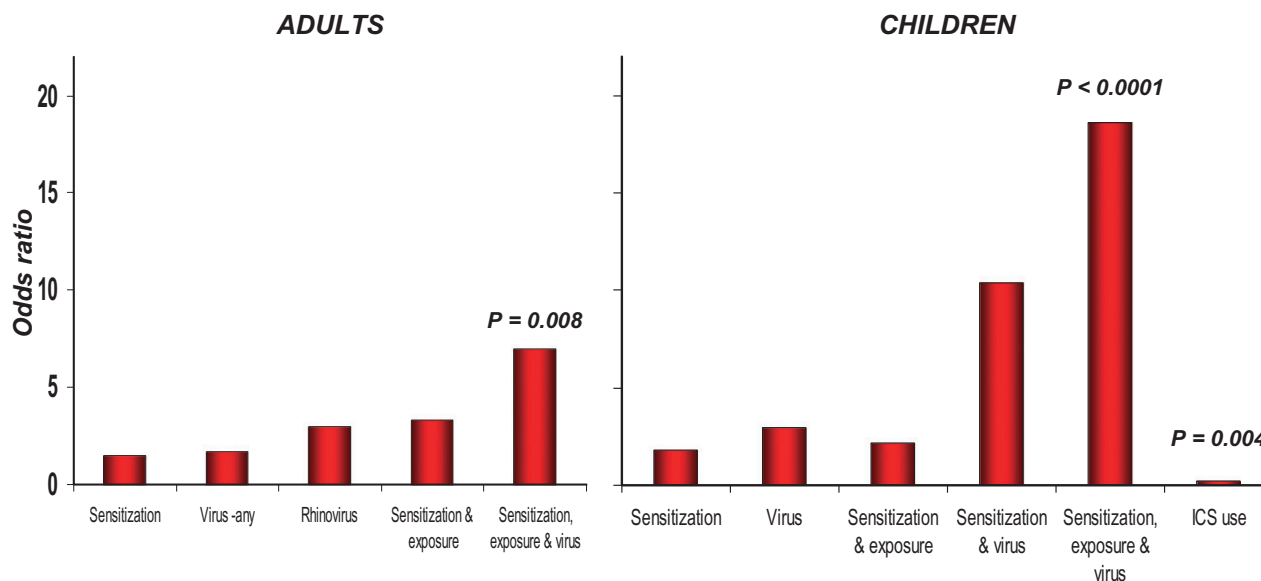


Figure 1 Allergen sensitization, high-level exposure to sensitizing allergen and respiratory virus infection synergistically increase the risk of in hospital admission with acute asthma both among adults and among children. (Redrawn based on the data from Green *et al.*¹⁶ and Murray *et al.*¹⁷ with permission.)

invited two highly respected academics and researchers to review and debate this question.

PRO

Adnan Custovic and Angela Simpson

Allergy and asthma exacerbations

A series of epidemiological studies have suggested that atopic sensitization is the strongest risk factor for asthma,⁵ which led to the notion that asthma is an allergic disease. In addition, several studies have demonstrated an increase in emergency room visits and hospital admissions with acute asthma attacks in children who are sensitized and exposed to high level of sensitizing allergen in their homes,⁶ and the association of allergen sensitization and high allergen exposure with the markers of asthma severity in children⁷ and adults,^{8–10} emphasizing the importance of ‘allergy’ in asthma exacerbations. However, there is a considerable variability in the strength of the relationship between ‘atopy’ and ‘asthma’ in different parts of the world (e.g. the fraction of wheeze that is attributable to atopy ranges from 0% in Turkey to 94% in China¹¹). One of the reviews of epidemiological evidence indicated that the proportion of asthma cases attributable to allergy may be overestimated, and that aetiological mechanisms other than allergy may be important in the causation of asthma.¹² For example, numerous studies have reported a strong association of asthma exacerbations with viral infection, and have suggested the mechanisms of virus-induced exacerbations.^{3,13–15} These data indicated that virus

infection, rather than allergy is a major determinant of asthma exacerbations.

Viruses and allergy: is there an interaction?

We would argue that rather than being mutually exclusive, viruses and allergy may interact in increasing the risk of exacerbation of asthma. We have demonstrated a synergistic effect of allergen sensitization, high-level exposure to sensitizing allergen and respiratory virus infection in increasing the risk of severe asthma exacerbations resulting in hospital admission, both among adults¹⁶ and among children¹⁷ (Fig. 1). These data suggested that neither of these risk factors *per se* (e.g. allergen sensitization, high allergen exposure or respiratory virus infection) increase the risk of exacerbation, but there may be a combined effect of natural virus infection and real life allergen exposure in allergic asthmatics in inducing asthma exacerbations.^{17,18} Recent studies have provided further evidence on the interplay between allergy and infection by demonstrating a relationship between bacterial-specific IgE and asthma susceptibility among teenagers, suggesting a role for bacterial-specific type-2 immunity in disease pathogenesis.¹⁹

What do we mean by the terms ‘asthma’, ‘atopy’ and ‘allergy’?

Critical to the argument about the relationship between allergy and asthma exacerbation is our understanding of the diagnostic labels of ‘asthma’, ‘atopy’ and ‘allergy’. One of the difficulties when trying

to decipher factors underlying asthma exacerbations is that asthma is not a single disease entity, but a collection of diseases presenting as a single syndrome or collection of symptoms.^{20–23} Thus, asthma symptoms and exacerbations may be considered a ‘final common pathway’ of expression of several diseases with distinct aetiologies, environmental triggers and genetic associates. Most studies investigating risk factors for asthma exacerbations define atopy as a positive allergen-specific serum IgE or skin test to any common food or inhalant allergen. However, when positive, these tests indicate only the presence of allergen-specific IgE, either in serum or bound to the membrane of mast cells in the skin; a sizeable proportion of individuals with positive tests have no evidence of allergic disease. We propose that the presence of a positive ‘allergy test’ (either serum-specific IgE or skin test) should not be considered a sole marker of ‘atopy’ or ‘allergy’ associated with exacerbation of asthma. We have demonstrated that atopy is not a simple yes/no phenomenon in relation to asthma onset and progression, and that the level of specific IgE antibodies offers more information than just the presence of IgE.²⁴ It is now recognized that among young wheezy children, quantification of allergen-specific serum IgE may help identify those who are at high risk of subsequent development of persistent asthma.²⁵ We have also shown that the level of IgE antibodies to inhalant allergens is associated with an increased risk of asthma hospitalization in childhood, with quantification of specific IgE to common inhalant allergens giving much more accurate prediction of exacerbation than using arbitrary cut-offs of serum IgE to define ‘atopy’.²⁶ In addition, we observed a strong and highly significant interaction between IgE concentration and respiratory virus infection in increasing the risk of exacerbation (Fig. 2).²⁶

At this point, we would like to propose that one of the reasons for the inconsistency of the findings on the association between allergy and asthma exacerbation is due to phenotypic heterogeneity, and that current diagnostic label of ‘atopy’ encompasses many different phenotypes, which differ in their association with asthma exacerbation.

In this conceptual framework, detectable serum IgE or positive skin tests do not define atopy, but should be viewed only as intermediate phenotypes of a true allergic vulnerability.

To test this hypothesis, we applied a machine learning approach (Bayesian inference for unsupervised clustering) to the rich dataset from an unselected birth cohort study (Manchester Asthma and Allergy Study); all available skin test and serum IgE data collected from birth to age 8 years were used to cluster the children into different sensitization classes, taking into account the timing and pattern of sensitization.²⁷ The unsupervised learning algorithm automatically discovered the latent structure and identified a five-class model, which best captured the underlying structure of the data. Most of children classified as ‘atopic’ (or ‘allergic’) using convention definitions were clustered into four distinct sensitization classes.²⁷ Based on their characteristics, we named

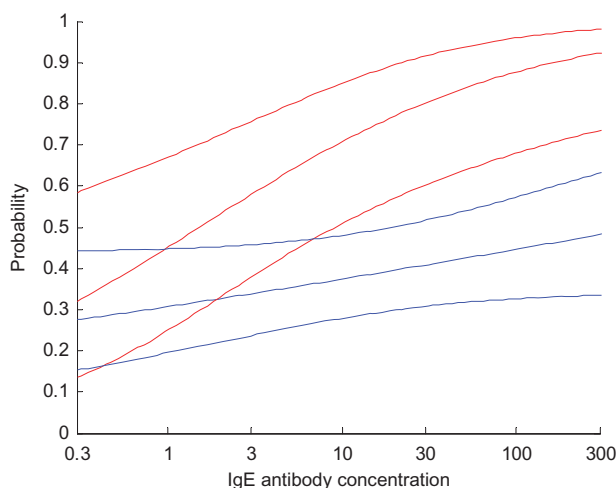


Figure 2 Interaction between the level of specific serum IgE to common inhalant allergens and respiratory virus infection in increasing the risk of asthma exacerbation. Fitted predicted probability curve (and 95% CI) for hospital admission at given IgE antibody concentrations (sum of mite, cat and dog specific IgE) alone (blue line) and with virus detected (red line) derived from multivariate logistic regression analysis. (From Murray *et al.*²⁶ with permission.)

them as multiple early, multiple late, predominantly house dust mite and predominantly pollen.²⁷ Multiple early class comprised 11% of the whole population, and only approximately a quarter of the children assigned as ‘atopic’ using conventional criteria. We then investigated the association between these classes and asthma exacerbations. A risk of hospital admission with acute asthma attack was highly and significantly increased only among children in the multiple early class, but not among those in any of the other atopy classes (hazard ratio 9.2; Fig. 3). This suggests that ‘atopy’ or ‘allergy’ is not a single phenotype, but a sum of many latent atopic vulnerabilities, only one of which (comprising approximately a quarter of children whom we consider to be allergic using standard diagnostic criteria) is associated with the development and exacerbation of asthma.²⁷

Conclusions

Asthma is a syndrome characterized by symptoms, which wax and wane throughout life, which are heterogeneous in the age of onset, severity and response to treatment. It is not a single disease, but a sum of many asthmas. Similarly, atopy is not a single phenotype, but a sum of many atopies (Fig. 4). So, is allergy an important factor in asthma exacerbation? Clearly, in some ‘asthmas’ symptoms are exacerbated predominantly due to one of the ‘allergies’. In other ‘asthmas’, none of the ‘allergies’ is important, and some ‘allergies’ are not associated with any of the ‘asthmas’ (or may even be protective). Unless we define all asthma and atopy-related phenotypes with

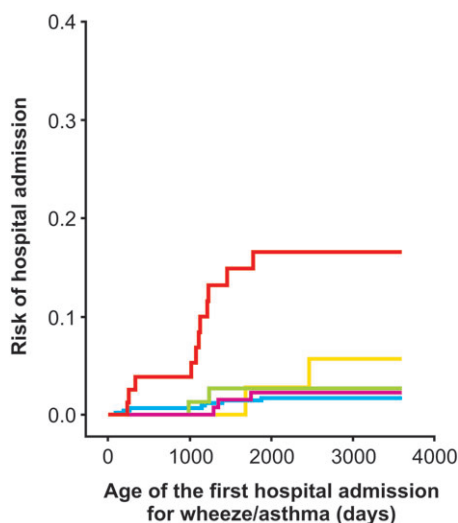


Figure 3 Significant increase in the risk of hospital admission with acute asthma attack only among children in the multiple early class, but not among those in any of the other atopy classes. Clusters: (—) no latent atopic vulnerability; (—) atopic vulnerability, not dust mite; (—) atopic vulnerability, dust mite; (—) atopic vulnerability, multiple late; (—) atopic vulnerability, multiple early. Kaplan–Meier estimates of cumulative risk of hospital admission with wheeze/asthma during the first 8 years among children who had a hospital admission after age 3 years stratified on a five-class model. (From Simpson *et al.*²⁷ with permission.)

$$\text{ASTHMA} = \sum_{i=1}^n \text{ASTHMA}_i$$

$$\text{ATOPY} = \sum_{i=1}^n \text{ATOPY}_i$$

Figure 4 Asthma is not a single disease, but a sum of many asthmas. Atopy is not a single phenotype, but a sum of many atopies.

much more precision, it will not be possible to accurately identify true risk factors, as any signal will be constantly diluted by phenotypic heterogeneity.

CON

Peter Le Souëf

A common error in medical science is to assume that a factor associated with a disease is causal. This now appears to be the case for allergy and asthma, as over the last 20 years or so, evidence has accumulated that allergy may not be as important as once thought in asthma. There is also now strong evidence to support the argument that allergy is not important in asthma exacerbations. The key points related to these changes in view are summarized in Table 1.

Table 1 Key points of the relationship between respiratory viruses, asthma exacerbations and allergy

- 1 Respiratory virus infections cause the majority of asthma exacerbations.
- 2 Asthmatics' immune systems have impaired function related to protection from viral infection.
- 3 Allergy is associated with deficits in T helper 1 (Th1) and innate immune responses.
- 4 The Th2 immune responses that underpin allergy do not appear to be important in protection from viral infection.
- 5 Allergy may therefore more correctly be seen as a marker for the more important immune system deficits that allow viruses to produce exacerbations.

1. Respiratory virus infections cause the majority of asthma exacerbations.

At all ages from infancy through childhood to adulthood and old age, virus infections are the most common cause of significant wheezing exacerbations. In infancy, human rhinovirus (HRV) is the most common cause of wheezing exacerbations in children in the community.^{28,29} Viral respiratory infections account for 80%–85% of asthma exacerbations in children³ and 75%–80% in adults³⁰ and of these, in both children and adults, HRV is responsible for around 60%.³¹ A similar picture is also seen in older adults with COPD; over 50% of exacerbations are due to respiratory viruses,³² mostly HRV.³³

2. Asthmatics have impaired T helper 1 (Th1) and innate immune responses.

Many studies have now shown that the immune responses that are related to protection from viral infection are impaired in asthmatics. In particular, interferon (IFN) responses are reduced in asthmatics. These are likely to be reduced from birth, as infants destined to become atopic by 6 years of age have reduced IFN γ responses from stimulated cord blood mononuclear cells.^{34,35} In children of smokers, peripheral blood mononuclear cell (PBMC) IFN γ responses were reduced compared with non-smokers³⁶ and parental smoking is a recognized risk factor for asthma. Asthmatic adults infected with RV16 show impaired IFN λ responses from PBMC.¹³ Bronchial epithelial cells from adult asthmatics also show impaired release of IFN β compared with healthy controls.³⁷ Interferon regulatory factor-1 is critical for IFN expression and polymorphisms that alter gene expression *in vivo* and protein expression *ex vivo* have recently been described and implicated in the impaired IFN responses in asthmatics.³⁸ Impairment of IFN responses is likely to make asthmatics especially vulnerable to infection with respiratory viruses. Supporting this view, symptoms from HRV infection were prolonged in asthmatics versus controls.³⁹ Hence, the evidence that Th1 and innate immunity is significantly impaired in asthmatics is substantial and this is likely to be the reason that asthmatics are particularly prone to problems when infected with a respiratory virus.

3. Allergy is associated with deficits in Th1 and innate immune responses.

Although allergy is characterized by enhanced Th2 immune responses, many studies have reported that subjects with allergy also have impaired Th1 and innate immune responses. As noted above, newborn infants destined to become atopic by 6 years of age have reduced IFN γ responses.^{34,35} Reduced IFN γ production by cord blood mononuclear cells in newborns has also been shown to be associated with cord blood allergen-specific IgE.⁴⁰ Interestingly, this association is also seen in children with pro-Th2 genotypes. In infants whose parents smoked, specific IgG to both diphtheria and tetanus vaccine antigens was found to be reduced in those with pro-Th2 alleles in the genes for IL-4, IL-4 receptor (IL-4R) IL-4R α and IL-13, and PBMC responses to tetanus toxoid were reduced for IFN γ and IL-13 for infants with a pro-Th2 IL-4R α genotype.⁴¹ A similar finding was made in older children, who showed impaired specific IgG production to pneumococcal vaccine components for the pro-Th2 alleles in the genes for CD14, IL-4, IL-4R α and IL-13.^{42,43} Why this relationship between enhanced Th2 and impaired Th1 and innate immune responses exists is unclear, as it does not appear to fit with an obvious advantage to survival. However, the existence of this relationship is clearly important in asthma, as children and adults with atopy are also likely to have a reduced ability to protect themselves from many different infective agents, especially respiratory viruses.

4. Enhanced Th2 immune responses that underpin allergy are not involved in protection from viral infection.

On current evidence, there is no reason to expect that Th2 immune responses have a role to play in protection from viral infection. On the other hand, viral infections may be important in promoting enhanced Th2 responses. For example, IgE levels are acutely increased in children at the time of an asthma exacerbation,⁴⁴ but in the period following the acute attack, antibacterial IgE levels increased and IgE levels to house dust mite antigens were reduced.⁴⁵ These findings are not easy to interpret, but they do demonstrate that infection with respiratory viruses induces substantial changes in IgE responses and this raises the possibility that repeated virus infections may be responsible for some of the enhanced Th2 responses that characterize atopics. Indeed, this may be the explanation for the finding of an association between allergen exposure, IgE responses and acute asthma exacerbations.¹⁸

5. Allergy is a marker for the more important immune system deficits that allow viruses to produce exacerbations.

From the evidence presented above, the argument that allergy is important for acute asthma exacerbations would be difficult to sustain. Clearly, there are other abnormalities of immune system responses that have a much more plausible role in asthma exacerbations. An important research question arising from these observations is why there is such a strong

relationship between enhanced Th2 and impaired Th1 and innate immune responses. Finally, increasing evidence suggests that viruses may enhance atopic responses.

DISCUSSION

Phil Bardin

We provided a nuanced question for debate by our experts. Clearly the issue of whether allergy *causes* exacerbations is no longer contested and this is acknowledged by both experts. However, the contribution of allergy to asthma exacerbation is the key issue and this is ably reviewed by the contributors.

Custovic and Simpson argue that asthma and allergy are not single entities, but rather conditions representing a number of phenotypes. The possible effect of allergy in asthma exacerbation may therefore be diluted by other allergy phenotypes that are either neutral or even protective. The authors cite recent information and suggest that a pattern of multiple antigens and early sensitization can increase risk of hospitalization during acute asthma.²⁸ This approach will help to further refine the concept of synergism between allergen and virus and hospital admissions that has been reported.¹⁷

Le Souëf acknowledges a role for allergy in asthma exacerbation—however, not along lines of ‘traditional’ allergy pathways. He argues that allergy is accompanied by flawed innate immune responses and that these link allergy with exacerbations. Indeed, he suggests that allergy may be a marker for immune deficits that permit more severe virus-associated exacerbations.

Recent evidence that asthma is a condition of chronic ‘wounding’ has meant that many physicians and researchers have discarded old Th1/2 paradigms and accepted that allergy has an association with asthma, but one that is not causative.^{46,47} In this new model of ongoing tissue damage and repair, the underlying disease process can reduce the ability of the host to withstand virus infection by numerous mechanisms. For example, overexpression of the transforming growth factor family may be critical in the context of chronic wound healing and repair. One molecule in this group, transforming growth factor- β supports wound healing but also has profound immune-suppressive actions that will impact on the severity of virus (rhinovirus) infections.⁴⁸ Other abnormalities such as epithelial damage and loss may also impair host resistance.

In many asthmatics experiencing severe exacerbations there is no detectable evidence of pre-existing allergy. It therefore seems likely that in these patients other virus–host interactions largely determine whether infection will occur, how severe it will be, which complications will come about and how the infection is resolved. New studies linking rhinovirus group C with more severe acute asthma events^{49,50} suggest that virulence of the invading organism may be the cardinal determinant of outcome in many exacerbations. It is encouraging that research that has

fostered a greater fundamental understanding of viruses, especially rhinovirus, causing asthma exacerbations has recently gained momentum.⁵¹ It may provide the foundational knowledge required to design and test vaccination strategies for respiratory viruses such as rhinovirus.

Both contributors provide robust arguments to support their views. Evidence abounds that asthma is phenotypically diverse and the same may be true of allergy. Moreover, several studies have supported a role for allergy (in the traditional sense) to contribute to both severity and duration of exacerbations.⁴² Further refinement of the allergy phenotype has potential to clarify this association even better. More controversially, allergy may be associated with or even cause the blunted innate immune responses postulated in asthma. On the other hand, appreciable synergism between allergen, virus infection and hospital admissions may reflect association rather than causation. Our debate has framed key questions for future research. These have the potential to unlock strategies that will lessen the impact of virus infections in allergic asthma.

REFERENCES

- 1 Fanta CH. Asthma. *N. Engl. J. Med.* 2009; **360**: 1002–14.
- 2 Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature* 2008; **454**: 445–54.
- 3 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.
- 4 Sykes A, Johnston SL. Etiology of asthma exacerbations. *J. Allergy Clin. Immunol.* 2008; **122**: 685–8.
- 5 Simpson BM, Custovic A, Simpson A *et al.* NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin. Exp. Allergy* 2001; **31**: 391–9.
- 6 Rosenstreich DL, Eggleston P, Kattan M *et al.* The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N. Engl. J. Med.* 1997; **336**: 1356–63.
- 7 Lowe LA, Woodcock A, Murray CS *et al.* Lung function at age 3 years: effect of pet ownership and exposure to indoor allergens. *Arch. Pediatr. Adolesc. Med.* 2004; **158**: 996–1001.
- 8 Langley SJ, Goldthorpe S, Craven M *et al.* Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. *J. Allergy Clin. Immunol.* 2003; **112**: 362–8.
- 9 Langley SJ, Goldthorpe S, Craven M *et al.* Relationship between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitized, atopic asthmatic subjects. *Thorax* 2005; **60** (1): 17–21.
- 10 Tunnicliffe WS, Fletcher TJ, Hammond K *et al.* Sensitivity and exposure to indoor allergens in adults with differing asthma severity. *Eur. Respir. J.* 1999; **13** (3): 654–9.
- 11 Weinmayr G, Weiland SK, Björkstén B *et al.* Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am. J. Respir. Crit. Care Med.* 2007; **176**: 565–74.
- 12 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; **54**: 268–72.
- 13 Contoli M, Message SD, Laza-Stanca V *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat. Med.* 2006; **12**: 1023–6.
- 14 Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr. Infect. Dis. J.* 2005; **24** (11 Suppl.): S217–22; discussion S220–1.
- 15 Johnston SL. Experimental models of rhinovirus-induced exacerbations of asthma: where to now? *Am. J. Respir. Crit. Care Med.* 2003; **168**: 1145–6.
- 16 Green RM, Custovic A, Sanderson G *et al.* Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002; **324** (7340): 763.
- 17 Murray CS, Poletti G, Kebabdzé T *et al.* Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006; **61**: 376–82.
- 18 Murray CS, Simpson A, Custovic A. Allergens, viruses, and asthma exacerbations. *Proc. Am. Thorac. Soc.* 2004; **1**: 99–104.
- 19 Hollams E, Hales B, Bachert C *et al.* Th2-associated immunity to bacteria in asthma in teenagers and susceptibility to asthma. *Eur. Respir. J.* 2010; doi:10.1183/09031936.00184109
- 20 Halder P, Pavord ID, Shaw DE *et al.* Cluster analysis and clinical asthma phenotypes. *Am. J. Respir. Crit. Care Med.* 2008; **178**: 218–24.
- 21 Henderson J, Granell R, Heron J *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; **63**: 974–80.
- 22 Moore WC, Meyers DA, Wenzel SE *et al.* Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am. J. Respir. Crit. Care Med.* 2010; **181**: 315–23.
- 23 Smith JA, Drake R, Simpson A *et al.* Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am. J. Respir. Crit. Care Med.* 2008; **177**: 1358–63.
- 24 Simpson A, Soderstrom L, Ahlstedt S *et al.* IgE antibody quantification and the probability of wheeze in preschool children. *J. Allergy Clin. Immunol.* 2005; **116**: 744–9.
- 25 Sly PD, Boner AL, Björkstén B *et al.* Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; **372** (9643): 1100–6.
- 26 Murray CSPG, Ahlstedt S, Soderstrom L *et al.* Probability of hospital admission with acute asthma exacerbation increases with increasing specific IgE antibody levels. *Allergy Clin. Immunol. Int. J. World Allergy Org.* 2007; (Suppl. 2): 270–3.
- 27 Simpson A, Tan VY, Winn J *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am. J. Respir. Crit. Care Med.* 2010; **31**: 232–7.
- 28 Jackson DJ, Gangnon RE, Evans MD *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am. J. Respir. Crit. Care Med.* 2008; **178**: 667–72.
- 29 Kusel MM, de Klerk NH, Holt PG *et al.* Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr. Infect. Dis. J.* 2006; **25**: 680–6.
- 30 Wark PA, Johnston SL, Moric I *et al.* Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. *Eur. Respir. J.* 2002; **19**: 68–75.
- 31 Johnston SL. Innate immunity in the pathogenesis of virus-induced asthma exacerbations. *Proc. Am. Thorac. Soc.* 2007; **4**: 267–70.
- 32 Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 2004; **1**: 115–20.
- 33 Seemungal T, Harper-Owen R, Bhowmik A *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2001; **164**: 1618–23.
- 34 Tang ML, Kemp AS, Thorburn J *et al.* Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet* 1994; **344**: 983–5.
- 35 Prescott SL, King B, Strong TL *et al.* The value of perinatal immune responses in predicting allergic disease at 6 years of age. *Allergy* 2003; **58**: 1187–94.
- 36 Tebow G, Sherrill DL, Lohman IC *et al.* Effects of parental smoking on interferon gamma production in children. *Pediatrics* 2008; **121**: e1563–9.

- 37 Wark PA, Grissell T, Davies B *et al.* Diversity in the bronchial epithelial cell response to infection with different rhinovirus strains. *Respirology* 2009; **14**: 180–6.
- 38 Schedel M, Pinto LA, Schaub B *et al.* Irf-1 gene variations influence ige regulation and atopy. *Am. J. Respir. Crit. Care Med.* 2008; **177**: 613–21.
- 39 Corne JM, Marshall C, Smith S *et al.* Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002; **359**: 831–4.
- 40 Pfefferle PI, Sel S, Ege MJ *et al.* Cord blood allergen-specific ige is associated with reduced ifn-gamma production by cord blood cells: the protection against allergy-study in rural environments (pasture) study. *J. Allergy Clin. Immunol.* 2008; **122**: 711–16.
- 41 Baynam G, Khoo SK, Rowe J *et al.* Parental smoking impairs vaccine responses in children with atopic genotypes. *J. Allergy Clin. Immunol.* 2007; **119**: 366–74.
- 42 Wiertsema SP, Baynam G, Khoo SK *et al.* Impact of genetic variants in il-4, il-4 ra and il-13 on the anti-pneumococcal antibody response. *Vaccine* 2007; **25**: 306–13.
- 43 Wiertsema SP, Khoo SK, Baynam G *et al.* Association of cd14 promoter polymorphism with otitis media and pneumococcal vaccine responses. *Clin. Vaccine Immunol.* 2006; **13**: 892–7.
- 44 Hales BJ, Martin AC, Pearce LJ *et al.* Ige and igg anti-house dust mite specificities in allergic disease. *J. Allergy Clin. Immunol.* 2006; **118**: 361–7.
- 45 Hales BJ, Martin AC, Pearce LJ *et al.* Anti-bacterial ige in the antibody responses of house dust mite allergic children convalescent from asthma exacerbation. *Clin. Exp. Allergy* 2009; **39**: 1170–8.
- 46 Holgate ST. Pathogenesis of asthma. *Clin. Exp. Allergy* 2008; **38**: 872–97.
- 47 Holgate ST, Polosa R. Treatment strategies for allergy and asthma. *Nat. Rev. Immunol.* 2008; **8**: 218–30.
- 48 Thomas BJ, Lindsay M, Dagher H *et al.* Transforming growth factor-beta enhances rhinovirus infection by diminishing early innate responses. *Am. J. Respir. Cell Mol. Biol.* 2009; **41**: 339–47.
- 49 Miller EK, Edwards KM, Weinberg GA *et al.* A novel group of rhinoviruses is associated with asthma hospitalizations. *J. Allergy Clin. Immunol.* 2009; **123**: 98–104 e1.
- 50 Tan BH, Loo LH, Lim EA *et al.* Human rhinovirus group C in hospitalized children, Singapore. *Emerg. Infect. Dis.* 2009; **15**: 1318–20.
- 51 Palmenberg AC, Spiro D, Kuzmickas R *et al.* Sequencing and analyses of all known human rhinovirus genomes reveal structure and evolution. *Science* 2009; **324**: 55–9.