



CORRESPONDENCE

Do the current house dust mite-driven models really mimic allergic asthma?

To the Editors:

Animal models play a key role in helping us determine the pathogenesis of diseases, and are vital for the discovery of new therapies and the improvement of existing medication. To do this, the model(s) need to closely mimic the clinical features and, where possible, be relevant to the disease in humans. Classically, the innocuous antigen ovalbumin (OVA) has been used to induce an allergic reaction in animals, and whilst it is possible to reproduce many of the features of the asthmatic lung, *i.e.* specific immunoglobulin (Ig)E levels, T-helper cell (Th)2-associated eosinophilic inflammation, early and late asthmatic responses (EAR and LAR, respectively), and airway hyperresponsiveness and associated tissue remodelling, researchers began to question the clinical relevance of using OVA as a model allergen [1]. In addition, it was commonly felt that the need for systemic delivery of OVA, with an adjuvant such as aluminium hydroxide, did not correctly mimic how asthmatic patients become sensitised to aeroallergens. To circumvent these issues, researchers switched to using topically delivered house dust mite allergen (HDM) to model allergic asthma [1], a route that, incidentally, is reported to induce tolerance when using OVA [2, 3]. A large proportion of human asthmatic patients have elevated levels of HDM-specific IgE and, after challenge with HDM, exhibit EAR, LAR and increases in airway inflammation [4–7]. For these reasons, the choice of HDM as the allergen to use in animal models seems like a logical one and explains the almost unilateral decision to switch to using them. Generally, these models are based around administering HDM topically into the airways, normally *via* the intranasal route, daily, over multiple weeks. This results in airway inflammation which features an increase in eosinophilia. However, a source of concern is the lack of evidence to show that the inflammation is part of an allergic (*i.e.* presence of HDM-specific IgE, B-cells and T-cells) phenotype. Unlike the classical OVA model, where, without prior sensitisation, airway inflammation is absent upon challenge, it is not clear whether HDM-induced inflammation is a truly allergic response or merely a consequence of repeated nasal insult with an inflammatory concoction. Indeed, it is possible to induce airway eosinophilia using a variety of non-IgE-associated stimuli, *i.e.* with Sephadex and endotoxin [8, 9].

The current dogma suggests that the line between “sensitisation” and “challenge” phases is blurred in the repeated HDM insult models. But yet, if these models do have a strong allergic component one would expect more reports of the classical allergic asthma phenotypes, such as increased HDM-specific IgE and respiratory symptoms, such as EAR and LAR. In contrast to the OVA–aluminium hydroxide models that show

high serum levels of specific IgE and antigen-induced mast cell degranulation (the prototypic type I hypersensitivity response), most studies using HDM models have either not measured specific IgE levels or have reported a very weak (approximately two-fold increase in optical density) total or specific IgE response. Whereas in patients with HDM allergic asthma, serum levels of specific IgE are usually 100-fold higher compared to non-allergic (<0.35 kU·L⁻¹) controls. What is more, if one uses the presence of specific IgG1 as a marker of HDM-specific B- and T-cell clonal expansion, it would appear that this event occurs after much of the airway inflammation is observed (*i.e.* interleukin (IL)-5 and IL-13 production, and airway eosinophilia) [10]. Studying the role of the key allergic asthma effector cells should help us to understand the mechanisms driving the repeat HDM challenge model. As yet, however, there are only limited reports on the role of cells, such as the mast cell, dendritic cell, B-cell and the Th2-cell in these modelling systems. In addition, to recapture some of the allergic asthma phenotypes currently missing from the repeat HDM challenge models, we suggest it may be necessary to revert to using a systemic sensitisation phase prior to HDM challenge.

Animal models play a key role in helping us to determine the pathogenesis of diseases and are vital for discovery of new therapies. However, we suggest one needs to understand the modelling systems used, what limitations they have and how relevant they are to the human disease before they are utilised in the search for new therapeutic entities. It could well be that repeated topical HDM challenge does adequately model allergic asthma but equally we, as a community, could end up developing a therapy for HDM-induced airway inflammation in rodents rather than a therapy to combat human disease.

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Risk factors of community-acquired pneumonia in children

To the Editors:

In a recent issue of the *European Respiratory Journal*, TEEPE *et al.* [1] published their interesting observations of determinants of community-acquired pneumonia (CAP) in children in primary care. The authors included 107 children with either radiologically or clinically diagnosed CAP treated as outpatients in four Dutch healthcare centres in 1999–2008, and compared the potential determinants of CAP between the cases and 321 controls from the same area with no CAP during the study period. In adjusted analyses, lower age (OR 1.14), asthma history (OR 3.57) and the number of previous visits for upper respiratory tract infections (URTIs) (OR 1.80 for one or two episodes and 2.46 for more than three episodes) were independently associated with CAP. The authors concluded that the association between CAP and the number of URTIs can be explained by infection susceptibility of the individuals [1].

In the discussion, the authors mentioned that their study was the first to explore the determinants of CAP in children in primary care. Actually, their study was the second one.

As part of the Savo Pneumonia Study performed in 1981–1982 in Eastern Finland [2, 3], we also analysed risk factors for CAP in children aged 3 months to 15 yrs [4]. The design of the study was prospective and strictly population-based. During a surveillance period of 12 months, all CAP cases were registered in a small manufacturing town and three rural municipalities. Chest radiographs were studied in all clinically presumptive cases, and only radiologically confirmed CAP cases were included in the analyses. The incidence of CAP was 36 per 1,000 per yr for <5 yrs and 16 per 1,000 per yr for 5–15-yr-old children [2]. 51% in the younger and 11% in the older age group were treated in hospital. *Pneumococcus* caused 28% of the cases overall [3], and *Mycoplasma* <10% at <5 and >50%

at >5 yrs of age, over 80% of mycoplasmal cases being treated at home [5].

To evaluate the possible risk factors for paediatric CAP, identical standardised questionnaires were sent to the parents of the 201 children with CAP and to 250 controls from the same four municipalities. In all, 176 (88%) cases and 233 (93%) controls answered.

In adjusted analyses, significant risk factors for CAP were a history of recurrent (at least three) URTIs within 12 months (OR 5.5), a history of wheezing at any age (OR 5.3) and a history of otitis media and tympanocentesis before 2 yrs of age (OR 3.6) in <5-yr-old children. The significant risk factors in 5–15-yr-old children were a history of recurrent URTIs within 12 months (OR 5.5) and a history of wheezing at any age (OR 5.3).

In line with the study by TEEPE *et al.* [1], wheezing tendency and susceptibility to respiratory infections were the only significant determinants of paediatric CAP in our prospective, population-based study [4]. Young age is an indisputable determinant of paediatric CAP, as also seen in our incidence figures. Interestingly, the urban *versus* rural place of residence and passive smoking were not associated with the risk of paediatric CAP [4].

In conclusion, pneumonia and other respiratory infections seem to cluster in the same children in the populations of high-income Western countries. Therefore, further studies should focus on the role of host factors in respiratory infections, including CAP in children. The CAP studies should be powered enough to allow the monitoring of the numerous environmental confounding factors, as well as age- and microbe-specific stratified analyses. The designs of the studies should be prospective and population-based to represent the whole spectrum of the disease, and in optimal cases should