Viral infection and allergy

To the editor:

A recent publication in *Nature Immunology* by Dahl *et al.*[1] reports that influenza infection can enhance allergic responses in the lung, which in many respects models the clinical situation. This finding has important implications for how we should, or could, make use of the popular 'hygiene hypothesis' in developing plans for preventing allergic diseases.

There is no doubt that in certain clinical situations viral infections can exacerbate asthma symptoms, and the work by Dahl *et al.* reinforces this. However, the interactions between viral responses and asthma are complex, and indeed, recent epidemiological studies have indicated a possible protective effect of some viral infections against the development of asthma[2]. We have investigated the significance of how the timing of allergen exposure, in relation to influenza infection, affects the development of allergic airway inflammation. Unlike Dahl *et al.*, we found that influenza infection can have both beneficial and detrimental effects upon the development of allergy.

If sensitized (allergic) mice inhale allergen during the acute stages of influenza infection and shortly afterwards (days 1 to 14 after infection), airway eosinophilia was exacerbated similar to what Dahl *et al.* have described[1]. In our model we found that dendritic cell (DC) migration to the draining lymph node, T helper cell type 2 (T_H2) recruitment into the lung, T_H2 cytokine production and airway hyperresponsiveness were similarly enhanced during this period[3].

In contrast to the findings of Dahl and colleagues, we found that at later time points after influenza infection (14 to >100 days after infection), airway eosinophilia, T_H2 cytokine production and airways hyperresponsiveness were suppressed[4] (and **Supplementary Fig. 1** online). The mechanism underlying this suppression was distinct from that mediating the exacerbation. We found that a long-lived population of lung-resident $CD8^+$ T cells could suppress the local (but not systemic) response to allergen inhalation in an interferon-γ-dependent manner[4].

It is important to note that although we see an influenza-mediated exacerbation of an allergic response, similar to Dahl *et al.*, the duration of exacerbation in our model is not long lasting, but rather limited to the acute stage of infection and shortly afterwards. Dahl *et al.* propose that the genetic background of different mouse strains may influence the effect of viral infections on allergic responses[1]. However, our data shows that the key factor is the timing of allergen challenge with respect to the stage of the viral infection[3]. It is likely that the genetic background, sex and age of mice may influence the duration and intensity of infection, but these factors are unlikely to restrict a response to either exacerbation or suppression.

These two contrasting effects of influenza infection on asthma highlight the need for rigorous analysis of multiple time points and models before experimental findings are applied to a broader clinical and epidemiological setting.

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Dahl *et al.* reply:

We thank Marsland *et al.* for their perspective on our work[1], which dealt with the effect of influenza infection on subsequent allergic sensitization and disease and not, as they did, on exacerbation of such preexisting disease. They found that pulmonary eosinophilia induced by immunization and intranasal challenge with *Nippostrongylus brasiliensis* larva–derived material was reduced in C57BL/6J mice previously infected with influenza A virus[2] and observed comparable suppression of allergic disease for at least 100 days after influenza infection using either *N. brasiliensis* material or ovalbumin (OVA) as allergen[3] (and Supplementary Figure 1 of their letter). In contrast, we found increased allergen-induced eosinophilia by sensitizing BALB/c/J mice to keyhole limpet hemocyanin (KLH) after influenza infection[1].

The experimental approach used may explain these differences. The pathogenesis of pulmonary eosinophilia in response to a defined protein allergen, such as KLH, may not be identical to that induced by the more complex *N. brasiliensis*-derived allergen. We also avoided OVA as a test allergen, because in pilot studies we found that the allantoic fluid of embryonated chicken eggs (our source of influenza virus or a negative control) contained OVA. Mice exposed to OVA by intranasal challenge with allantoic fluid had altered immune responses, after subsequent OVA sensitization and challenge, when compared to mice that initially received intranasal PBS alone (unpublished data). Thus, our KLH model may better assess the effect of prior influenza infection by avoiding effects from simultaneous infection and allergen exposure. Our sensitization protocol, which was longer and used more doses of intranasal allergen[1] compared with that of Marsland *et al.*[2], may have induced a more robust allergic disease that overcame any protective mechanisms of influenza infection that may be operative at lower levels of allergen sensitization and challenge.

We agree that further analysis of the impact of influenza infection on allergen