

Influenza Specific Serum IgE is Present in Non-Allergic Subjects

To the Editor

The recently emerging highly pathogenic avian influenza H5N1 virus, spreading from South-East Asia and now throughout Europe, is becoming of global concern. This virus subtype is more promiscuous, breaking the species barrier by infecting and causing severe disease in man associated with a high mortality rate. The potential for shift of the influenza A subtype circulating in man, which could result in a severe pandemic, is now higher than it ever has been since the last shift in 1968. Preparing and implementing protection strategies for this threat is a huge challenge. Vaccination is still the most commonly used and effective prophylactic measure against influenza [1], although antiviral agents are available for use either alone or in combination with vaccination. Improvements in the vaccine formulation and vaccination strategy are crucial in order to prepare for the new threat.

As a contribution to this field, we have focused our research efforts on understanding the underlying host immune response to influenza vaccination in humans. We have conducted a number of clinical vaccine trials and one of the exclusion criteria when selecting subjects for our studies has been allergy, mainly due to possible traces of egg and antibiotics in the vaccine. Volunteers have answered questionnaires about known allergies and subjects have also been tested against a large panel of commonly occurring allergens.

In an allergy study we decided to test the patients against influenza virus. Incidentally, we found that those patients with a history of allergy, although they had not been recently infected or vaccinated with influenza, had very low levels of serum IgE against influenza (Fig. 1A). We were curious to find out what this meant, so as a consequence we re-examined samples from a previous influenza vaccine trial [2], and screened for IgE antibodies against influenza in pre- and post-vaccination serum samples (Fig. 1B). To our surprise we found that these healthy subjects, with no known or documented allergy, had an IgE response against influenza. Furthermore, the level of serum IgE significantly increased after influenza vaccination. The vaccine was well tolerated, and we did not receive any reports of anaphylactic reactions or other serious side effects associated with vaccination. The different basal levels of IgE in the two study groups (Fig. 1) have no direct relevance, as the studies are from different populations and samples were collected at different time points.

Our results are of interest since a recent study reported virus specific IgE antibodies in the serum of BALB/C mice after an intranasal influenza infection [3]. In addition, the mice developed an active and passive cutaneous anaphylaxis after rechallenge with the influenza antigen. The finding that specific IgE was significantly raised after influenza vaccination is supported by earlier studies in mice [4], and is important since IgE is present on mast

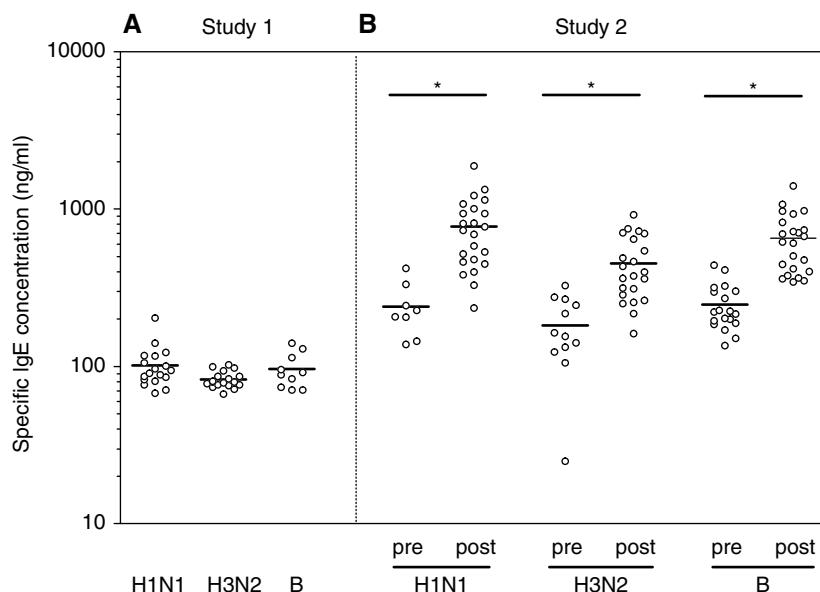


Figure 1 The level of influenza specific IgE in serum (ng/ml) against influenza A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H1N1) and B/Yamanashi/166/98 (B), determined by enzyme linked immunosorbent assay described elsewhere [2]. A: Study 1 contained 20 subjects diagnosed with allergic rhinitis, and samples were collected out of birch pollen season in Sweden 2002. B: Study 2 comprised samples collected from 23 volunteers with recurrent tonsillitis before and after influenza vaccination in Norway 2000 [2]. The asterisk (*) denotes a significantly statistical change ($p < 0.05$) in the pre- and post-samples by paired t-test. Both studies have been approved by local ethics committees. Informed and written consent was obtained from all volunteers included in this study.

cells. Histamine from, for example, mast cells, is known to influence histamine receptors and production of cytokines in a Th1 type profile through histamine 1 receptor (H1R) and proliferation of CD4+ T cell subsets, and to negatively regulate both Th1 and Th2 responses through histamine 2 receptor (H2R) [5]. Mast cells also produce several cytokines of importance in viral defence and in allergic reactions. This is of interest since we found a significantly higher level of influenza specific IgE after vaccination with influenza which might indicate a participation of IgE in viral defence. IgE may attach to virus and if connected to mast cells cause activation and participation in the viral defence, as mediators released from mast cells may turn the immunological response towards a Th1 profile, recruiting for example, T lymphocytes, and thus protect against viral infection.

Investigations of the local and systemic immune mechanisms will increase understanding of the complex basic inflammatory activities, immunological memory and protection against respiratory pathogens and may lead to development of improved vaccines. Our study supports the view that influenza vaccination is a safe procedure and the involvement of IgE probably does not have a direct adverse effect in this context. There may even be a beneficial role for IgE by initiating a rapid local inflammatory response quickly recruiting lymphocytes and by modulating the immune response.

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