Commentary: The end of the hygiene hypothesis?

Jeroen Douwes* and Neil Pearce

Accepted 1 April 2008

Three years ago, we published a commentary in the *International Journal of Epidemiology*, which concluded that the observed increases in asthma prevalence in Western countries had peaked or even begun to decline. Further evidence for this is presented in the paper by Ponsonby et al. that appears in the current issue of the journal. However, although there is now substantial evidence that the ‘epidemic’ of asthma in Western countries has begun to decline, the reasons for the decline remain as mysterious as the reasons for the epidemic itself. In recent years, it has become routine to attribute the epidemic to the ‘hygiene hypothesis’, particularly with regards to the protective effects of microbial exposure early in life, but there are many anomalies in the epidemiological evidence that raise questions about this interpretation of the global asthma prevalence time trends.

The ‘hygiene hypothesis’ has been prompted by evidence that overcrowding, unhygienic conditions and larger family size were associated with a lower prevalence of atopy, eczema, hay-fever and asthma. An increase in infections as well as increased exposures to specific microbial agents with strong pro-inflammatory properties, such as bacterial endotoxin has been proposed as an explanation for these findings. Although the specific immune mechanisms are not clear, it is believed that microbial exposures may activate innate immune pathways through expression of Toll-like receptors (TLRs) and CD14. These exposures may thereby suppress T-helper-2 (TH2) cell expansion and the development of IgE-antibodies and TH2 dependent diseases, including allergic asthma, hay fever and eczema. It has, therefore, been hypothesized that increased cleanliness, reduced family size and subsequent decreased microbial pressure in the past few decades could explain the increase in global asthma prevalence.

This new paradigm has gained considerable support from asthma researchers worldwide, and has resulted in new aetiological theories, and inspired basic scientists to develop novel laboratory-based studies. However, despite great enthusiasm and rapid uptake of this new theory there is reason for caution, and the findings reported by Ponsonby et al. provide further reason for scepticism. They examined asthma trends in 22,882 Australian children aged 4–6 using annual questionnaires from 2000 to 2005 inclusive. In contrast to what would be expected based on the hygiene hypothesis, asthma symptom prevalence showed a steady decline. The prevalence of eczema symptoms on the other hand, significantly increased. Ponsonby et al. also found that immigrant and non-immigrant children showed similar asthma time trends, which argues against the suggestion that the immunological reactivity expressed in childhood is predominantly established within the first year of life or even in the prenatal period—a view often associated with the hygiene hypothesis.

These findings add to other contradictory evidence that warrants scepticism about the hygiene hypothesis as the primary explanation for global asthma prevalence time trends.

First, it has now been well established that the proportion of asthma cases that are attributable to atopy is usually less than one-half. Similarly, recent studies have demonstrated that <50% of asthma cases are attributable to eosinophilic airway inflammation, the hallmark of allergic asthma. Thus, evidence from studies of eosinophilia and asthma is consistent with that from studies of atopy and asthma: in both instances, at most about one-half of asthma cases appear to be due to ‘allergic’ mechanisms. The hygiene hypothesis suggests that a decrease of exposure to microbes would—through enhanced atopic immune responses—increase the incidence of allergies and allergic asthma. If true, then the protective effects would be most pronounced for the atopic asthma phenotype as well as other atopic conditions such as eczema. Interestingly, in the study by Ponsonby et al., a steady increase in eczema was observed, suggesting that some atopic conditions may indeed still be on the rise. If so, then the observed decrease in asthma may be explained by a decline in non-atopic asthma, potentially masking the (smaller) increase in atopic asthma. Similarly, the past increase in asthma may not have been exclusively attributable to an increase

* Centre for Public Health Research, Massey University Wellington Campus, Private Box 756, Wellington, New Zealand.

* Corresponding author. E-mail: j.douwes@massey.ac.nz
in allergic asthma. In fact, there is some evidence that non-atopic asthma may have increased more than atopic asthma. Furthermore, in a repeated population survey among pre-school children, an increase in asthma prevalence was not only found in children with the classic asthma pattern of wheeze, but also in all wheezing phenotypes including viral-induced wheezing. Thus, at least some of the time trends may be due to temporal variation in factors affecting non-allergic asthma. Ponsonby et al. also observed a decline in hay fever that may be seen as an argument against the hypothesis that the observed decline is due to non-allergic mechanisms, but we have previously shown that rhinitis, like asthma, is a heterogeneous condition with an important non-atopic component. Unfortunately, most time-trend studies have not included comparable measures of atopy, and differential time-trend patterns for different asthma/rhinitis phenotypes can, therefore, not be established at this time.

Second, as noted earlier, asthma prevalence has begun to decline in both children and adults in Western countries, but it appears unlikely that these countries have become less clean in recent decades and there is certainly no evidence that family size has increased. There are also a number of anomalies in the evidence from studies conducted within these countries. For example, although housing conditions are unlikely to have become more hygienic in United States inner city populations, asthma prevalence has increased significantly in those populations, particularly among African Americans living in poverty. Furthermore, studies of specific infections and asthma risk have not consistently demonstrated a protective effect.

Third, a further anomaly is the high asthma prevalence in countries in Latin America, which appear unlikely to have lower infection rates than European countries such as Spain and Portugal, which have the same dominant languages—and to a large extent, culture—and lower asthma symptom prevalence.

Fourth, although the hygiene hypothesis is generally explained as a protective effect of early life exposures resulting in long-lasting health benefits, recent studies suggest that exposures throughout life may be important and that long-term continual exposure to protective factors including microbial agents may be required to maintain optimal protection. These data are consistent with the data presented by Ponsonby et al., which suggest that the immunologic reactivity expressed in later life is not exclusively established in the prenatal period or first year of life.

On the other hand, none of these anomalies are fatal for the hygiene hypothesis in general, but only for the very ‘narrow’ version of it in which microbial pressure early in life protects against atopic asthma by suppressing TH2 immune responses. It is possible that this very specific form of the hygiene hypothesis may be invalid, or at least incomplete, but that a more general version of the hygiene hypothesis is still valid. In particular: (i) the hygiene hypothesis is a very useful model to explain the significant protective effects of farming on asthma and allergies observed in many studies worldwide; (ii) the hygiene hypothesis is consistent with findings that pets in the home may protect against allergies and asthma and (iii) many aspects of the hygiene hypothesis can be reproduced in mice models of allergic asthma. However, although the hygiene hypothesis may be a valid explanation for some of the observed differences in asthma prevalence between populations, it is unlikely that the hygiene hypothesis on its own can explain the large asthma prevalence increases observed over the last decades or the decline in asthma prevalence observed more recently in western countries. Furthermore, it appears unlikely that the immunologic reactivity expressed in later life is exclusively established in early life as is often assumed in the hygiene hypothesis. As we have previously noted, it is important that we consider the ‘forest’ of changes that occur with westernization, as well as the specific ‘trees’, and that the package of changes that come with westernization and increased hygiene may increase asthma risk, but not necessarily exclusively through an imbalance of TH1/TH2 immunity. New aetiological theories of global asthma prevalence are, therefore, required that are more consistent with the epidemiological evidence and which take into account factors affecting the time trends for both allergic and non-allergic asthma.

Acknowledgements

The Centre for Public Health Research is supported by a Programme Grant from the Health Research Council (HRC) of New Zealand. Jeroen Douwes is supported by an HRC funded Sir Charles Hercus Fellowship.

References