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A modern miasma hypothesis and back-to-school asthma exacerbations

E.R. Tovey [a,b,*], W.D. Rawlinson [c,d,e]

[a] Allergen Group, Woolcock Institute of Medical Research, Missenden Road, Glebe, NSW 2050, Australia
[b] Sydney Medical School, University of Sydney, NSW 2006, Australia
[c] Virology Division, SEALS Microbiology, Prince of Wales Hospital, Randwick, NSW 2031, Australia
[d] School of Biotechnology and Biomolecular Sciences, Faculty of Science, University of New South Wales, Sydney, Australia
[e] School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia

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SUMMARY

A sudden increase in the rate of asthma exacerbations has been observed among young children in many countries 2–3 weeks after their return-to-school following the summer holidays. These exacerbations are frequently associated with human rhinovirus (hRV) infections, with possible interactions with allergen sensitisation, allergen exposure and medication use. It was originally proposed that the sudden increase resulted from new strains of respiratory viruses acquired during the holidays spreading rapidly on return to school. While there is compelling evidence implicating hRV in these exacerbations, recent observations on virus transmission, infection patterns and immune responses to both viruses and allergens have led us to propose an additional hypothesis for this increase in exacerbations. We propose that classrooms typically provide persistent exposure to a mixture of airborne viruses, viral proteins, endotoxin, community allergens and other human-derived aerosols – a modern miasma. During the preceding school term, this exposure establishes and maintains a level of immune tolerance and herd immunity, which then declines during the two-month holidays due to lack of such exposure, creating a transitory window of susceptibility to viral infections and asthma. The return to school re-establishes exposure to these aerosols resulting in an acceleration of exacerbations, until the tolerance and herd immunity are re-established. Thus, the peak in return-to-school asthma is more a function of a transitory increase in susceptibility due to a temporary lack of this complex exposure, than it is to novel, locally endemic strains of hRV.

Childhood asthma and respiratory viral infections

Acute exacerbations of symptoms are a serious clinical problem for young children with asthma, and are a common reason for emergency hospital treatment [1]. These can occur despite adequate medication and management. In children aged 2–12 years, such exacerbations are strongly associated with hRV infections, which are detected in 60–90% of episodes [2,3]. Children have several different hRV infections per year, due to the large number of circulating strains of virus (>100 plus hRV-C types and recombinants) [4,5] and the limited immune protection provided by previous infections.

The frequency of asthma exacerbations in children follows a seasonal pattern. In the Northern Hemisphere there is an early peak in May, a nadir in July and then a gradual rise in August with a sudden acceleration to a larger peak in September tapering at the end of the year [6,7]. These autumnal peaks are observed in many climate zones, ranging from tropical islands [8] to high northern latitudes [9,10] with the time-lag varying from 10 [6] to 24 [11] days after return to school, synchronise with the local start date of school [6,12]. Several studies [11,13] have noted additional smaller fluctuations in exacerbations associated with shorter school holidays, these include both reductions in exacerbations at the start of holidays and increases shortly after the return to school. The question is, what creates the timing of these peaks?

The current hypothesis

The original explanation for the timing of this peak was that during the holidays, some children acquired new strains of hRV while mixing with people from outside their community. The return to school synchronised the rapid spread of these new virus strains within the school population when it reassembled [13]. A difference in the time-lag of peaks between different communities has been attributed to the differences in local climate and lifestyles, affecting virus survival, transmission and circulation patterns.

Numerous other seasonal risk factors are suggested to contribute to the peaks, in addition to the occurrence of novel virus strains. These risks include a reduction in medication use in the

* Corresponding author at: Allergen Group, Woolcock Institute of Medical Research, Missenden Road, Glebe, NSW 2050, Australia. Tel.: +61 2 9114 0348; fax: +61 2 9114 0013.
E-mail address: ert@med.usyd.edu.au (E.R. Tovey).

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holidays [7,10], stress associated with return to school [14], seasonal changes in vitamin D [15], increased exercise [16] and seasonal exposure to allergic pollen [17] or fungi [18]. Allergen sensitisation is a recognised major risk factor for viral exacerbations [19–22] and the combination of sensitisation, current allergen exposure and the presence of virus have been shown to act synergistically in adults [23] and children [24]. While each of these extrinsic factors probably contributes to the severity or risk of seasonal exacerbations, it can again be questioned whether they provide the consistency and precision in timing.

A modern miasma hypothesis

We propose that the air of classrooms is a modern miasma, containing an aerosol of respiratory viruses, viral proteins, community allergens shed from clothing, bacterial products and other molecules derived from people which may modulate immune function, cause inflammation or increase susceptibility to viral infections. During the preceding school term, this on-going exposure maintains a level of herd immunity to viral infections and a tolerance to allergen and endotoxin exposure. A reduction in this exposure during the school holidays creates a transient increase in susceptibility to viral disease and asthma in young children when they return to school.

Recent observations about viral infection patterns

Earlier studies based on culture and serology of children with acute diseases suggested that different hRV strains circulated in waves with seasonal outbreaks of dominant strains [25,26]. Recent studies collectively show a more complex picture. These have used molecular techniques that are both more sensitive and identify additional strains that cannot be cultured, and have sampled symptomatic and healthy populations both in cross-section and longitudinally. These studies show that during the 'seasons' of May or September, almost all children have at least one hRV infection [19] although about half these in children over 7 years of age are asymptomatic [27]. In cohorts the size of approximately two classes of children, in one study, 12 hRV different strains circulated [27] and in another study 18 strains circulated at one time, while 57 strains circulated during the entire study [19]. Between 80 and 100% of these strains differed between seasons [19]. There is a lack of information about the diversity of strains in between these 'seasons' and in holidays. Longitudinal studies, which have not typed the strains, show only moderate seasonal differences in the prevalence of hRV infections [28] suggesting strains circulate all year. It is also recognised that seasonal influenza infections decline in the school holidays among children, but not adults [29].

Thus while the current explanation of novel virus strains is feasible, there is no experimental data to show that in holidays such strains accumulate in isolation and then spread rapidly on return to school. An alternative explanation is that the on-going churning in virus strains in the community is not markedly different during the holidays compared to other times but that during holidays other factors increase susceptibility to existing viral infections and this leads to well-timed peak, irrespective of local climate differences and outdoor allergen exposures.

Miasma and exposure

'Miasma' is described by the Merriam–Webster dictionary as 'a vaporous exhalation formerly believed to cause disease' [30]. We would argue that the air of classrooms contains a variety of biological materials that constitute a modern equivalent of miasma.

In classrooms, children are probably frequently exposed to viruses, based on the documented prevalence [19,28] and persistence [28] of symptomatic and asymptomatic infections, and the associated production of exhaled aerosols [31,32] and droplets. These are analogous to aerosols of RSV and influenza recently detected in rooms containing infected subjects [33,34]. We speculate that additional aerosol exposure may also occur to hRV viral antigens, such as VP0, VP1 and VP3 [35,36], which may be analogous to the decoy antigens produced by RSV [37]. The immunological effect of persistent and at times sub-clinical exposure to both hRV virus and proteins may be analogous to the community exposure to H1N1'09 which results in high levels of asymptomatic seroconversion [38] and development of adaptive herd immunity.

Classrooms also provide exposure to non-seasonal, community allergens such as mites, cats, dogs, cockroaches and mice (depending on location). Such allergens are dispersed into the air from clothing which are an overlooked source of exposure [39–41]. While schools tend to have lower mean concentrations of allergens in dust than houses, [42,43] some children have much greater exposure at school than home. The relevance of this is discussed in the later section dealing with modulation of immune responses. Finally, in classrooms there are several additional bioaerosols components whose contribution to a miasma is speculative. Although the concentrations of pro-inflammatory bacterial endotoxin tends to be similar in the dust from houses and schools [44–46], children have a high personal 'endotoxin cloud', directly linked to asthma symptoms [47] and a risk for viral infections [48]. Another common inhaled component of indoor air in schools is the human skin shed by other children. In transplant models, tolerance to foreign tissue is regulated by mast cells [49], which are attracted to the site of alloantigen presentation. In this case it would be the lung, and, as mast cells are pivotal in allergic responses, such alloantigen exposure in school may increase acute asthma risk in allergic children via mast cell recruitment. A more curious observation is that male mice exposed to the bedding of female mice are partly protected from influenza infection, accompanied by an increased aggregation of leukocytes in the lung [50]. Whether exposure to other people induces either protective or inflammatory cellular effects via an unrecognised analogous mechanism is unknown.

Miasma and tolerance

The second component of our modern miasma hypothesis is that exposure at school establishes multiple and limited forms of immune tolerance and herd immunity, these decrease during the holidays, such that on return to school there is increased susceptibility to viruses, allergens and asthma. While earlier data shows IgA in nasal mucus confers dose-dependent and strain-specific protection against the initiation of infection [51], there has been no study of the natural decline of these antibodies where natural aerosol exposure to virus was markedly reduced, although a recent review [52] noted protective IgA titres decreased only 2 months after infection. If this were the case then a decrease in mucosal IgA over the holidays may lead to a temporary increase in susceptibility to infection on return to school. There is also supportive data [53,54] that exposure–induced allergic tolerance [55] to community allergens declines in the school holidays and re-exposure results in asthma exacerbations on return to school. Whether a role for endotoxin exposure also occurs with schools is complex, as endotoxin tolerance is a well-recognised but poorly understood phenomenon [56].

Implications and predictions from the miasma hypothesis

This hypothesis implies that the susceptibility to viral infections and asthma exacerbations among young children in the community are the consequence of both their current and prior exposure