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EDITORIAL

Rhinovirus infections in infants: is respiratory syncytial virus ready for the challenge?

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Human rhinoviruses are the leading cause of upper respiratory tract infections (*i.e.* the common cold) in both adults and children [1]. On average, adults experience one rhinovirus infection each year, whereas, in young children, it is a more frequent occurrence. Although rhinovirus infections are limited to the common cold in most cases, they are also a frequent cause of acute sinusitis and otitis media (subsequently leading to antibiotic overuse). Rhinovirus tropism and replication, however, is not limited to the upper respiratory tract. It has been recognised that rhinoviruses can replicate in the lower respiratory tract and lead to lower respiratory tract illnesses, particularly in the elderly, in immunocompromised patients and in children. It is has also been established that rhinoviruses contribute to the majority of asthma exacerbations in both adults and children, and to nearly half of all chronic obstructive pulmonary disease (COPD) exacerbations. Given the technical difficulties involved in isolating rhinovirus in cell cultures, it has only been in recent years, with the advent of viral genome detection *via* RT-PCR, that a clearer understanding of the impact of these infections has emerged [2].

In infants, acute viral respiratory illnesses are the major cause of morbidity and mortality. Several recent community-based studies of infants at high risk of atopy or those attending day care have consistently found rhinoviruses to be the most frequent viruses associated with acute respiratory infections or wheezing illnesses [3–5]. The leading role of rhinoviruses in infancy was recently corroborated in a birth cohort study of otherwise healthy infants, who were studied at the first acute respiratory infection with cough or wheeze [6]. In addition, the potential severity of rhinovirus-associated diseases has been demonstrated by case series describing bronchiolitis, pneumonia and wheezing illnesses in hospitalised infants with rhinovirus infection [7–10].

In this issue of the *European Respiratory Journal* (*ERJ*), JARTTI *et al.* [11] present a study of the viral aetiology of respiratory illnesses in a subgroup of infants of the Childhood Origins of ASThma (COAST) study, a prospective birth cohort study that enrolled ~300 newborns from Wisconsin (USA) who were at increased risk of developing asthma (*i.e.* at least one parent with allergies and/or asthma). The authors focused on infants who were frequently ill (27 infants out of 285), *i.e.* those who had five or more moderate-to-severe respiratory illnesses during their first year of life. JARTTI *et al.* [11] found that in this group of patients, rhinoviruses were the most commonly detected viruses in nasal washes (detected in 61% of cases of moderate-to-severe respiratory illnesses and in 43% of mild illnesses). Rhinovirus infections occurred early in life, with the mean age at first rhinovirus infection being 4 months. They were usually associated with wheezing, had severity similar to other infections, such as respiratory syncytial virus (RSV), and, interestingly, were the result of reinfections, *i.e.* two consecutive rhinovirus infections in an infant were usually caused by two different strains and not by a protracted infection with one virus strain.

What are the important messages to take from this study? The study of JARTTI *et al.* [11] adds to the increasing evidence that rhinoviruses play a so far underestimated role in respiratory morbidity in infancy. Secondly, it demonstrates that at least in the population studied, recurrent rhinovirus infections are not the result of chronic, persistent infections, but are the result of reinfections with different serotypes. Since >100 serotypes have been characterised and as most of them circulate in the community, reinfection is expected to occur throughout life. Certainly, some cross-protection does exist between close serotypes but this has an overall limited effect given the large variability of viral capsid protein 1 and other surface viral glycoproteins targeted by the immune response. In addition, new rhinovirus subtypes have been recently identified [12–14], highlighting the potential ability of these viruses to diversify and to escape pre-existing immune responses. Thus, the diversity of circulating strains and the limited ability of previous immunity to protect against reinfection are key determinants to consider for any strategy aimed at preventing or treating rhinovirus infections in infants.

Despite these observations, several questions regarding rhinovirus infections in infancy remain unanswered. Most importantly, the clinical significance of the detection of rhinoviruses in respiratory samples from infants has not yet been clearly established. In the study of JARTTI *et al.* [11], rhinoviruses were the most common viruses detected not only during periods of illness but also during asymptomatic visits (where they were detected in 35% of cases). These figures are in agreement with

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other studies, which have found that respiratory specimens from 11–20% of infants asymptomatic at the time of sampling were positive for rhinovirus [4, 15–17]. These asymptomatic infections may represent remnant RNA from a previous symptomatic infection (although the findings of JARTTI *et al.* [11] argue against this hypothesis), the beginning of a developing symptomatic infection or they may simply reflect the fact that the spectrum of rhinovirus infections includes episodes with minimal clinical disease. A recent prospective community-based birth cohort study of infants at high risk of atopy provided important information regarding this issue; KUSEL *et al.* [4] calculated attributable risks for each virus detected, *e.g.* the proportion of infection attributable to a particular virus. It was found that 47% of upper respiratory infections and 32% of lower respiratory infections in infants were attributable to rhinoviruses. In comparison, only 3% of upper respiratory infections and 10% of lower respiratory infections were attributable to RSV. Unfortunately, such information is missing from the paper of JARTTI *et al.* [11], but it could be estimated that roughly a quarter of the moderate-to-severe respiratory illnesses (rhinovirus detection rate in moderate-to-severe respiratory illnesses minus rhinovirus detection rate during asymptomatic visits) were attributable to rhinoviruses.

Current evidence leaves no doubt that rhinoviruses are associated with significant respiratory morbidity in infants. It now remains to be investigated what determines the disease severity in a particular infant. Differences in the virus or the susceptibilities of the host (*e.g.* pre-existing immunity) may play a role. Recent work has suggested that new rhinovirus subgroups may be associated with specific clinical manifestations [12–14]. However, definitive proof of this concept is lacking, although it is acknowledged that enteroviruses, which share similar genomic organisation, include variants with different tropism and clinical phenotype. In contrast, there is clear evidence that there are genetic, environmental and immunological factors that affect the clinical manifestation of any viral infection. Asthmatic patients, for instance, show an increased susceptibility to viral infections, in particular to rhinoviruses [18, 19]. Whether an increased susceptibility toward rhinovirus infections could play a role in the at-risk population studied by JARTTI *et al.* [11] has to be considered. Further research should address the relative contribution of viral and host factors and allow a better understanding of the pathophysiological role of rhinovirus infections in infancy.

So what do these findings mean for the paediatrician in clinical practice? Will the detection of rhinoviruses change the management of children with respiratory infections? Although implementation of rapid picornavirus detection assays has been proposed for the clinical diagnosis of respiratory infections in paediatric patients with bronchiolitis [8], the evidence that such a practice will affect clinical management is lacking. Conversely, it is well established that the rapid diagnosis of influenza or RSV infection in children has a significant impact on physician decision-making, and these tests are routinely used [20].

Will ''wheeze with rhinovirus'' be implemented in algorithms predicting the development of asthma? LEMANSKE *et al.* [3] have already provided important prognostic information for the practicing physician with regard to this issue. They have shown that in infants at increased risk of developing asthma, the most significant risk factor for the development of preschool wheezing is the occurrence of symptomatic rhinovirus illnesses during infancy; 63% of infants who wheezed during the rhinovirus season continued to wheeze in the third year of life, compared with 20% who wheezed during the RSV season. However, these findings and their potential impact on early childhood asthma need to be validated in unselected infant populations. At this stage, it may therefore be too early to draw firm conclusions about the role of rhinovirus diagnosis in daily clinical practice.

In summary, the paper by JARTTI *et al.* [11] underscores the major role of rhinovirus infections in early life. In the mind of most paediatricians, rhinovirus is not ready to compete with respiratory syncytial virus, the so far unchallenged leader of viral infections in infancy. However, systematic screening for rhinovirus could change perceptions and lead us to revisit this dogma. The underdog is challenging the leader. Paediatricians: be aware and watch out for rhinoviruses!

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