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EDITORIAL COMMENTARY

Respiratory Viruses in Babies: Important Insights From Down Under

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(See the major article by Sarna et al, on pages 418–27.)

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For those of us interested in respiratory viruses, there is a lot to like about the study by Sarna et al that appears in this issue of *The Journal of Infectious Diseases* [1]. The study analyzes data from a birth cohort established as part of the Observational Research in Childhood Infectious Diseases (ORChID) Project, based in Brisbane, Australia [2]. Impressive study attributes include large size, community base, enrollment from birth, scheduled frequent longitudinal sampling with or without illness, high percentage of specimen acquisition rate, even enrollment of subjects throughout the year to account for virus seasonality, and testing of samples with an extensive panel of real-time polymerase chain reaction (PCR) assays. Participating babies had anterior nasal and "dirty nappy" swabs obtained at birth and weekly thereafter by parents trained by research staff. Parents also kept daily symptom diaries listing predefined symptoms. The present manuscript reports only on the respiratory swabs. This massive undertaking yielded analyzable data on 9594 samples from 152 participants, corresponding to 163 098 individual virus-specific PCR queries!

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This intensive prospective study of respiratory viruses in infants finds that human rhinovirus (HRV) is by far the most frequent virus detected in the infant respiratory tract. This single-stranded, positive-sense RNA virus is increasingly recognized as an important human pathogen, with a strong relationship to childhood asthma [3]. Significantly, Sarna et al found that HRV was detected in an impressive 20.0% of all samples tested, accounting for 77.3% of all virus-positive swabs. By 2 years of age, 98% of participating infants had experienced HRV-C, 94% HRV-A, and 56% HRV-B. Although impressive, this large proportional load of HRV should not be surprising, as it has also been shown in previous community-based studies using molecular tests, including an earlier study by these authors [4] and several others [5–8]. Similarly, laboratories using multiplex respiratory virus panels that include sensitive rhinovirus detection capability usually find rhinovirus/enterovirus to be the most common positive result. The US Food and Drug Administration (FDA)–cleared multiplex respiratory panels do not distinguish between rhinoviruses and enteroviruses, but apart from outbreak situations, such as occurred in 2014 with enterovirus D-68 [9], most of the positive results from rhinovirus/enterovirus assays reflect HRV infection. It has become clear that in relation to respiratory viruses, HRV is the elephant in the room.

In comparison to the universal occurrence of HRV, infections with other respiratory viruses were less frequent. RSV and parainfluenza viruses were each detected in 58% of subjects, influenza A in 8%, influenza B in 3%, human metapneumovirus in 21%, human coronaviruses in 72%, adenovirus in 51%, human polyomaviruses in 77%, and human bocavirus in 75%. The 58% occurrence of RSV is surprisingly low, as common understanding is that almost all infants experience RSV within the first 2 years of life [10]. Possible explanations for the discrepancy include inadequate sample collection (samples were collected by parents), seasonal variation in the occurrence of RSV, and complete reliance on molecular assays. In some studies, serology has indicated some infections are not detected by PCR [11]. The authors point out the difference between their estimate and that of the Houston family study [12], which is a basis for the concept of universal RSV infection early in life and which relied heavily on serology [12]. However, they also cite a number of more recent studies that support their finding of less than universal infection. These results suggest that we may need to fine-tune our understanding of the frequency of RSV infection early in life.

The focus of the Sarna et al study was first respiratory virus infections, and the frequency of first HRV infections in young infants is noteworthy. Of the 152 infants followed, 81% experienced a first infection with HRV by 6 months of age, compared to 8.5% for RSV, and 0.7%–9.4% for the other respiratory viruses. Influenza A and B infections were infrequent, with only 0.8% and

1.4% experiencing first influenza A and B, respectively, by 6 months of age. The curves mapping virus occurrence by age show that all viruses other than HRV were relatively unusual in the first 6 months of life, with upward inflection points evident at approximately 6 months of age, consistent with diminishing maternal immunity. Notably, the HRV occurrence curve is different, with rapid increase through the first 6 months and no obvious inflection point. The shape of this curve suggests that maternal immunity is not preventing HRV infections, although it is possible that it is mitigating clinical manifestations. This finding has important implications for HRV control strategies, and calls for mechanistic studies to further define the differences between the behavior of HRV and other respiratory viruses.

With mounting undeniable evidence for the frequent occurrence of HRV infection in the first 2 years of life, it is important to assess the impact of these infections, and Sarna et al provide relevant data. Based on symptom diaries kept by parents, virus-positive episodes were characterized as symptomatic or asymptomatic and, if symptomatic, as involving the upper or lower respiratory tract. If we direct attention to the episodes in which only a single virus was detected (data shown in Supplementary Table 2 of the Sarna et al manuscript), we see that first HRV detections were less likely than first infections with the other RNA viruses to correspond to symptomatic episodes (52% compared to 70%–85% for the other RNA viruses), but were comparably likely compared to the DNA viruses for which 46%–59% of first detection episodes corresponded to symptomatic infections. Likewise, only 6% of first HRV infections were classified as lower respiratory infections, compared with 20%–46% for the other RNA viruses and 10%–15% for the DNA viruses. Only 13% of the first HRV detections were associated with a medical visit, compared with 25%–42% for the other RNA viruses and 8%–28% for the DNA viruses. It should be noted that direct comparison of severity of HRV infections to the other respiratory viruses is complicated by the fact that a much higher proportion of first episode HRV infections occurred in infants <6 months of age, and data are not provided (and may not have been available because of the infrequency of infection with the non-HRV respiratory viruses during that age period) that allow us to ascertain whether an age effect is present. Nevertheless, it is clear that most of the first HRV infections were mild, in spite of the fact that they were occurring predominantly in infants <6 months of age, an age when the immune system is not fully developed and some viral infections can disseminate.

However, as the authors correctly point out, the mildness of the clinical illness associated with first HRV detections may not be the whole story. They cite a recent study by Wolsk et al [13] showing that HRV infection in the first 4 weeks of life, even if asymptomatic, may program immune memory with an exaggerated T-helper 2 mucosal immune response and impaired antiviral responses. The implication is that HRV infection in young infants, even if asymptomatic, might promote the development of asthma later in life. This interaction may be viewed as HRV serving as an educator (or miseducator) of the immune system by virtue of early-in-life virus–host interactions. This concept fits well with an emerging view that one of the key functions of the infant's microbiome is education of the immune system [14]. The ORChID study has made an important contribution by directing our attention to the extremely frequent interaction between HRV and the immature immune system, the implications of which clearly merit further study.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. Author confirmed no potential conflicts. The author have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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