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Association of Rhinovirus Species with Common Cold and Asthma Symptoms and Bacterial Pathogens

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To the Editor

Most exacerbations of asthma in children are initiated by viral infections, most commonly due to rhinoviruses (RV). RV-A and RV-C species are more likely to cause moderate to severe illnesses and wheezing in infants, and exacerbations of asthma leading to hospitalization.^{1, 2} Bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* have also been linked to acute wheezing illnesses and exacerbations of asthma in young children.^{3, 4} In a prospective study of school-aged children during peak RV season in September (“RhinoGen”), we previously reported that viral infections often precede increased detection of these bacteria.⁵ Furthermore, viral infections with concurrent or subsequent detection of bacterial pathogens were more likely to be associated with symptomatic illnesses and exacerbations of asthma.⁵ These studies suggest that RV-A and RV-C infections could lead to more severe wheezing illnesses by promoting the proliferation of bacterial pathogens.

To test this hypothesis, we obtained weekly nasal mucus samples during both September and April as part of the RhinoGen study, and analyzed them for RV species (RT-PCR and partial sequencing)⁶ and the bacterial pathogens *S. pneumoniae*, *M. catarrhalis* and *H. influenzae catarrhalis* (quantitative PCR; full methods in online supplement).⁵ Children with the help of their parents were instructed to record daily common cold and asthma symptoms, morning peak expiratory flow, and albuterol use on calendars during their enrollment in the study.

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This study was approved by the University of Wisconsin Human Subjects Committee, written informed consent was obtained from the parents, and written assent obtained from children ages 7 years and older.

The study population consisted of 167 outpatient children with asthma and 143 children without asthma ages 4–12 years (Supplemental Table I and online supplement). Children scored cold and asthma symptom severity based on a 4-point scoring system (Supplemental Table II),⁵ and moderate asthma exacerbations were defined in accordance with ATS and NHLBI guidelines (see online supplement).

During the two-month monitoring period, there were 755 respiratory illnesses reported in the 310 children. In the 3028 nasal mucus samples, RV was the virus most commonly detected, and RV-A (n=566 solo, 674 total) was detected over twice as often as either RV-B (n=203 solo, 250 total) or RV-C (n=195 solo, 251 total). RV-B was detected more frequently in September, while RV-A and RV-C were detected more often in April (Supplemental Table III). For each RV species, we also determined the number of infections (one or more consecutive weeks with detection of the same viral type, Supplementary Table IV). The mean duration of viral infection varied by species ($p < 0.001$); RV-B was longest (mean 2.09 weeks, 95% CI [1.92, 2.25]), followed by RV-A (1.77 weeks [1.68, 1.86]) and then RV-C (1.37 weeks [1.23, 1.50]).

Compared to weeks with no virus detected, weeks that were positive for any RV species had significantly greater cold symptom scores (Figure 1A). Both RV-A and C were associated with increased cold symptoms compared to RV-B ($p < 0.02$). Similarly, RV-A and RV-C were associated with greater asthma symptoms (Figure 1B) and a greater probability of exacerbation (Figure 1C) compared to RV-B. Relative to no virus detection, RV-B detection was not associated with increased cold or asthma symptoms or exacerbations of asthma.

Of the 310 participating children, 276 had at least one clinically defined respiratory illness (see online data supplement for criteria) during the study period, with a total of 755 illnesses. Compared to periods with no virus detected, RV-A, RV-C, and multiple RV were each associated with increased risk for illness (OR = 2.35, 2.61, and 2.41, $p < 0.0005$) while RV-B was not (OR = 0.99, $p = 0.95$, Supplemental Figure 1).

We next tested whether detection of bacterial pathogens was differentially related to infection with specific RV species. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* were detected in 45%, 21% and 19% of samples respectively, and were more often detected in younger children (Supplemental Figure 2). RV-C was associated with increased detection and quantity of *H. influenzae* (detection: OR 2.36 [1.65, 3.38]; quantity: ordinal OR 2.48 [1.64, 3.75]) and *M. catarrhalis* (OR 1.52 [1.04, 2.22]; ordinal OR 1.52 [1.01, 2.30]), RV-A was associated with increased *H. influenzae* (OR 2.43 [1.90, 3.10]; ordinal OR 2.60 [1.96, 3.45]) and *S. pneumoniae* (OR 1.52 [1.23, 1.89]; ordinal OR 1.97 [1.59, 2.43]), while RV-B was not associated with increased bacterial detection (Fig. 2).

We previously reported that during sampling of nasal mucus obtained in September, detection of both RVs and bacteria contributed to the probability of respiratory illness.⁵ In an analysis including samples from April and September (Supplemental Table V), detection of

RV together with either *M. catarrhalis* (OR 1.79 [1.16, 2.78]) or *H. Influenzae* (OR 1.44 [1.01, 2.05]), but not *S. pneumoniae* (OR 1.22 [0.78, 1.62]), significantly increased the probability of respiratory illness compared to infection with RV alone. When detected in the absence of virus, none of the bacterial pathogens were significantly associated with respiratory illness.

The results of this study verify that infections with RV-A and RV-C species cause more severe illnesses and are more likely associated with exacerbations of asthma than infections with RV-B. We also demonstrated that RV-A and RV-C are more likely than RV-B to be associated with detection of bacterial respiratory pathogens. Strengths of this study include the large sample size, inclusion of children with and without asthma, and prospective collection of samples during periods of illness and health. Limitations include sample collection for only two months out of the year; however, these months were selected for the highest prevalence of RV infections and asthma morbidity. In addition, there may be effects of other seasonal factors such as allergens that were not measured in this study.

These findings suggest that RV virulence could be partly related to secondary effects on the overgrowth of bacterial pathogens. This relationship is plausible, as these bacteria can stimulate inflammatory responses that might lead to airway narrowing and acute exacerbations.⁷ Accordingly, two randomized studies have demonstrated that treatment with azithromycin improves outcomes of wheezing illnesses in high-risk preschool children.^{8, 9} Mechanisms for these effects are unclear, however, and use of antibiotics for respiratory illnesses could have unintended adverse effects including selecting for drug-resistant organisms, and killing beneficial microbes. Additional studies are needed to test whether other types of treatments (e.g. vaccines, probiotics) can prevent overgrowth of bacterial pathogens during viral respiratory infections and reduce the risk of more severe illnesses and exacerbations of asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

RV rhinovirus

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Clinical Implications

Rhinovirus infections may cause clinical symptoms in part by promoting the proliferation of bacterial pathogens in the airway, suggesting that preventive treatments might target the bacterial pathogens.

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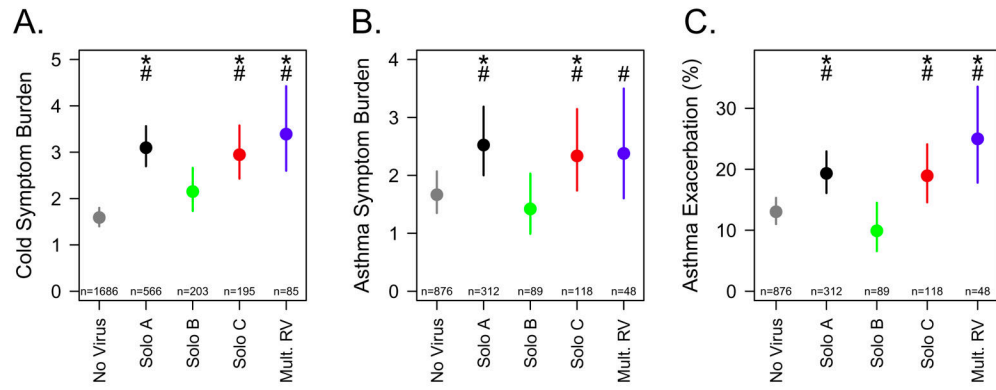


Figure 1.

Association of viral detection with clinical outcomes. Detection of RV species in weekly samples were compared to contemporaneous reports of cold symptom scores (A), asthma symptom scores (B), and risk for exacerbation of asthma (C). Points and lines represent means and 95% confidence intervals. *p<0.05 vs no virus; #p<0.05 vs RV-B.

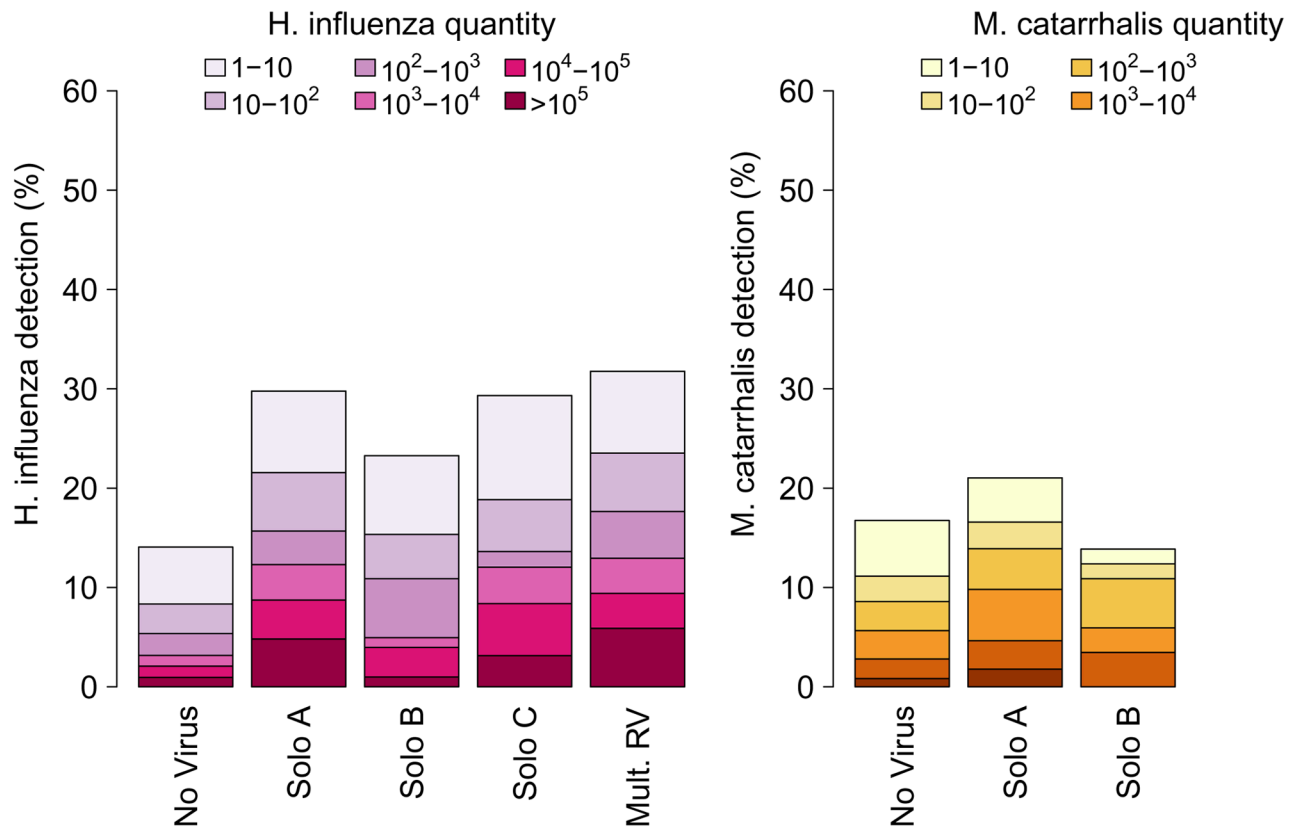


Figure 2. Association of RV species with quantity of bacterial pathogens.