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LETTER

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# How did respiratory syncytial virus and other pediatric respiratory viruses change during the COVID-19 pandemic?

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To the Editor,

The seasonal cycle of pediatric respiratory viral illnesses in temperate regions, like the United States, occurs in a similar pattern every year. Cases of respiratory syncytial virus (RSV) typically surge in the fall and winter months; then sporadic cases are seen during the spring and summer months.[1] Interestingly, in 2021 there was a drastic epidemiological shift in the prevalence of respiratory viruses, with some studies showing many cases of RSV during the spring while SARS-CoV-2 cases were still present.[2,3] This was likely due to public health interventions to reduce the transmission of respiratory viruses during the COVID-19 pandemic, which may have altered the dynamics of subsequent seasonal cycles in 2021.[2,3] As a result, the spring and summer months of 2021 offered a unique opportunity to see how RSV and other respiratory viruses changed in the presence of an emergent virus (SARS-CoV-2). In this study, we examined two questions related to this unique phenomenon: Were SARS-CoV-2 co-infections with RSV and other respiratory viruses a common occurrence during the spring/summer of 2021? Did the viral (e.g., RSV subtypes) and/or host factors (e.g., age) of pediatric respiratory viral infections change during 2021 because of the drastic epidemiological shift caused by the COVID-19 pandemic?

## 1 | METHODS AND RESULTS

We conducted a retrospective review of PCR-confirmed viral respiratory cases from March 2021 to August 2021 at Children's National Hospital in Washington, D.C. ($n = 2274$). We used available historical data from our institution (2013–2014) to examine the epidemiological shift of each virus during 2021. The Institutional Review Board of Children's National Hospital granted a waiver of informed consent given that this study involved materials (data, documents, records, or specimens) collected solely for non-research purposes (clinical indications). The data that support the findings of this study are available from the corresponding author upon reasonable request.

The total number of cases per respiratory viruses during the study period is reported in Figure 1. As reported in other parts of the globe,[2,3] we found that the epidemiology of RSV, as well as other pediatric respiratory viruses, shifted during 2021 (Figure 1A). Specifically, we identified an increased number of RSV cases during the spring/summer months of 2021 relative to historical data (Figure 1B). Furthermore, with the exception of parainfluenza viruses, the prevalence of other respiratory viruses such as rhinovirus (RV), influenza, adenovirus, and human metapneumovirus was decreased during the spring/summer of 2021 relative to our historical data from 2013 (Figure 1A).

We next conducted an analysis of RSV co-infection, including only positive cases detected by multiplex PCR. A total of 936 cases were identified after excluding SARS-CoV-2 cases detected by single PCR (which did not have other viruses tested). Notably, we identified that the number of cases with SARS-COV-2 and RSV was only 1.4% of positive RSV cases (4 out of 276; Figure 1C). The number of cases with rhinovirus and SARS-COV-2 co-infection was also only 0.19% of positive RV cases (1 out of 540; Figure 1C). This is drastically less than what was identified as co-infections with RSV and rhinovirus, which were 17.4% (Figure 1C) similarly to 2013 and 2014 (19.7% and 15%, respectively; Figure 1D), and in line with previously published data of RSV coinfections with RV and other respiratory viruses.[1] The reason why SARS-COV-2 did not cause co-infections with common respiratory viruses (RSV and RV) remains unclear but there are several possible explanations. First, viral factors (co-suppression) and virus-specific response differences in host immunity may play a role. Type I IFNs are elevated in most viral respiratory infections, but this response is diminished in COVID-19 infections in vivo and in vitro.[4,5] RSV and RV infections have been shown to enhance TH2 immune responses, which may reduce SARS-CoV2 infectivity.[6] In fact, pre-infection of airway epithelial cell cultures with RV markedly reduces SARS-CoV-2 replication.[4] Second, the host risk factors linked to severe SARS-CoV2 are very different from those seen with other respiratory viruses. While severe RSV infections usually occur in young children, increasing age is associated with greater SARS-CoV-2 severity.[5] Finally, epidemiological factors could have influenced the detection of SARS-CoV-2 co-infection with other respiratory viruses. Children were often required to get tested for daycare/school, while others may have stayed home (even with mild respiratory symptoms possibly due to RSV) out of fear of contracting SARS-CoV-2 at testing sites. In addition, many SARS-CoV-2 cases could have been asymptomatic contacts, which may have skewed the detection of clinically relevant viral co-infections.

We also examined if viral and/or host factors of pediatric respiratory viral infections were altered by the emergence of SARS-CoV2. Specifically, we examined whether the surge of RSV cases during spring/summer of 2021 was accompanied by a change in the distribution of RSV subtypes (A/B) and/or the age of the host infected. As shown in Figure 2A, during spring/summer of 2021 a greater number of RSV B cases relative to RSV A was observed, which was different relative to historical data from 2013 to 2014 (Figure 2A). This is a potentially important difference to note, as RSV subtype A has been associated with more severe disease, likely in part because RSV subtype B has a decreased ability to induce NF-κB.[1] Studies in cell culture and in vivo models also provide clear evidence that individual RSV type A isolates differ substantially in their infectivity, virulence, and immunopathogenicity.[1] Both these subtypes generally occur simultaneously and in predictable patterns in temperate regions,[1] however it is common for one subtype to become dominant over the other because of the change in the

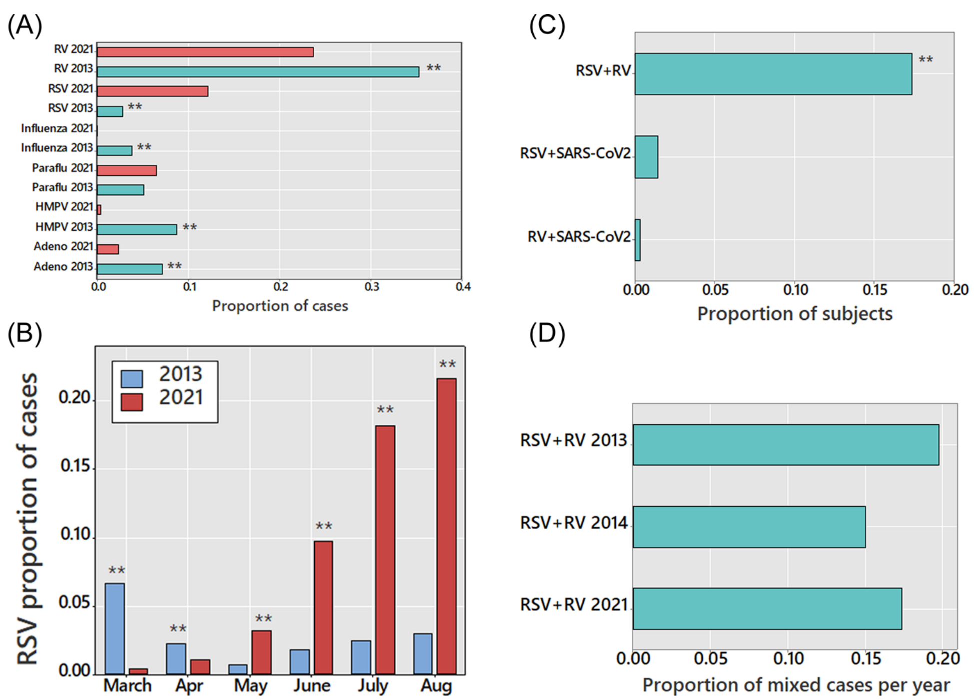


**FIGURE 1** Pediatric respiratory viral infection data during the spring/summer of 2021. (A) PCR-confirmed viral respiratory cases from March to August 2021 ($n = 2274$) and 2013 ($n = 643$) and shown as total proportion of cases (B) and monthly data for RSV. (C) Co-infections for SARS-CoV-2 and RV or RSV during 2021. (D) Comparison of proportion of RV and RSV coinfections during 2013, 2014, and 2021. $^{**}p < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

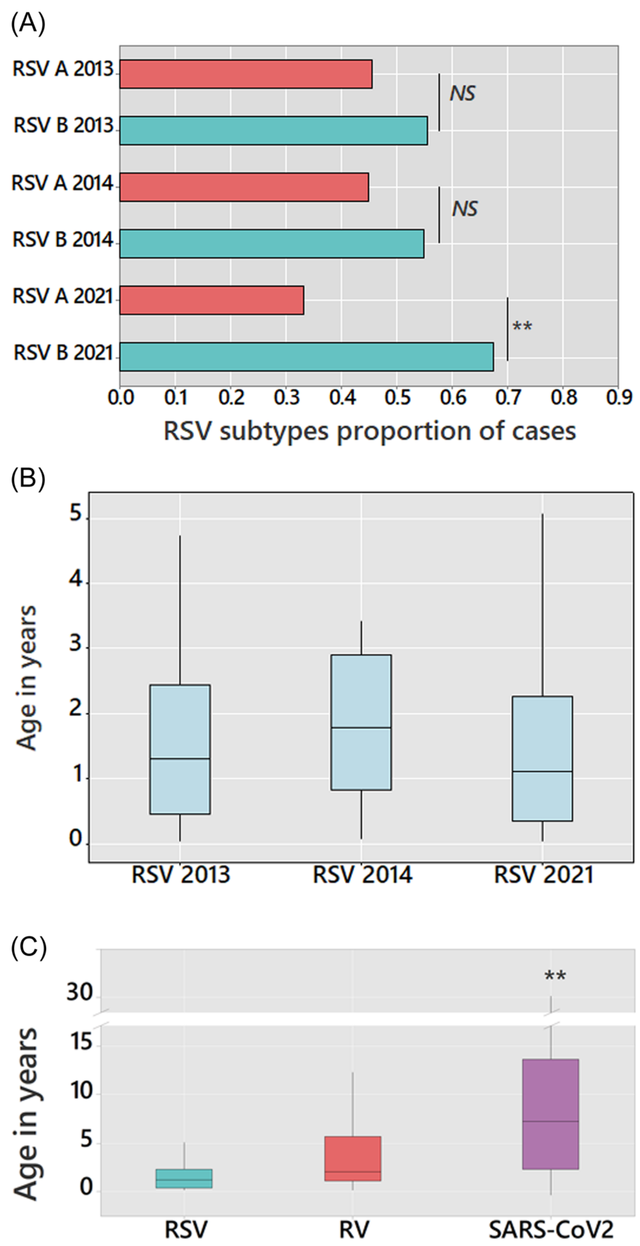


**FIGURE 2** Pediatric respiratory viral infection data during the spring/summer of 2021. (A) RSV cases for subtypes A and B from March to August in 2013, 2014, and 2021. (B) Age comparison in RSV cases during spring/summer 2013, 2014, and 2021, and (C) for RSV, RV, and SARS-CoV-2 during the spring/summer of 2021. $^{**}p < 0.01$ in (A) for pair comparisons. $^{**}p < 0.01$ in (C) for RSV versus SARS-CoV-2. NS, nonsignificant; RSV, respiratory syncytial virus; RV, rhinovirus. [Color figure can be viewed at wileyonlinelibrary.com]

environment and circulating viruses,[1] which may explain what we observed during the COVID-19 pandemic. In terms of host factors, we did not identify significant age changes in RSV cases during spring/summer of 2021 relative to prior data (Figure 2B). Overall, during 2021, we observed that RSV affected younger individuals relative to RV, and SARS-CoV-2 (Figure 2C), which is consistent with the prevailing notion that most RSV infections occur mostly during the first 2 years of life.[1]

## 2 | CONCLUSION

Our study shows that there was a significant epidemiological change in RSV and other pediatric respiratory viruses during spring/summer 2021. While most respiratory viruses were less prevalent during this period, RSV cases were increased—demonstrating a shift from the typical peak in the winter and fall to a peak in the spring and summer of the year after the beginning of the COVID-19 pandemic. The age range of individuals affected by RSV did not significantly change during 2021. Notably, we found that co-infections of either RSV or RV with SARS-CoV-2 were extremely rare and that RSV subtype B became significantly increased relative to RSV subtype A. Collectively, these data indicate that there is a complex interplay between respiratory viruses that may be linked to viral factors, host immunity, individual susceptibility, and epidemiological factors. Additional studies are needed to understand how RSV and other pediatric respiratory viruses interact with each other and may change in the presence of an emergent pathogen like SARS-CoV-2. The molecular mechanisms governing the coregulation of mixed viral respiratory infections, including beneficial or deleterious effects in infectivity, host immunity and clinical outcomes should be further explored in human-based studies, as recently reported.[4] Through further investigations and pediatric data analysis of the COVID-19 pandemic, we may be able to determine whether co-infections with SARS-CoV-2 result in worse acute and/or long-term outcomes; we can also discern if the incidence of certain respiratory viral subtypes are decreased either directly by SARS-CoV-2 or only indirectly by ever-changing community viral mitigation measures including social distancing, masking, and vaccinations.

### AUTHOR CONTRIBUTIONS

**Gustavo Nino, Ryan Kahanowitch:** Conceptualization; data collection. **Ryan Kahanowitch, Hector Aguilar Giuliana Gayoso, Susana Gaviria:** Drafting, analysis and review of literature. **Elizabeth Chorvinksy, Betelehem Bera, Maria J. Gutierrez, Carlos E. Rodríguez-Martínez, Gustavo Nino:** Final writing. **Gustavo Nino, Ryan Kahanowitch:** Approval of final manuscript.

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### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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