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LETTER

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Respiratory syncytial virus and SARS-CoV-2 coinfections in children

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To the Editor,

The measures implemented during the COVID-19 pandemic resulted in an off-seasonal surge of respiratory syncytial virus (RSV) infections that coincided with the Delta wave in the US in the summer of 2021. Despite the high number of RSV (>2000) and severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) (>6000) infections identified in children in our center during that period, the proportion of children with RSV/SARS-CoV-2 codetections was low (3%). Nonetheless, we identified a severe clinical phenotype in children with RSV/COVID-19 coinfections. On the basis of viral loads, it appeared that clinical outcomes were worse in children with convalescent COVID and acute or convalescent RSV infection.

RSV is the leading cause of acute lower respiratory tract infections (LRTI) in infants and young children globally. The seasonality of RSV has been greatly impacted by the COVID-19 pandemic. After RSV "skipped" a traditional respiratory season during the first year of the pandemic, an unprecedented off-season surge of RSV was experienced in many countries, including the USA, during the summer of 2021.[1] At Nationwide Children's Hospital (NCH), in Columbus, OH, USA, the 2021 RSV season started June 26th, after greater than 10% positivity rates for RSV were documented for 2 consecutive weeks. The season lasted until December 18, 2021, with a total of 2324 RSV infections identified by rapid antigen testing or polymerase chain reaction (PCR) during that period. The peak of RSV activity coincided with an increase in the circulation of the SARS-CoV-2 Delta variant, with 6744 confirmed COVID-19 infections in children at NCH during that period (Figure 1). Since mid-December 2021, the circulation of RSV decreased with 3%–5% positivity rates as of April 2022.

To determine whether RSV/SARS-CoV-2 coinfections occurred and if they were associated with different clinical phenotypes, we identified children with RSV and SARS-CoV-2 codetection using the FilmArray Respiratory Panel (BioMérieux), which allows for the simultaneous detection of 22 pathogens including RSV and SARS-CoV-2 in naso-pharyngeal (NP) samples.[2] We then performed a retrospective chart review and analyzed the clinical characteristics of children that were hospitalized with RSV/SARS-CoV-2 codetection as missing data extracted from electronic health records was negligible compared with outpatients. To further ascertain the impact of SARS-CoV-2, RSV, or both on clinical presentations, we prospectively identified the NP samples corresponding to those patients and performed individual reverse transcription-PCRs for SARS-CoV-2 and RSV, as the FilmArray panel does not provide viral load information. We used two separate laboratory-developed PCR assays. The SARS-CoV-2 PCR assay was based on the probes and primers developed by the Center for Disease Control and Prevention that targeted two regions of the N gene as described.[3] The RSV PCR assay targeted the F gene using the following primers and probes: RSVA: F5′ GTAAGCAGCTCCGTTATCACATCTC3′; R5′TATTGGATGCTGTACATTT

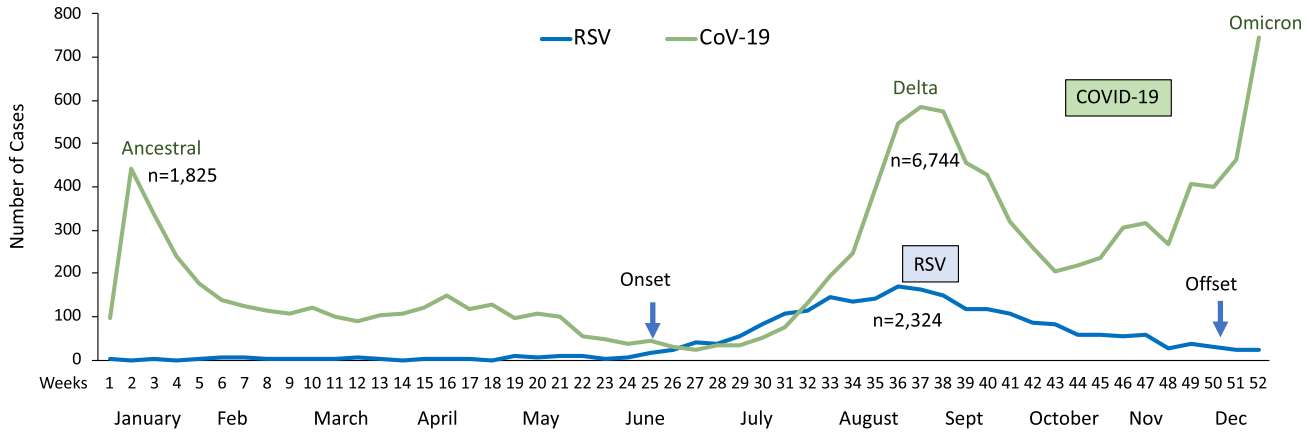

FIGURE 1 Total number of positive tests at Nationwide Children's Hospital for RSV and COVID-19 from January to December 2021. Epidemiologic weeks are depicted below the *x*-axis. The arrows indicate the 2021 RSV season onset and offset. RSV, respiratory syncytial virus. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of hospitalized children with SARS-CoV-2/RSV coinfections

	Group 1 aRSV/aCOVID-19 (*n* = 5)	Group 2 aRSV/cCOVID-19 (*n* = 8)	Group 3 cRSV/cCOVID-19 (*n* = 5)	*p*-value
Age (months)	4 (2-36)	6.5 (1–12.5)	8 (3–19)	0.72
Male sex	2 (40.0%)	5 (62.5%)	4 (80.0%)	0.60
Oxygen administration	2 (40.0%)	4 (50.0%)	3 (60.0%)	1.00
ICU admission	1 (20.0%)	5 (62.5%)	3 (60.0%)	0.48
Mechanical ventilation	0 (0.0%)	2 (25.0%)	0 (0.0%)	0.47
Duration of hospitalization	2 (1–3)	6.5 (5–17.5)	5 (4–6)	0.02

Note: Oxygen administration including invasive and noninvasive ventilation. Continuous variables are expressed as medians (25%–75% IQR) and analyzed by Kruskal–Wallis, and categorical data as numbers and percentages and analyzed using χ^2.

Abbreviations: a, acute; c, convalescent; ICU, intensive care unit; IQR, interquartile range; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

RGTTTTGC-3′; P5′VIC-AGGAGCCATTGTGTCATG-3′, and RSVB: F5′ TCAATAAGCAAGAAGAGGAAACGA-3′; R5′ACTTGCTATTGCAGATCC TACACCTA-3′; P5′FAM-ATTTCTGGGCTTCTTC-MGB-3′. Using these assays, we obtained cycle threshold (C_t) values for each virus separately as a surrogate of semiquantitative viral loads, acknowledging that those values are nonstandardized.[4] The study was approved by the Institutional Review Board at NCH.

From May 2021 to April 2022, to include the tales of the RSV season, we identified 1974 children with RSV infection using the FilmArray panel. Of those, SARS-CoV-2 was codetected in 3% (60/1974). During that same period rates of codetection of other respiratory viruses in children with RSV were higher and ranged from 9% with adenovirus to 27% with rhinovirus/enterovirus (RV/EV) (Supporting Information: Table 1).

The median age of children with SARS-CoV-2/RSV codetection was 1.8 (interquartile range [IQR]: 0.4–5.5) years, 47 (78.3%) were ≤5 years of age, and 18 (30%) were hospitalized. Among the 18 children hospitalized with RSV/SARS-CoV-2 codetection, the median age was 6 months (IQR: 2–36 months), and the majority were infants (12/18; 66.7%), with no underlying chronic medical conditions (16/18; 89%). Overall, 9 of those 18 children (50%) received oxygen supplementation and 9 (50%) required intensive care unit (ICU) admission. To assess the impact of viral loads on the clinical presentation and outcomes, children were stratified according to RSV and SARS-CoV-2 C_t values. On the basis of previous studies and clinical practice, we used a C_t value of 30 as the cutoff to stratify children as moderate-high ($C_t < 30$) or low viral loads ($C_t \geq 30$) for each of the two respiratory viruses (Supporting Information: References). We identified three groups of children (Table 1). Children in *Group 1* (acute infections; $n = 5$) with high viral loads for both: RSV (C_t [20–23]) and SARS-CoV-2 (C_t [17–26]); those in *Group 2* (acute RSV/convalescent COVID-19; $n = 8$) with high RSV viral loads (C_t [20–29])/low SARS-CoV-2 viral loads (C_t [32–38]); and children in *Group 3* (convalescent infections; $n = 5$) with low viral loads for both viruses (C_t: RSV [32–37]; SARS-CoV-2 [30–38]). We did not identify children with convalescent RSV/acute COVID-19 based on C_t values and thus a fourth group was not included. The median age for children in

Group 1 and Group 2 was 4 months, and 8 months for those in Group 3. Two children had underlying comorbidities, a 9-month-old born at 29 weeks of gestation and with no additional risk factors (in Group 2), and a healthy 3-month-old born at 36 weeks of gestation (in Group 3). We found that 62.5% of children in Group 2 and 60% in Group 3 required ICU admission compared with 20% of children in Group 1 ($p = 0.48$). The duration of hospitalization was significantly higher in children in Group 2 with acute RSV/convalescent COVID-19. Only two patients, also in Group 2, required mechanical ventilation. Three children had codetection of additional respiratory viruses, one in Group 1 with RV/EV, and two children in Group 2 one with RV/EV and the other with RV/EV/parainfluenza virus, respectively.

Despite the limitations of the small sample size and single-center experience, we found that the rates of RSV/SARS-CoV-2 coinfections were lower than that expected based on previous experience with endemic coronaviruses, which typically range from 8% to 12%,[5] suggesting the possibility of viral interference. In fact, before the COVID-19 pandemic endemic coronaviruses have been the second most common codetected viruses in infants with RSV-LRTI. In addition, for reasons that are not fully known this initial report suggests that convalescent SARS-CoV-2 infections in the context of RSV coinfection might be associated with increased severity. We found that the proportion of children with that phenotype requiring ICU admission was higher than the 10%–30% described for RSV alone, or the 10%–20% that has been reported for SARS-CoV-2 single infections in healthy infants and young children.[6] It is unclear why we did not identify children with convalescent RSV/acute COVID-19. Future studies across different seasons are needed to assess whether a prior RSV infection confers protection against SARS-CoV-2 infections or if it was merely absent due to our small sample size. These initial observations have important clinical implications. Although the timing of the next RSV season remains speculative, the continued circulation of SARS-CoV-2 variants with higher tropism for the upper respiratory tract makes it likely that SARS-CoV-2/RSV coinfections will continue to occur. This study also emphasizes the importance of continued surveillance with assays that detect multiple respiratory viruses, not only to define and track epidemiologic trends but for infection prevention purposes and to help with patient clinical management. Further studies are needed to better understand the interplay between SARS-CoV-2 and RSV and the mechanisms associated with disease severity.

AUTHORS CONTRIBUTIONS

Katia C. Halabi: Formal analysis, data curation, investigation, and writing–original draft and editing. **Huanyu Wang**: Investigation, data curation, writing, and editing. **Amy L. Leber**: Investigation, writing, and editing. **Pablo J. Sánchez**: Investigation, writing, and editing. **Octavio Ramilo**: Investigation, writing, and editing. **Asuncion Mejias**: Manuscript conceptualization, investigation, data curation, visualization, supervision, and writing and editing.

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CONFLICTS OF INTEREST

Asuncion Mejias has received research grants from the National Institutes of Health (NIH), Janssen, and Merck to institutions, fees for participation in advisory boards from Janssen, Sanofi-Pasteur, and Merck, and fees for educational lectures from Sanofi-Pasteur and AstraZeneca. Octavio Ramilo has received research grants from NIH, the Bill & Melinda Gates Foundation, Merck, and Janssen to institutions; fees for participation in advisory boards from Merck, Sanofi-Pasteur, Adagio, Lilly, and Pfizer; and fees for lectures from Pfizer, Sanofi-Pasteur, and AstraZeneca. Amy L. Leber has received research grants from Biofire, Cephied, Luminex, and Diasorin, and consulting fees from Medscape, Biorad, and Biofire. The remaining authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.