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RESPIRATORY SYNCYTIAL VIRUS IN OUTPATIENT CHILDREN WITH BRONCHIOLITIS

Continuous Virus Circulation During the Nonepidemic Period

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Abstract: We aimed to estimate the respiratory syncytial virus positivity rate among ambulatory children with bronchiolitis according to the bronchiolitis epidemic period as defined by the French Public Health Institute. The positivity rate was 28.9% during the nonepidemic period and 50.6% during the epidemic period, which suggests continuous virus circulation between bronchiolitis annual peaks.

Key Words: respiratory syncytial virus, bronchiolitis, nonpharmaceutical intervention, epidemic period

Accepted for publication August 3, 2023

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A.R. received personal fees from MSD and Sanofi and nonfinancial support from Pfizer and AstraZeneca. R.C. received personal fees and nonfinancial support from Pfizer; reported personal fees from Merck, GSK, Sanofi and AstraZeneca outside the submitted work. R.K. and M.B. are employed by Sanofi. C.L. received personal fees and nonfinancial support from Pfizer and Merck outside the submitted work. The other authors have no conflicts of interest to disclose.

This work was supported by Sanofi Pasteur and by AstraZeneca.

Data are available upon reasonable request.

Study conception: A.R., R.C., R.K., S.B., M.B. and C.L. Data collection: R.C., J-F.D., V.D., F.V.L.S., P.D. and A.W. Data analysis and interpretation: A.R., R.C., R.K., S.B., M.B. and C.L. Drafting the manuscript: A.R., R.C., R.K., S.B., M.B. and C.L. Revising the manuscript for important intellectual content: all authors. Approved the final version submitted: all authors. Study supervision: A.R., R.C., R.K., S.B., M.B. and C.L.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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DOI: 10.1097/INF.0000000000004105

Respiratory syncytial virus (RSV) infection is a major cause of death in low-income countries and hospitalization in high-income countries.[1] RSV is also associated with a high outpatient burden.[2] Because of the lack of curative or preventive therapeutics available in the general population, reducing this burden remains a global challenge.[1]

Bronchiolitis is the most characteristic clinical syndrome, constitutes the best proxy for RSV epidemics,[3] and is the main cause of hospitalizations in young children.[4]

Several countries have a national RSV surveillance network.[5,6] However, most RSV cases are detected at hospitals in patients with bronchiolitis and/or acute respiratory infection. Surveillance data in primary care is scarce,[5] despite the significant burden of RSV detected in the outpatient setting.[2]

Before the COVID-19 pandemic, epidemics of bronchiolitis occurred annually in the winter season, so surveillance networks focused on this period.[5] This timing allowed healthcare systems to prepare for the annual bronchiolitis epidemic. In February/March 2020, unprecedented nonpharmaceutical interventions were implemented globally to reduce the spread of COVID-19. These measures had a striking and immediate impact on viral and nonviral diseases, which led to major epidemiologic changes in bronchiolitis epidemics.

In this context, in February 2021, we started a study on RSV diseases in outpatient children that used rapid antigen detection tests for RSV, influenza viruses (A and B) and SARS-CoV-2.[7] Because of an unusual epidemic duration and seasonality of bronchiolitis and the interest in detecting the 3 other viruses, the study continued even after the annual epidemic period was finished.

This strategy allowed us to estimate the RSV positivity rate among ambulatory children with bronchiolitis during and outside the epidemic periods, which we report here.

METHODS

In France, parents have the choice to visit pediatricians or general practitioners as first-line clinicians for their children. In addition, children <6 years old can visit free public centers (mother and infant health protection centers) which are mainly for follow-up visits and immunizations than for acute illnesses. About 40% of the visits for children <1 year old, and 30% for children <2 years old are by pediatricians. For children <2 years old, about 65% of the visits are performed by general practitioners.[8] For this study (outpatients respiratory syncytial virus study), children were enrolled by 45 pediatricians from the pediatric and ambulatory research in infectious diseases network between February 9, 2021 and May 2, 2022.[7] These pediatricians were located in 10 of the 13 regions in metropolitan France. Children <2 years old with a first episode of bronchiolitis were prospectively enrolled after parental written informed consent.[7] As required by the French law, research study participation was only proposed for children with social health insurance. Bronchiolitis was defined as the association of 1 or more symptoms among fever, cough, otalgia, rhinopharyngitis or decrease in appetite with 1 or more symptoms among wheezing, crackles, diminished vesicular murmur and breathing difficulties.[7] For each patient, a single nasopharyngeal swab was taken for triple rapid diagnostic testing for RSV, SARS-CoV-2 and influenza. The BioSynex triple test (BioSynex Combo COVID-FLU-RSV BSS test) was used for younger children with small nostrils while for older children, the triple test AAZ (COVID-VIRO ALL IN TRIPLEX; AAZ-LMB) was used. Then, the pediatrician completed an electronic case report form in a secure database. Data on hospitalization were completed at day 0 by the pediatrician who enrolled the patient.

For each patient, we created a variable corresponding to the weekly regional bronchiolitis epidemic level as defined by the French National Public Health Institute (Santé Publique France). We assumed that the patient lived in the same region as their pediatrician. We compared the following epidemic levels: no epidemic, pre- or post-epidemic and epidemic.

Categorical variables were analyzed by χ^2 test or Fisher exact test and quantitative variables by ANOVA. Statistical tests were 2-sided, with $P < 0.05$ considered statistically significant. All

statistical analyses involved using STATA v15.1 (https://www.stata.com/).

The study was approved by an ethics committee (Ile-de-France 1, 2020-A02876-33) and was registered at ClinicalTrials.gov (NCT04743609).

RESULTS

During the study period, 984 outpatients <2 years old with a first episode of bronchiolitis were included: 583 (59.3%) were boys (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/F254). Figure 1 details the weekly number of bronchiolitis cases enrolled and RSV-positive cases over time. Overall, 437/983 (44.4%) children were positive for RSV, 11/978 (1.1%) for influenza A and/or B and 26/978 (2.7%) for SARS-CoV-2. During the study, the RSV positivity rate was 28.9% [95% confidence interval (CI): 23.5–34.8] for children presenting bronchiolitis during the nonepidemic period versus 45.2% (95% CI: 32.5–58.3) during the pre- or post-epidemic period and 50.6% (95% CI: 46.6–54.4) during the epidemic period. Rates of hospitalization at day 0 were higher for children with a positive than negative RSV test result [16/420 (3.7%) vs. 8/530 (1.5%), $P = 0.03$]. Influenza and SARS-CoV-2 positivity rates were 4.6% and 2.3% during the nonepidemic period, 4.8% and 0% during the pre- and post-epidemic period and 1.7% and 0.8% during the epidemic period, respectively.

DISCUSSION

We report that 50.6% of outpatients <2 years old in this study had a positive RSV test result when presenting a first episode of bronchiolitis during the epidemic period. Of note, during the nonepidemic period, the RSV positivity rate was substantial (28.9%). However, this rate should be interpreted considering the low bronchiolitis incidence during these periods, for example, the incidence of bronchiolitis in children <2 years old ranged from 176 to 2152/10,000 emergency visits over the study period in the region (Ile-de-France), where most children were enrolled.[9]

The off-season RSV circulation remains unclear.[10] Between 2010 and 2016, 15 European countries with a national RSV surveillance network reported a quasi-absence of RSV detection between the epidemic periods.[6] RSV may continue to circulate in older children and adults during the off-season period.[1] Our results showed continuous RSV isolation without a concomitant bronchiolitis epidemic. These results support that some conditions, independent of viral circulation, may be necessary for an outbreak. This situation can be compared to a fire spark in a wet forest versus a spark during a dry summer. First, people's behavior during winter, with increased indoor interaction in poorly ventilated rooms, may explain in part a higher viral transmission.[11] The role of poor indoor ventilation in airborne pathogen dissemination was particularly described during the COVID-19 pandemic.[12] Second, the RSV antibody level in the population may play a major role. Indeed, a strong temporal association between low maternal antibodies from cord-blood samples at birth and RSV outbreak suggested that RSV infection in adults may induce cyclic RSV outbreaks.[13] A higher RSV antibody level may prevent the epidemic during the nonepidemic period.

Our results question the definition of the RSV epidemic, which is used especially for the beginning of immunoprophylaxis against RSV and the epidemic period. In France, the definition uses the data on physician visits for bronchiolitis, which could differ from RSV circulation. Continuous surveillance may be required because RSV infection is not limited to the epidemic periods, particularly in ambulatory care.

The main limitation of our study is the use of a rapid antigen detection test rather than PCR. Although the specificities of

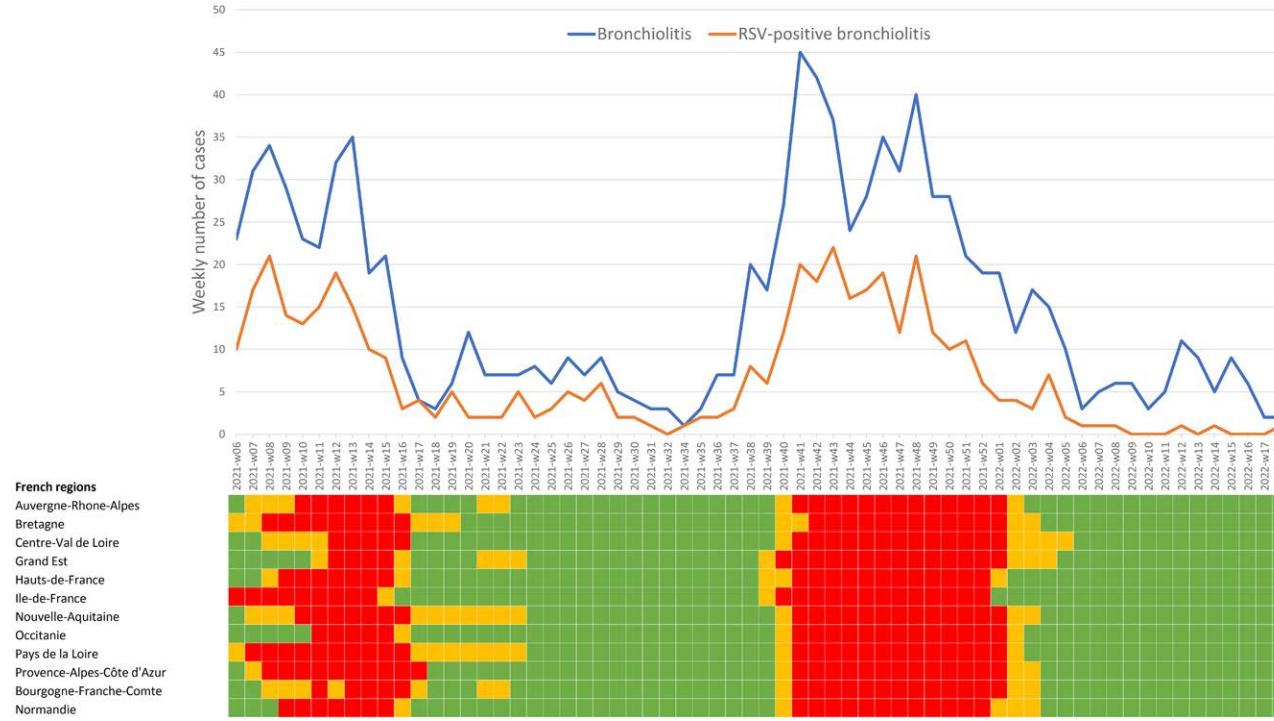

FIGURE 1. Weekly number of bronchiolitis and respiratory syncytial virus (RSV)-positive cases over time along with the regional bronchiolitis epidemic level according to Santé Publique France. No epidemic (green), pre- or post-epidemic (orange) and epidemic (red).

the test for these viruses are excellent (>95% and in some studies close to 100%), the sensitivities are not optimal (between 75% and 95%).[14,15] However, if the sensitivity seems to be better in children than adults, we have certainly underestimated the burden of these viruses and particularly RSV. Different clinical situations (e.g., clinical laboratory of the hospital vs. ambulatory care) will require different diagnostic solutions, considering the ease of sample collection, the absence of equipment, the time of the result and especially the cost. In ambulatory pediatrics, the rapid antigen test seems an acceptable compromise: the use of rapid antigen tests optimized and facilitated enrollment in primary care. The second limitation is the absence of data before the COVID-19 pandemic. Nonpharmaceutical interventions have induced major RSV epidemiological changes, and long-term RSV surveillance would help support our findings.

In conclusion, surveillance systems may need to consider continuous surveillance to accurately capture and describe RSV circulation in the COVID-19 era, especially to inform the start of immunoprophylaxis against RSV. Monitoring multiple viruses (RSV, influenza, SARS-CoV-2) may help optimize the value of year-round surveillance systems.

ACKNOWLEDGMENTS

We are grateful to the investigators of the OURSYN study: Andre Jean-Marie, Ansoborlo Sophie, Auvrignon Anne, Bakhache Pierre, Batard Christophe, Bellemin Karine, Cahn Sellem Fabienne, Cheve Anne, Cohen Robert, Dagrenat Véronique, Deberdt Patrice, Delavie Nadège, Delobbe Jean-François, Desandes Roxane, Desvignes Véronique, D'ovidio Nadia, Dubreuil Barbara, Devuldier Christine, Elbez Annie, Gebhard Françoise, Gelbert Nathalie, Gorde Grosjean Stéphanie, Grue-Fertin Pascaline, Hassid Frédéric, Kherbaoui Louisa, Kochert Fabienne, Langlais Sophie, Le Mouel Fanny, Lecailler Francine, Louvel Murielle, Michot Cottias Anne-Sylvestre, Nold Bénédicte, Pressac Isabelle, Ravilly Sophie, Roques Gaëlle, Salaun Jean-François, Sellam Aurélie, Seror Elisa, Thiebaylt Georges, Thollot Franck, Vie Le Sage François, Vigreux Jean-Christophe, Werner Andreas, Wollner Alain, Zouari Morched.

The authors are grateful to the Association Clinique Thérapeutique Infantile du Val de Marne (ACTIV) team for their technical assistance: Isabelle Destel, Mathilde Servera, Isabelle Ramay, Pauline Daumerie, Johanna Chalte and Aurore Prieur. We thank Laura Smales (http://www.biomedediting.com) for editing the manuscript for English language

REFERENCES

1. Pinquier D, Crepey P, Tissieres P, et al. Preventing respiratory syncytial virus in children in France: a narrative review of the importance of a reinforced partnership between parents, healthcare professionals, and public health authorities. *Infect Dis Ther*. 2023;12:317–332.
2. Barbieri E, Cavagnis S, Scamarcia A, et al. Assessing the burden of bronchiolitis and lower respiratory tract infections in children </=24 months of age in Italy, 2012-2019. *Front Pediatr*. 2023;11:1143735.
3. Schindeler SK, Muscatello DJ, Ferson MJ, et al. Evaluation of alternative respiratory syndromes for specific syndromic surveillance of influenza and respiratory syncytial virus: a time series analysis. *BMC Infect Dis*. 2009;9:190.
4. Demont C, Petrica N, Bardoulat I, et al. Economic and disease burden of RSV-associated hospitalizations in young children in France, from 2010 through 2018. *BMC Infect Dis*. 2021;21:730.
5. Staadegaard L, Caini S, Wangchuk S, et al. The global epidemiology of RSV in community and hospitalized care: findings from 15 countries. *Open Forum Infect Dis*. 2021;8:ofab159.
6. Broberg EK, Waris M, Johansen K, et al. Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016. *Euro Surveill*. 2018;23:17–00284.
7. Rybak A, Levy C, Jung C, et al. Delayed bronchiolitis epidemic in French primary care setting driven by respiratory syncytial virus: preliminary data from the OURSYN study, march 2021. *Pediatr Infect Dis J*. 2021;40:e511–e514.
8. Inspection générale des affaires sociales. *La pédiatrie et l'organisation des soins de santé de l'enfant en France*. Available at: https://www.igas.gouv.fr/IMG/pdf/2020-074r.pdf. Accessed August 2, 2023.
9. Santé Publique France. *Observatoire Géodes*. Available at: https://geodes.santepubliquefrance.fr/?view=map2&indics=sursaud_bronchio.prop_bronchio_pass_sau&lang=fr&iframe=1. Accessed June 14, 2023.
10. Griffiths C, Drews SJ, Marchant DJ. Respiratory syncytial virus: infection, detection, and new options for prevention and treatment. *Clin Microbiol Rev*. 2017;30:277–319.
11. Mallapaty S. Why COVID outbreaks look set to worsen this winter. *Nature*. 2020;586:653.
12. Wang CC, Prather KA, Sznitman J, et al. Airborne transmission of respiratory viruses. *Science*. 2021;373:eabd9149.
13. Stensballe LG, Ravn H, Kristensen K, et al. Seasonal variation of maternally derived respiratory syncytial virus antibodies and association with infant hospitalizations for respiratory syncytial virus. *J Pediatr*. 2009;154:296–298.
14. Chartrand C, Tremblay N, Renaud C, et al. Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: systematic review and meta-analysis. *J Clin Microbiol*. 2015;53:3738–3749.
15. Ferrani S, Prazuck T, Béchet S, et al. Diagnostic accuracy of a rapid antigen triple test (SARS-CoV-2, respiratory syncytial virus, and influenza) using anterior nasal swabs versus multiplex RT-PCR in children in an emergency department. *Infect Dis Now*. 2023;53:104769.

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HUMAN PARECHOVIRUS CENTRAL NERVOUS SYSTEM INFECTION IN A YOUNG INFANT COHORT

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Abstract: In 2022, a surge in cases of pediatric human parechovirus (HPeV) central nervous system infections in young infants was seen at our institution. Despite the dramatic increase in the number of cases seen that year, the clinical features of the illness were similar to prior years. The recent pediatric HPeV surge highlights the need to evaluate treatment options and standardize follow-up to better understand the long-term prognosis of infants with HPeV infection.

Key Words: infants, neonates, human parechovirus, CNS, immunoglobulin

Accepted for publication August 28, 2023
The authors have no funding or conflicts of interest to disclose.
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DOI: 10.1097/INF.0000000000004122