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MAJOR ARTICLE

Use of Rapid Antigen Triple Test Nasal Swabs (COVID-VIRO ALL-IN TRIPLEX: Severe Acute Respiratory Syndrome Coronavirus 2, Respiratory Syncytial Virus, and Influenza) in Children With Respiratory Symptoms: A Real-life Prospective Study

Robert Cohen,[1,2,3,4,5] Hervé Haas,[5,6] Olivier Romain,[5] Stéphane Béchet,[1,4] Catherine Romain,[5] Camille de Truchis de Lays,[5,7] Alain Wollner,[1,4] Cécile Guiheneuf,[4] Loic de Pontual,[5,7] and Corinne Levy[1,2,3,4,5,]

[1]Pediatric Department, Association Clinique et Thérapeutique Infantile du Val-de-Marne, Créteil, France, [2]Clinical Research Center, Centre Hospitalier Intercommunal de Créteil, Créteil, France, [3]Institut Mondor de Recherche Biomédicale-Groupe de Recherche Clinique, Groupe d'Etude des Maladie Infectieuses Néonatales et Infantiles, Université Paris Est, Créteil, France, [4]Pediatric Department, Association Française de Pédiatrie Ambulatoire, Orléans, France, [5]Pediatric Department, Groupe de Pathologie Infectieuse Pédiatrique, Créteil, France, [6]Service de pédiatrie, Hôpital Princesse Grace, Monaco, and [7]Service de pédiatrie, Hôpital Avicenne, Assistance Publique–Hôpitaux de Paris, Bondy, France

Background. In autumn 2022, the epidemics due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), and influenza overlapped, and these diseases can present with the same symptomatology. The use of a triple antigen test (SARS-CoV-2 + influenza A/B + RSV) seems crucial for accurate viral diagnosis in the context of implementing long-acting monoclonal antibody vaccination against RSV in the upcoming RSV season.

Methods. We assessed the usefulness of the triple test in real life in this prospective study performed from October 2022 to May 2023 and involving 116 pediatricians (2 emergency department pediatricians and 114 ambulatory pediatricians). Children <15 years old with flu-like illness (with fever), bronchiolitis (dyspnea ± wheezing), otitis, and croup were enrolled and sampled with a nasal triple test.

Results. For 8329 children with flu-like illness (65.3%), bronchiolitis (17.9%), otitis (8.8%), and croup (6.3%), the use of the triple test led to a viral diagnosis in 47.9% of cases. The highest RSV positivity occurred in children with bronchiolitis (32.9%). The highest influenza A and B positivity (24.6% and 19.6%) occurred in children with flu-like illness. A succession of 3 epidemics (RSV and influenza A and B) occurred over time with several overlap periods.

Conclusions. The triple test allowed for a viral diagnosis in half of our cases. The upcoming introduction of RSV prevention will emphasize the need for active surveillance with viral results both in ambulatory settings and hospitals.

Clinical Trials Registration. NCT0441231.

Keywords. children; influenza; rapid antigen test; respiratory tract infection; RSV.

From the beginning of the coronavirus disease 2019 (COVID-19) pandemic, guidelines related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing in symptomatic children were implemented in many countries [1]. In France, the first guidelines were published in September 2020, and many changes occurred during the different pandemic waves [2]. For children, the safe return to school (or daycare center) had driven the testing strategies to control the virus transmission [3–5]. Several studies have shown that the clinical symptoms induced by SARS-CoV-2 in ambulatory children are not specific or sensitive and may cover the whole range of clinical syndromes induced by respiratory viruses in children—for example, the common cold, pharyngitis, flu-like illness, bronchiolitis, otitis, and croup [2].

During the first 2 years of the COVID-19 pandemic, with the implementation of nonpharmaceutical interventions (NPIs), annual epidemics of major respiratory viruses such as influenza or respiratory syncytial virus (RSV) have not occurred or have shown modest intensity [6]. In autumn 2022, with the lifting of NPIs, respiratory epidemics such as RSV or influenza returned to extremely high levels, with SARS-CoV-2 continuing to circulate at low to intermediate levels [7]. In many countries, the epidemics due to SARS-CoV-2, RSV, and influenza overlapped, and the pediatric healthcare system in ambulatory settings

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Correspondence: Corinne Levy, Association Clinique et Thérapeutique Infantile du Val-de-Marne, 31 rue Le Corbusier, 94000 Créteil, France (corinne.levy@activ-france.fr); Robert Cohen, Association Clinique et Thérapeutique Infantile du Val-de-Marne, 31 rue Le Corbusier, 94000 Créteil, France (robert.cohen@activ-france.fr).

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and hospitals was strained [8]. All viral respiratory infections obviously impose hygiene measures while the identification of these viruses may lead to particular therapy or school or day-care center duration exclusion. Moreover, the accurate viral diagnosis—by reducing diagnostic uncertainty—enables the appropriate prescription of antiviral drugs or even contributes to reduce the prescription of antibiotics [9].

Performing 3 different tests to distinguish these viruses when epidemics overlap is time-consuming for healthcare workers and uncomfortable and unpleasant for children even if not painful. Indeed, children, most families, and practitioners have become reluctant to have the tests performed [4, 6, 10–13]. A recent study showed acceptable clinical performance of a SARS-CoV-2 + influenza A/B + RSV combined test as compared with multiplex reverse-transcription polymerase chain reaction (RT-PCR) [10]. Moreover, a rapid antigen triple test from self-collected anterior nasal swabs (COVID-VIRO ALL-IN TRIPLEX, SARS-CoV-2 + influenza A/B + RSV) in children showed better performance results [14]. In our knowledge, no study has evaluated the relevance and usefulness of a triple antigen test in real life for children with symptoms suggesting viral respiratory tract infections. Therefore, the aim of our study is to provide data regarding the viral respiratory diagnosis according to different clinical syndromes during the respiratory virus season prior to the licensure of RSV preventive approaches [15, 16].

Patients and Methods

From October 2022 to May 2023, we performed a manufacturer-independent, cross-sectional, prospective, multicenter study. Among the 116 pediatric centers throughout France, 2 involved pediatric emergency department pediatricians and 114 ambulatory care pediatricians. The pediatricians involved in this study were those of the Association Clinique et Thérapeutique Infantile du Val-de-Marne (ACTIV) network [6]. After informing the parents of the participating children about the study (information sheet), an electronic case report form (eCRF) was prospectively completed by the pediatrician in a secure database.

This study was part of the VIGIL study, with methods described previously [17, 18]. In brief, the study enrolled symptomatic children <15 years old who presented respiratory symptoms; children were administered a nasal triple test for SARS-CoV-2 + influenza A/B + RSV: COVID-VIRO ALL-IN TRIPLEX (AAZ-LMB, Boulogne-Billancourt, France) [14, 19]. The recommended sampling duration was 30 seconds (15 seconds per nostril) [20]. To evaluate the interest of the triple test according to the symptoms, we defined 4 groups of clinical syndromes that were mutually exclusive: bronchiolitis (dyspnea with or without wheezing, with or without otitis, croup, and fever), otitis (without bronchiolitis, with or without croup and fever), croup (without otitis/bronchiolitis, with or without fever), and flu-like illness (with fever, without otitis/bronchiolitis/croup).

Although the performance of this triple antigen test was already published [14], we did a validation on a subset of hospitalized patients. The methodology and the results of this validation are summarized in the Supplementary Materials.

Data were entered in the eCRF (PHP/MySQL) and analyzed by using Stata/SE version 15 software (StataCorp, College Station, Texas). Quantitative data were compared by Student *t* test and categorical data by χ^2 or Fisher exact test. Confidence intervals (CIs) were calculated using exact binomial (Clopper–Pearson) method. All tests were 2-sided, and results were considered significant at $P < .05$.

Patient Consent Statement

The protocol was approved by an ethics committee (Centre Hospitalier Intercommunal de Créteil, France) and was registered at ClinicalTrials.gov (identifier NCT0441231). Our study does not include factors necessitating patient consent. Any child or parent had the right to object to the data collection for this study.

RESULTS

From October 2022 to May 2023, 8329 children (mean age, 3.7 ± 3.1 years; median, 3.0 years) were sampled. Boys accounted for 54.2% of cases. Flu-like illness, bronchiolitis, otitis, and croup accounted for 65.3% (5440/8329), 17.9% (1488/8329), 8.8% (732/8329), and 6.3% (525/8329) of cases, respectively. The remaining 144 children not included in any of these 4 clinical syndromes were analyzed in the overall population as they represented only 1.7% of the cohort. During the study period, a diagnosis of virus infection was possible for 47.9% (3991/8329) of the children (Table 1). The prevalence of SARS-CoV-2, RSV, and influenza A and B infection was 3.1% (95% CI, 2.7%–3.5%), 9.2% (95% CI, 8.6%–9.9%), 21.3% (95% CI, 20.5%–22.2%), and 15.9% (95% CI, 15.1%–16.7%), respectively. Multiple positive test results accounted for 0.7% of cases (56/8329).

Table 1 shows the prevalence of SARS-CoV-2, RSV, and influenza A and B infection by clinical syndrome. The rate of a positive viral diagnosis was significantly lower for children with otitis (40.9%) than flu-like illness (49.6%) or bronchiolitis (47.2%). The highest RSV positivity occurred in children with bronchiolitis (32.9%) while influenza A and B accounted for 14.1% of bronchiolitis cases. For flu-like illnesses, the main virus involved was influenza A or B (24.6% and 19.6%, respectively), but RSV and SARS-CoV-2 could also be involved. For otitis, although the burden of influenza (A and B) was high (33.2%), that of RSV was not negligible and accounted for 7.2% of cases. As expected, SARS-CoV-2 infection could be implicated whatever the clinical syndrome and study period.

Children with SARS-CoV-2 and RSV were significantly younger than children with influenza ($P < .001$). For children

Table 1. Age of Children and Prevalence of Positive Test Result for Severe Acute Respiratory Syndrome Coronavirus 2, Respiratory Syncytial Virus, and Influenza A and B by Clinical Syndrome

Characteristic	Clinical Syndrome				
	Flu-like Illness (n = 5440)	Bronchiolitis (n = 1488)	Otitis (n = 732)	Croup (n = 525)	Overall Respiratory Symptoms (n = 8329)
Age, y					
Mean ± SD	4.2 ± 3.1	1.9 ± 2.2	2.6 ± 2.1	4.6 ± 3.5	3.7 ± 3.1
Median	3.0	1.1	2.0	4.0	3.0
Positive for at least 1 of the 4 viruses, No. (%) (95% CI)	2698/5440 (49.6) (48.3–50.9)	703/1488 (47.2) (44.7–49.8)	299/732 (40.9) (37.3–44.5)	254/525 (48.4) (44.1–52.7)	3991/8329 (47.9) (46.9–49.0)
SARS-CoV-2 positive, No. (%) (95% CI)	184/5350 (3.4) (3.0–3.9)	36/1458 (2.5) (1.7–3.4)	12/719 (1.7) (0.9–2.9)	11/513 (2.1) (1.1–3.8)	254/8182 (3.1) (2.7–3.5)
Age, y					
Mean ± SD	2.7 ± 3.6	1.3 ± 2.0	1.2 ± 1.0	3.1 ± 3.5	2.5 ± 3.4
Median	1.0	0.5	1.0	1.8	1.0
RSV positive, No. (%) (95% CI)	181/5293 (3.4) (2.9–3.9)	480/1459 (32.9) (30.5–35.4)	51/709 (7.2) (5.4–9.3)	27/506 (5.3) (3.5–7.7)	747/8108 (9.2) (8.6–9.9)
Age, y					
Mean ± SD	2.0 ± 1.6	1.3 ± 1.2	2.0 ± 1.9	2.6 ± 2.0	1.6 ± 1.5
Median	1.9	0.9	1.5	2.0	1.2
Influenza A positive, No. (%) (95% CI)	1323/5376 (24.6) (23.5–25.8)	148/1467 (10.1) (8.6–11.7)	153/722 (21.2) (18.3–24.4)	119/517 (23.0) (19.5–26.9)	1755/8225 (21.3) (20.5–22.2)
Age, y					
Mean ± SD	4.5 ± 3.2	3.1 ± 3.0	2.7 ± 2.2	5.1 ± 3.4	4.3 ± 3.2
Median	4.0	2.0	2.0	4.0	3.0
Influenza B positive, No. (%) (95% CI)	1042/4274 (19.6) (23.1–25.7)	58/1436 (4.0) (3.1–5.2)	86/719 (12.0) (9.7–14.6)	102/517 (19.7) (16.4–23.4)	1295/8128 (15.9) (15.1–16.7)
Age, y					
Mean ± SD	5.0 ± 2.9	3.1 ± 2.6	3.1 ± 1.9	5.1 ± 3.2	4.8 ± 2.9
Median	5.0	3.0	3.0	5.0	4.0

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

with bronchiolitis, 14.9% were reported in children >3 years of age (Supplementary Table 1) and in this age group, RSV was significantly less frequent than influenza A and B.

Figure 1 shows the prevalence of SARS-CoV-2, RSV, and influenza A and B during the study period for overall respiratory symptoms. Supplementary Figure 1*A–D* shows the prevalence of SARS-CoV-2, RSV, and influenza A and B during the study period for each clinical syndrome. Whatever the clinical syndrome and study period, SARS-CoV-2 always circulated and was predominant for only 2 weeks (maximum 15% of positive results: week 17, 2023). A succession of 3 epidemics (RSV, influenza A and B) occurred over time with several overlap periods. The highest viral diagnosis (68.8%) occurred at week 51, when 654 children with flu-like illness were tested, during the peak of the influenza A epidemic.

DISCUSSION

For 8329 children with respiratory symptoms, this study is among the largest to investigate a triple antigen test (SARS-CoV-2 + influenza A/B + RSV) in real-life and ambulatory settings during a long period, 8 months (October 2022–May 2023). Moreover, this study provides data regarding the viral diagnosis according to different clinical syndromes, flu-like illness, bronchiolitis, otitis, and croup for children <15 years of age. To the best of our knowledge, our study is unique and novel as other studies have been performed primarily to assess the performance of an antigen multiple test rather than to evaluate their relevance or usefulness in real life [10, 21]. Moreover, other studies predominantly focused on patients aged <1 year, hospitalized for bronchiolitis, with a lower number of patients, and with a viral diagnosis done by multiplex PCR [21–23].

Like many other countries, France faced a rebound of respiratory infections in autumn of 2022 [7, 8]. Indeed, the use of the triple test enabled pediatricians to establish a diagnosis of virus infection in half of the children presenting respiratory symptoms, and this rate increased to 68.8% during the peak of the influenza A epidemic. Our manuscript describing the viral epidemiology of this significant respiratory season of 2022–2023 is timely because our study was performed prior to the anticipated licensure of broadly available RSV preventive approaches, including RSV vaccine for pregnant mothers or elderly persons and single dose of RSV immunoglobulin for infants.

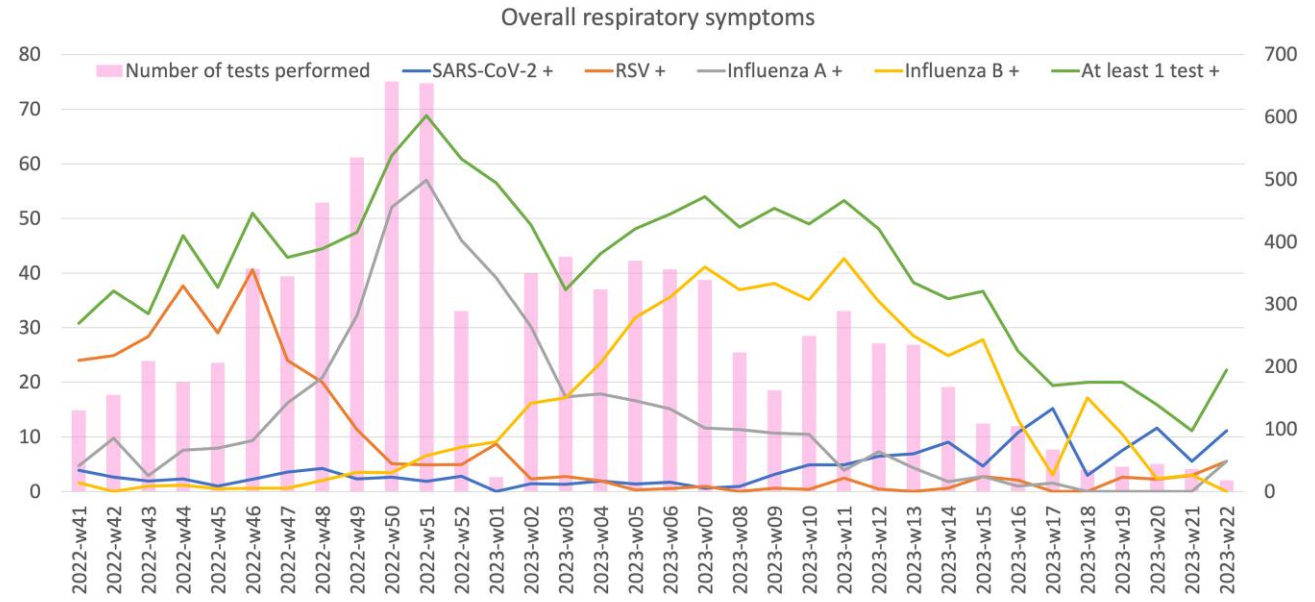

Figure 1. Number of tests and positivity (+) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), and influenza A and B during the study period for overall respiratory symptoms.

Moreover, beside the RSV immunization with monoclonal antibody introduced in France on 14 September 2023 for infants born after 6 February 2023, other interventions occurred in France such as widespread influenza vaccination for all children aged 2–17 years (recommended and reimbursed since 2023) and SARS-CoV-2 vaccination for at-risk children [15, 16]. Therefore, this first year of surveillance will serve as a baseline to contribute to assess the effectiveness of these prevention measures on the epidemiology of childhood respiratory infections.

Although the triple test used had a sensitivity for RSV, which was lower than that of influenza or SARS-CoV-2 (Supplementary Materials), for children with bronchiolitis, during the epidemic peak, the rate of positive RSV tests was very high and reached 60%. From a clinical point of view, the sensitivity seems not optimal; however, from a public health point of view, because of the ease of use of the triple test and its low cost as compared with RT-PCR, it is an essential tool for epidemiological monitoring of epidemics. Even though our data underestimated the burden of the different viruses involved in respiratory infections, particularly the RSV burden, we found high positivity of RSV (9.2% [95% CI, 8.6%–9.9%]), influenza A (21.3% [95% CI, 20.5%–22.2%]), and influenza B (15.9% [95% CI, 15.1%–16.7%]). In addition, this high positivity for influenza can be explained by the high circulation of the H3N2 virus during the study period (rapid antigen tests have better sensitivity for H3N2 than H1N1 or influenza B) and by the enrollment of children and not adults [24, 25]. Although the information regarding the date of symptom onset was not reported, we observed a high rate of positive tests, and our results were likely not negatively affected, probably because children are often brought to the clinic soon after the onset of symptoms [11, 26].

Although human metapneumovirus (HMPV) is also detected more frequently in children with respiratory infections, other viruses such as adenovirus or rhinovirus are detected in both healthy children and in children with respiratory infections [27]. In ambulatory settings, data regarding the circulation of HMPV are scarce [28]. Although the triple test targets the main respiratory viruses such as SARS-CoV-2, RSV, and influenza (well-established etiologies of respiratory infections), HMPV is not yet included in this test [27, 29]. The addition of an HMPV antigen test in the current triple test could be relevant. Moreover, there are several similarities in epidemiology and clinical presentation between HMPV and RSV infections [29].

Finally, our study showed a succession of 3 epidemics (RSV, influenza A and B) occurring over time with several overlap periods, but what was the individual benefit of an accurate viral diagnosis for a child with a respiratory syndrome? For SARS-CoV-2, the positivity of the test imposed containment measures. For influenza, by reducing the uncertainty diagnosis, the knowledge of the result could reduce both the prescription of unnecessary antibiotics and chest X-rays or blood samples [9, 30]. Moreover, a specific antiviral agent can be prescribed if the diagnosis is performed soon after disease onset. For RSV, antiviral treatment is not yet available, and we do not have proof that an accurate RSV diagnosis leads to a decrease

in antibiotics prescription. However, again the diagnostic uncertainties for clinicians represent an important cause of antibiotic prescriptions [9]. These tests allowing for a diagnosis of viral infection in 50%–70% of cases, accompanied by education and policies of the judicious use of antibiotics, could lead to a reduction in antibiotic prescriptions. RSV prevention with a long-acting monoclonal antibody has been shown to reduce hospitalizations and healthcare visits for RSV in infants by about 80% [31]. The upcoming introduction of this monoclonal antibody in a few countries such as France, the United States, and Spain emphasizes the need for active surveillance with viral results both in ambulatory settings and hospitals [31].

Supplementary Data

Supplementary materials are available at *Open Forum 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.

Notes

Author contributions. R. C. and C. L. designed the study and wrote the article. All authors analyzed and interpreted the data and drafted the article. C. L. and S. B. performed the statistical analysis. All authors revised and approved the manuscript.

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