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## Running title

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## Abstract

**Objectives**: Viral respiratory infections are common in children, and usually associated with non-specific symptoms. Respiratory panel-based testing was implemented during the COVID-19 pandemic, for the rapid differentiation between SARS-CoV-2 and other viral infections, in children attending the emergency department (ED) of the teaching hospital of Lille, northern France, between February 2021 and January 2022.

**Methods**: Samples were collected using nasopharyngeal swabs. Syndromic respiratory testing was performed with two rapid multiplex molecular assays: the BioFire® Respiratory Panel 2.1 - plus (RP2.1 plus) or the the QIAstat-Dx Respiratory SARS-CoV-2 Panel. SARS-CoV-2 variant was screened using mutation-specific PCR-based assays and genome sequencing.

**Results**: A total of 3517 children were included in the study. SARS-CoV-2 was detected in samples from 265 children (7.5%). SARS-CoV-2 infected patients were younger than those without SARS-CoV-2 infection (median age: 6 versus 12 months, $p< 0.0001$). The majority of infections (61.5%) were associated with the Omicron variant. The median weekly SARS-CoV-2 positivity rate ranged from 1.76% during the Alpha variant wave to 24.5% with the emergence of the Omicron variant. Most children (70.2%) were treated as outpatients, and seventeen patients were admitted to the intensive care unit. Other respiratory viruses were more frequently detected in SARS-CoV-2 negative children than in positive ones (82.1% versus 37.4%, $p< 0.0001$). Human rhinovirus/enterovirus and respiratory syncytial virus were the most prevalent in both groups.

**Conclusions**: We observed a low prevalence of SARS-CoV-2 infection in children attending pediatric ED, despite the significant increase due to Delta and Omicron variants, and an important circulation of other respiratory viruses. Severe disease was overall rare in children.

**Keywords:** syndromic testing, SARS-CoV-2, respiratory viruses, children, emergency department.

## Introduction

Viruses are the leading cause of acute respiratory tract infections in children [1]. Respiratory viruses are diverse, with variable circulation patterns, even if most common viral respiratory infections tend to follow seasonal patterns with a peak incidence during winter in temperate regions [2]. Reinfections are possible and co-infections have been frequently reported in symptomatic young children [3].

The emergence and the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have modified the existing overall picture. The burden of SARS-CoV-2 infection in children, although remaining low as compared to adults [4], has increased with the emergence of more transmissible variants such as the Delta or Omicron variants [5]. During the SARS-CoV-2 pandemic, the non-pharmaceutical interventions implemented to reduce the spreading of the virus, have also impacted the dynamics of other seasonal diseases that commonly affect children, most notably on respiratory syncytial virus (RSV) and influenza [6]. However, the magnitude, timing, and duration of this impact varied among viruses. Indeed, several respiratory viruses continued to circulate in the midst of the pandemic and could even rapidly return to prepandemic levels when COVID-19 mitigation practices become less stringent [7].

Respiratory viral infections lead to variable symptoms and disease severity in children, contributing to substantial morbidity, and cannot often be differentiated clinically. Therefore, testing for other pathogens, beyond SARS-CoV-2, is useful for clinical management.

Multiplex molecular assays have significantly improved the diagnosis of infectious diseases, and especially viral infections because they allow simultaneous detection of multiple pathogens in the same analysis. Moreover, some of these technologies with short turnaround time and minimal technical expertise allow rapid screening of pathogens associated with a

specific infectious syndrome. This so-called 'syndromic approach' can provide a rapid result, with the promise of timely clinical decisions such as hospital admission, isolation, and antimicrobial treatment or lack thereof [8,9].

We here describe data provided by the implementation of respiratory panel-based testing for the rapid differentiation between SARS-CoV-2 and other viral infections, in children attending the emergency department (ED) of the teaching hospital of Lille, northern France between February 2021 and January 2022.

## Materials and methods

### *Patients and samples*

This is a retrospective monocentric study conducted at the Lille University Hospital (CHU Lille), France. Children aged ≤ 15 years, attending the pediatric ED with suspicion of respiratory infection i.e. children presenting with fever and/or respiratory symptoms and/or digestive symptoms on admission [10], and who underwent a syndromic testing between February 15$^{th}$, 2021 and January 30$^{th}$, 2022, were included.

Nasal or naso-pharyngeal specimens were collected using flocked swabs eluted in 3 mL of viral transport medium (Yocon, Beijing, China).

This study was based on medical and laboratory records, in strict compliance with the French reference methodology MR-004 established by French National Commission on Informatics and Liberties (CNIL), and approved by the Institutional data protection authority of CHU Lille under the number DEC21-364.

### *Laboratory methods*

Upon admission, samples were heat-inactivated (incubation at 56°C for 30 min) before analysis. Two assays were used for rapid respiratory-panel testing depending on reagents availability: (i) the BioFire® Respiratory Panel 2.1 - plus (RP2.1 plus) – by bioMérieux® on the FILMARRAY Multiplex Real-Time PCR System (bioMérieux®, Lyon, France), and (ii) the the QIAstat-Dx Respiratory SARS-CoV-2 Panel – by Qiagen® on the QIAstat-Dx Analyzer (Qiagen®, Les Ulis, France). A brief description of the two methods is provided in Table 1.

SARS-CoV-2 variant screening was routinely performed using mutation-specific PCR-based assays, including VirSNiP SARS B117 (Tib MolBiol, Roche Diagnostics, Meylan, France), EurobioPlex SARS-CoV-2 SNPs (Eurobio Scientific, Les Ulis, France). Inconclusive results were confirmed using viral whole genome sequencing for samples with optimal viral load (Ct value ≤ 28). Briefly, total RNA extraction was performed with the MGIEasy Nucleic Acid Extraction Kit on the MGISP-960 instrument (BGI®, Shenzen, China). The libraries were prepared using Illumina® COVIDSeq protocol, and paired-end sequencing with 150 bp read length was carried out on NextSeq 550 platform. Data were processed using DRAGEN COVIDSeq Test Pipeline 1.0.0 (Illumina®, Evry, France).

***Statistical analysis***

GraphPad Prism software was used for statistical analyses. Data were presented as median and interquartile range (IQR), or as percentage. Fisher's exact test was used to compare categorical variables. Mann–Whitney U and Kruskal-Wallis tests were used to compare quantitative variables when appropriate. A two-sided p-value <0.05 was considered statistically significant.

## Results

A total of 3517 children admitted at the pediatric (ED during the study period were included. Children were mainly male (56.1%), and the median age was 12 months. Children aged less than 5 years represented the majority (92.8%) of the population. The age distribution is shown in Table 2.

***SARS-CoV-2 infection***

SARS-CoV-2 was detected in samples from 265 children (7.5%). SARS-CoV-2 infected patients were younger than those without SARS-CoV-2 infection (median age: 6 months versus 12 months, p< 0.0001) (see Table 2). Most patients (234/265, 88.3%) presented with acute upper respiratory tract infections. Fourteen patients (5.3%) did not present respiratory symptoms on admission. Ten (3.8%) and seven (2.6%) patients were diagnosed on admission with moderate and severe pneumonia respectively.

The majority of children (70.2%) were treated as outpatients. The hospitalization occurred for 94.1% (16/17) of children with lower respiratory tract infections and for 25% (63/248) of other children. A total of 62 children (23.4%) were hospitalized in general pediatric wards, including six hospitalizations (2.3%) not related to COVID-19. Seventeen admissions (6.4%) to the intensive care unit (ICU) were recorded (Table 3). Overall, they were either very young needing a respiratory or enteral support, or presenting a viral coinfection and/or an underlying condition. One death was recorded in a 2-month-old boy who presented with severe pneumonia on admission, and who rapidly developed an acute respiratory distress syndrome. A bacterial pulmonary co-infection with E coli K1 was also evidenced. The death occurred two days post-admission.

The distribution of cases over time is shown in Figure 1, and the number of tests and positive results per week is detailed in table S1 (supplementary material).

SARS-CoV-2 variant information was available for 208 patients (78.5%). Alpha, Delta and Omicron variants were detected in 19 (9.1%), 60 (28.8%) and 128 (61.5%) samples respectively. B.1.640 lineage was found in one sample.

Alpha variant has been detected in children until week 28 (2021). The Delta variant was detected from week 29 (2021) to week 3 (2022), and the Omicron variant was detected since week 51 (2021). The median weekly SARS-CoV-2 positivity rate (ratio between cases and total number of tested children) was 1.76% and 3.5% during the Alpha wave, and the “Delta only” circulation period respectively. This rate increased to 24.5% with the emergence of Omicron variant (p= 0.0002). The median age was 7, 4 and 5 months in the Alpha, Delta and Omicron cases, respectively (p=0.12). The hospitalization rate during the Alpha wave (5/19, 26.3%) was similar to that observed in Delta cases (22/60, 36.7%, p= 0.58) and in Omicron cases (31/128, 24.2%, p= 0.78).

**Other respiratory viruses**

At least one other respiratory virus was detected in 2768 children (78.7%). The two most common viruses were human rhinovirus/enterovirus (HRV/EV) and respiratory syncytial virus (RSV) detected in 39.5% and 29.1% of the study population, respectively. The weekly

distribution of these viruses is shown in Figure 2. The median weekly proportion of HRV/EV positive samples was 37.7%, with prevalence ranging from 14% to 80% during the study period (Figure 2). The highest prevalences were observed during weeks 18 to 28 (May to July), and weeks 36-45 (September to November). RSV circulation was detected throughout the study period, with a median weekly proportion of positive samples at 24.4% (Figure 2). A first peak was observed from February to April (weeks 7-16). A second important circulation period was observed from week 44 (November) to week 1 (January 2022).

Respiratory viruses were detected in 99 out of 265 (37.4%) SARS-CoV-2 positive patients and in 2669 out 3252 (82.1%) of SARS-CoV-2 negative children, showing a more important circulation of other respiratory viruses in SARS-CoV-2 negative children ($p< 0.0001$).

The repartition of detected viruses in COVID-19 and non-COVID-19 patients is presented in Table 4. Of note, the circulation of influenza virus weakly started in weeks 38-40, and peaked from week 51. Beyond viruses, the panel testing allowed the detection of *Bordetella pertussis* in 2 children.

## Discussion

The measures adopted to contain the COVID-19 pandemic in our hospital included a systematic screening of SARS-CoV-2 infection in children attending pediatric emergency department, especially those with respiratory symptoms. Since these symptoms are usually non-specific, testing for other viral pathogens seemed reasonable, and a respiratory syndromic testing approach was implemented.

The overall prevalence of SARS-CoV-2 infection during the study period was 7.5%. However the prevalence before the emergence of the Omicron variant ranged from 1.76 to 3.5% , and was similar to that previously reported [11]. SARS-CoV-2 infected children were younger than those without SARS-CoV-2 infection. This observation is probably related to milder SARS-CoV-2 symptoms in older children, and therefore fewer ED visits. No difference

189 regarding the age was observed between children infected with the different variants. In
190 addition, the hospitalization rates were similar between all groups.
191 The emergence of more transmissible variants of concern was associated with an increase
192 of infection rates in unvaccinated populations, including children. However, previous data
193 with the Alpha and Delta variants showed that hospitalization rates remained stable in
194 children, suggesting that these variants do not lead to more severe disease in children [12].
195 More interestingly, a recent analysis (preprint paper) of the Omicron wave suggested even
196 fewer hospitalizations and less severe outcomes in children under 5 years, as compared to
197 the Delta wave [13].
198 Findings in this study suggest that severe disease is overall rare in children because the few
199 patients admitted to ICU were fragile or presenting a viral coinfection and/or an underlying
200 disease. Nevertheless, COVID-19 can lead to death in children [14].
201 The multiplex testing approach also gave us the opportunity to investigate the circulation of
202 the other respiratory viruses. We found that more than a third of COVID-19 patients had a
203 coinfection with another virus. However, the detection rate of other respiratory viruses was
204 significantly higher in the non-COVID-19 patients than in SARS-CoV-2 infected children.
205 The HRV/EV complex was the most detected in samples, with high detection rates
206 maintained all over the year. Rhinoviruses and other respiratory enteroviruses (belong to the
207 genus Enterovirus) are usually grouped and targeted together in commercial respiratory
208 assays.
209 Rhinovirus detection is very common in children and is usually asymptomatic or associated
210 with mild symptoms; however acute and severe symptoms (wheezing and asthma
211 exacerbations) can be observed in younger children [15–17].
212 Our data are in agreement with previous studies that reported an unchanged rhinovirus
213 circulation during the COVID-19 pandemic (data of year 2020), with no impact of social
214 restrictions [18–21].
215 The mode of transmission of rhinoviruses or other enteroviruses can explain this observation.
216 These non-enveloped viruses are usually transmitted by direct contact, and can survive on

fingers with possible self-inoculation of the nose or conjunctiva following inadvertent contamination of the fingers [22].

Regarding RSV circulation in 2021, this study clearly confirms the unusual delay of the 2020/2021 winter outbreak previously reported in France [23], with a peak around weeks 10-13. This observation is probably related to an increase in social restrictions with a second lockdown between end October and mid-December 2020, even if less strict than the first one. Our data also suggest that the third lockdown that started in Week 13 at the peak of 2020/2021 epidemic might contribute to the following decrease in the number of cases. We also observed the return to prepandemic patterns regarding the circulation of RSV and influenzavirus during 2021/2022 winter.

The main strength of our study is the high number of samples tested, using a multiplex approach yielding a result within 4 hours after sampling and available 24h/24h. The study is limited by the lack of comparison with data from previous years and the absence of impact evaluation of such testing.

In conclusion, the implementation of the syndromic testing approach aimed to timely differentiate between SARS-CoV-2 and other viral infections in order to improve patient management in a context of reduced hospital beds. Overall, we observed a low prevalence of SARS-CoV-2 infection in children attending pediatric ED, despite the significant increase due to Delta and Omicron variants, and an important circulation of other respiratory viruses.

The identification of a viral etiology can reduce unnecessary investigations and promote antibiotic stewardship. However, this diagnostic approach is expensive, and its utility and contributions need to be further evaluated [24].

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**Conflicts of interest**: none

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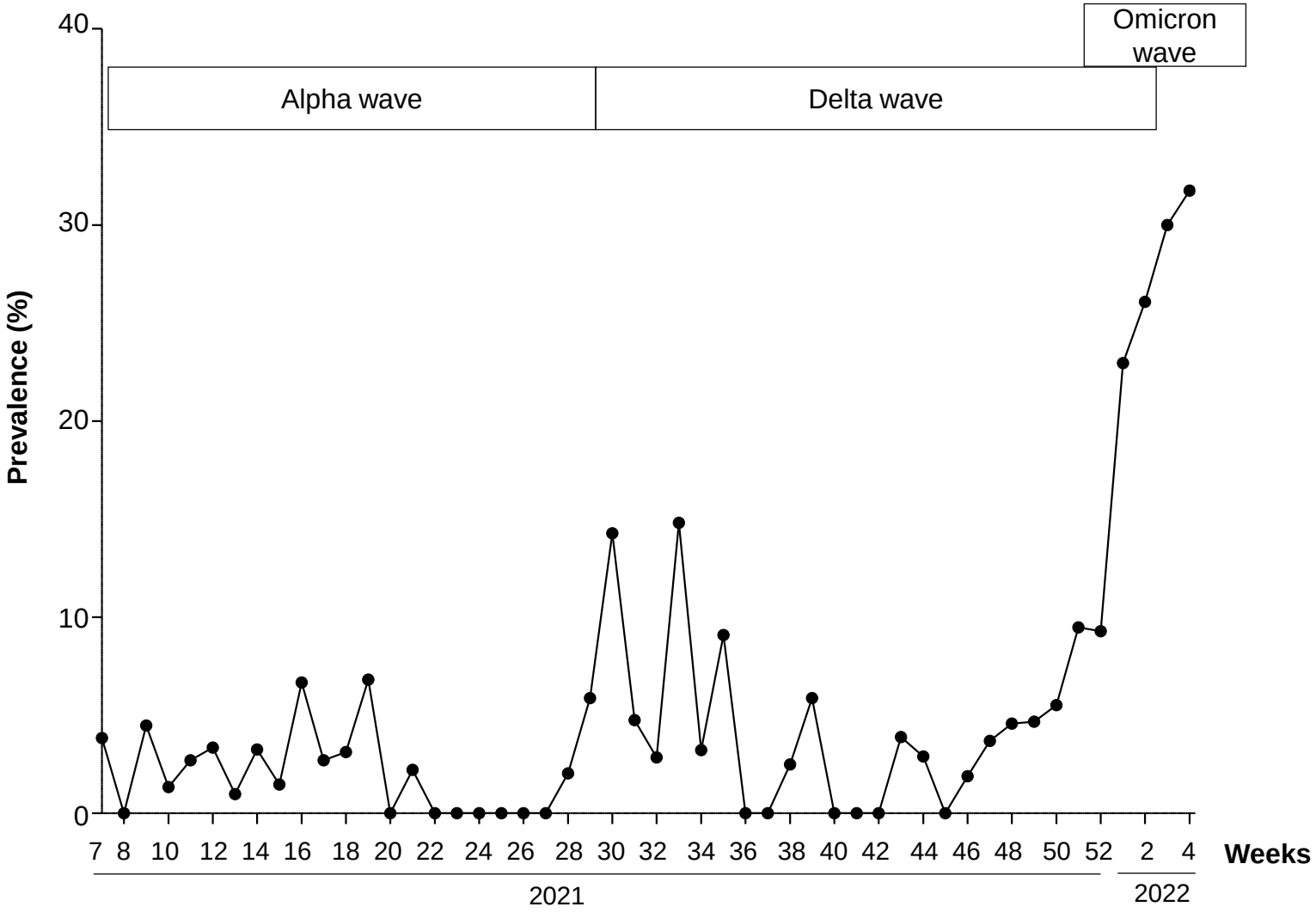
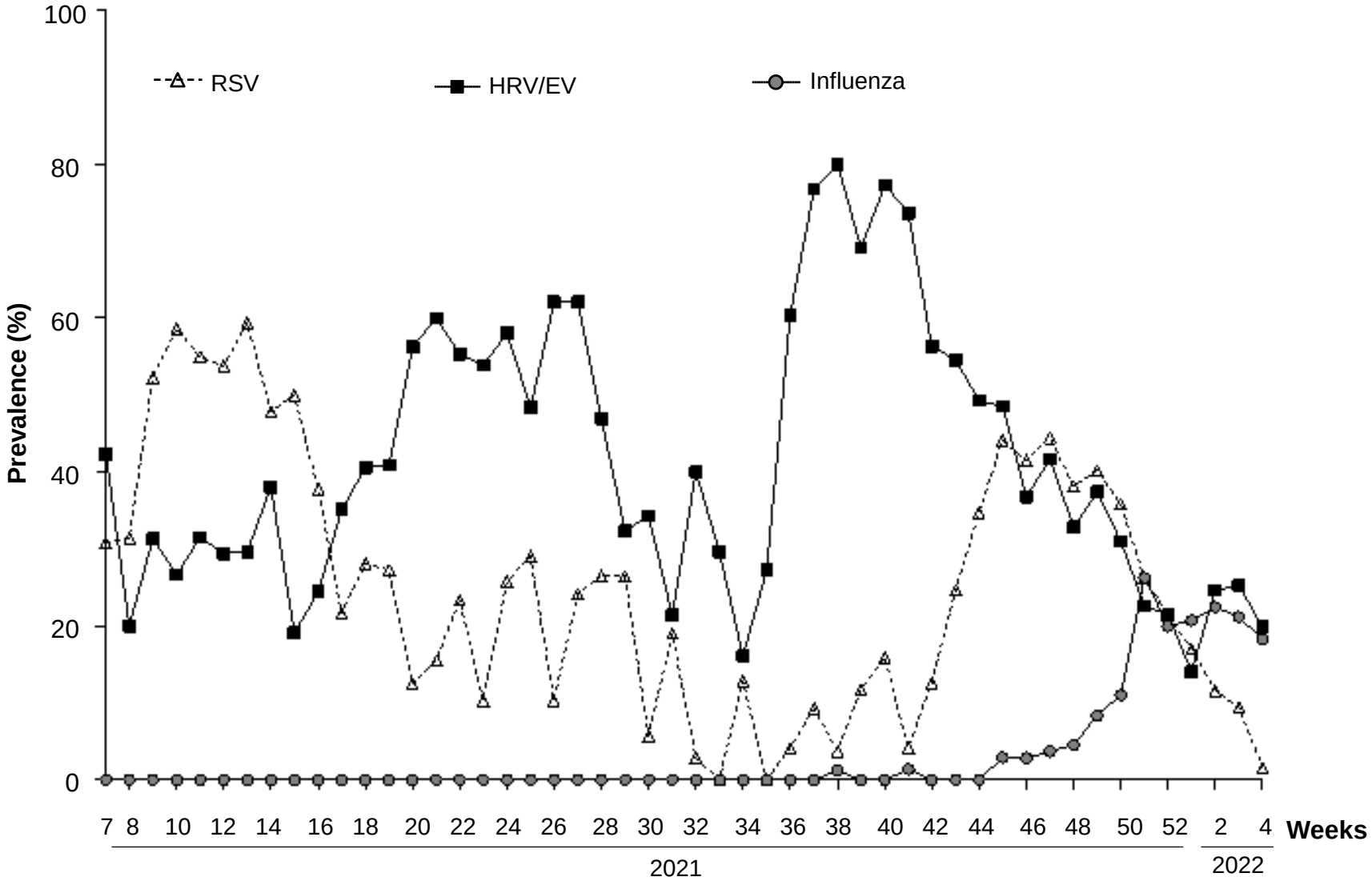



**Figure 1. Distribution over time of SARS-CoV-2 infections**




**<u>Figure 2</u>. Distribution over time of Respiratory syncytial virus, rhinovirus/enterovirus and influenzavirus infections**

**Table 1.** Diagnostic assays

| Characteristics | BioFire ® Respiratory Panel 2.1 - plus | QIAstat-Dx Respiratory SARS-CoV-2 Panel |
|---|---|---|
| **Pathogens detected** | - Viruses: Adenovirus, Coronaviruses 229E, HKU1, NL63, and OC43, SARS-CoV-2, Human Metapneumovirus A/B, Influenza A (with differentiation of Influenza A/H1, A/H3, A/H1-2009), Influenza B, Parainfluenza virus 1,2 3 and 4, MERS-CoV, Rhinovirus/Enterovirus, Respiratory Syncytial Virus A/B, SARS-CoV-2<br>- Bacteria: Bordetella pertussis, Bordetella parapertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae | - Viruses: Adenovirus, Bocavirus, Coronaviruses 229E, HKU1, NL63, and OC43, SARS-CoV-2, Human Metapneumovirus A/B, Influenza A (with differentiation of Influenza A/H1, A/H3, A/H1-2009), Influenza B, Parainfluenza virus 1,2 3 and 4, Rhinovirus/Enterovirus, Respiratory Syncytial Virus A/B, SARS-CoV-2<br>- Bacteria: Bordetella pertussis, Mycoplasma pneumoniae, Legionella pneumophila |
| **Turnaround time** | 45 min | 60 min |
| **Sample input volume** | 300 µL | 300 µL |
| **Report of Ct value** | No (melting curves) | Yes |

**Table 2**. Demographics of patients

| Characteristics | All patients (n= 3517) | SARS-CoV-2 positive patients (n= 265) | SARS-CoV-2 negative patients (n= 3252) |
|---|---|---|---|
| Sex ratio, % of male | 56.1 | 53.2 | 56.3 |
| Median age (IQR), months | 12 (4 – 26) | 6 (2 – 20.5) | 12 (5 – 27) |
| Age distribution, % | | | |
| < 1month | 4.6 | 5.3 | 4.5 |
| 1 – 23 months | 66.4 | 73.6 | 65.8 |
| 24 - 59 months | 21.8 | 12.1 | 22.6 |
| 60 – 119 months | 4.9 | 4.9 | 4.9 |
| ≥ 120 months | 2.3 | 4.1 | 2.2 |

**Table 3. Description of SARS-CoV-2 positive children admitted to ICU**

| Patient number | Age | Underlying condition | Clinical features | Outcome |
|---|---|---|---|---|
| 1 | 22 days | None | Acute upper respiratory tract infection. Non-invasive respiratory support needed. No viral coinfection | Alive |
| 2 | 23 days | None | Acute upper respiratory tract infection. Non-invasive respiratory support and enteral nutrition support needed. No viral coinfection. | Alive |
| 3 | 1 month | None | Acute upper respiratory tract infection. Enteral nutrition support needed. No viral coinfection. | Alive |
| 4 | 1 month | None | Severe acute bronchiolitis. Non-invasive respiratory support needed. Coinfection with influenzavirus | Alive |
| 5 | 1 month | None | Gastrointestinal symptoms. Enteral nutrition support needed. No viral coinfection | Alive |
| 6 | 1 month | Preterm birth | Acute upper respiratory tract infection. Non-invasive respiratory support needed. Coinfection with Parainfluenzavirus 3 | Alive |
| 7 | 1 month | None | Severe acute bronchiolitis. Non-invasive respiratory support needed. Coinfection with RSV | Alive |
| 8 | 1 month | None | Severe acute bronchiolitis. Non-invasive respiratory support needed. Coinfection with RSV | Alive |
| 9 | 1 month | None | Severe acute bronchiolitis. Non-invasive respiratory support needed. Coinfection with RSV | Alive |
| 10 | 1 month | None | Gastrointestinal symptoms. Enteral nutrition support needed. No viral coinfection | Alive |
| 11 | 2 months | None | Severe pneumonia with evolution to acute respiratory distress syndrome. No viral coinfection. Bacterial pulmonary co-infection with E. coli K1 | Death |
| 12 | 2 months | None | Severe acute bronchiolitis. Non-invasive respiratory support needed. Coinfection with RSV | Alive |
| 13 | 2 months | None | Severe pneumonia following aspiration from dysphagia. Non-invasive respiratory support needed. No viral coinfection. | Alive |
| 14 | 4 months | polycystic kidney disease | Moderate pneumonia. Non-invasive respiratory support needed. Corticosteroid therapy. No viral coinfection. | Alive |

| | | | | |
|---|---|---|---|---|
| 15 | 3.2 years | Asthma | Severe pneumonia. Coinfection with RSV and HRV/EV | Alive |
| 16 | 3.8 years | sickle cell disease | Acute chest syndrome and acute hemolytic anemia. No viral coinfection | Alive |
| 17 | 8.4 years | Pansinusitis complicated by cerebral empyema | Postoperative ICU admission. Not related to COVID-19 | Alive |

**Table 4**. Other respiratory viruses

| **Respiratory viruses** | **COVID-19 children (n= 265)** | **Non-COVID-19 children (n= 3252)** | **p value** |
|---|---|---|---|
| Enterovirus/human rhinovirus | 43 (16.2%) | 1283 (39.5%) | p< 0.0001 |
| Respiratory syncytial virus | 21 (7.9%) | 947 (29.1%) | p< 0.0001 |
| Adenovirus | 16 (6%) | 373 (11.5%) | p< 0.0001 |
| Human parainfluenza virus 1-4 | 10 (3.8%) | 362 (11.1%) | p< 0.0001 |
| Human metapneumovirus | 4 (1.5%) | 188 (5.8%) | p= 0.002 |
| Coronaviruses (OC43, HKU1, 229E, NL63) | 18 (6.8%) | 345 (10.6%) | p= 0.06 |
| Influenzavirus | 8 (3%) | 216 (6.6%) | p= 0.02 |
| Bocavirus | 11 (4.2%) | 151 (4.6%) | p= 0.9 |