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1 **Rapid syndromic testing for respiratory viral infections in children attending the**
2 **emergency department during COVID-19 pandemic in Lille, France, 2021-2022**

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1 **Rapid syndromic testing for respiratory viral infections in children attending**
2 **the emergency department during COVID-19 pandemic in Lille, France, 2021-**
3 **2022**

4

5 **Abstract**

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

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

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

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

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

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55 **Introduction**

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

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

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

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

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

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

86

87 **Materials and methods**

88 ***Patients and samples***

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

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

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

100 ***Laboratory methods***

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

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

116 ***Statistical analysis***

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

122

123 **Results**

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

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

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

135 The majority of children (70.2%) were treated as outpatients. The hospitalization occurred for
136 94.1% (16/17) of children with lower respiratory tract infections and for 25% (63/248) of other
137 children. A total of 62 children (23.4%) were hospitalized in general pediatric wards, including
138 six hospitalizations (2.3%) not related to COVID-19. Seventeen admissions (6.4%) to the
139 intensive care unit (ICU) were recorded (Table 3). Overall, they were either very young
140 needing a respiratory or enteral support, or presenting a viral coinfection and/or an
141 underlying condition. One death was recorded in a 2-month-old boy who presented with
142 severe pneumonia on admission, and who rapidly developed an acute respiratory distress
143 syndrome. A bacterial pulmonary co-infection with E coli K1 was also evidenced. The death
144 occurred two days post-admission.

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

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

150 Alpha variant has been detected in children until week 28 (2021). The Delta variant was
151 detected from week 29 (2021) to week 3 (2022), and the Omicron variant was detected since
152 week 51 (2021). The median weekly SARS-CoV-2 positivity rate (ratio between cases and
153 total number of tested children) was 1.76% and 3.5% during the Alpha wave, and the “Delta
154 only” circulation period respectively. This rate increased to 24.5% with the emergence of
155 Omicron variant ($p= 0.0002$). The median age was 7, 4 and 5 months in the Alpha, Delta and
156 Omicron cases, respectively ($p=0.12$). The hospitalization rate during the Alpha wave (5/19,
157 26.3%) was similar to that observed in Delta cases (22/60, 36.7%, $p= 0.58$) and in Omicron
158 cases (31/128, 24.2%, $p= 0.78$).

159 **Other respiratory viruses**

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

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

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

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

177

178 **Discussion**

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

184 The overall prevalence of SARS-CoV-2 infection during the study period was 7.5%. However
185 the prevalence before the emergence of the Omicron variant ranged from 1.76 to 3.5% , and
186 was similar to that previously reported [11]. SARS-CoV-2 infected children were younger
187 than those without SARS-CoV-2 infection. This observation is probably related to milder
188 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

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

219 Regarding RSV circulation in 2021, this study clearly confirms the unusual delay of the
220 2020/2021 winter outbreak previously reported in France [23], with a peak around weeks 10-
221 13. This observation is probably related to an increase in social restrictions with a second
222 lockdown between end October and mid-December 2020, even if less strict than the first
223 one. Our data also suggest that the third lockdown that started in Week 13 at the peak of
224 2020/2021 epidemic might contribute to the following decrease in the number of cases. We
225 also observed the return to prepandemic patterns regarding the circulation of RSV and
226 influenza virus during 2021/2022 winter.

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

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

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

239

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241

242 **Conflicts of interest:** none

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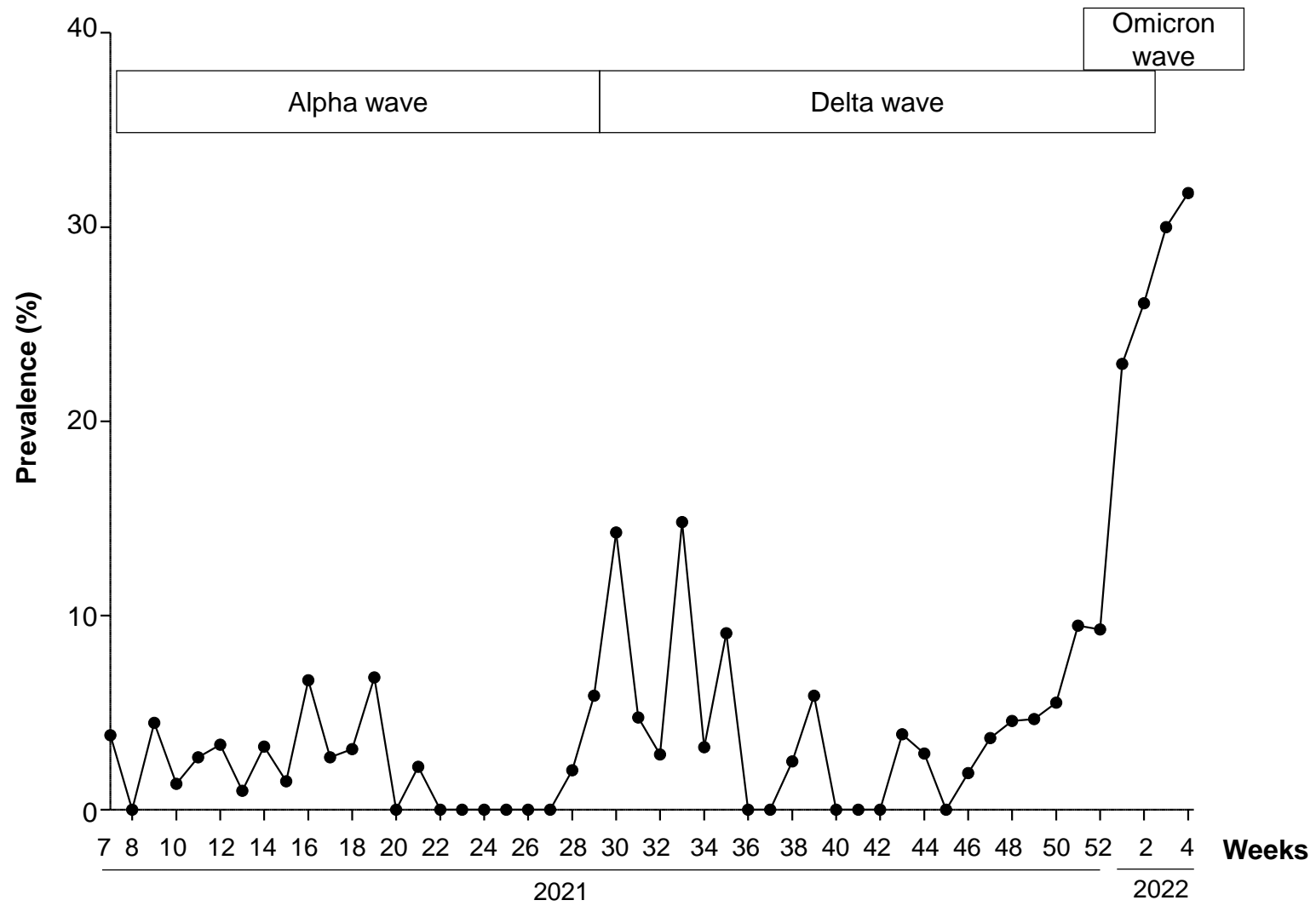


Figure 1. Distribution over time of SARS-CoV-2 infections

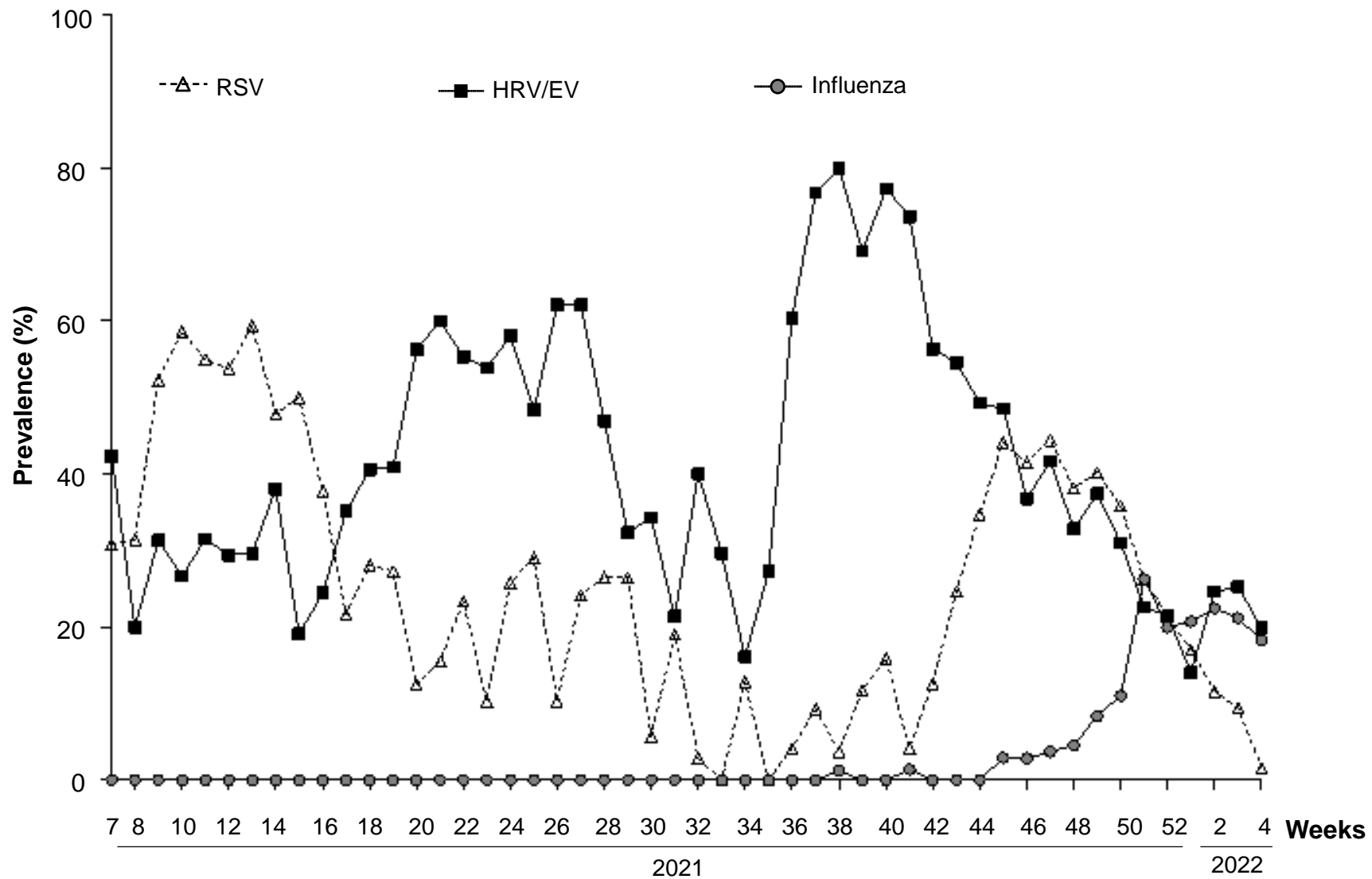


Figure 2. Distribution over time of Respiratory syncytial virus, rhinovirus/enterovirus and influenzavirus infections

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 - 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 - 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