BMJ Open Respiratory Research

Changes in respiratory viruses in infancy during the SARS-CoV-2 pandemic: a prospective cohort study

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To cite: Steinberg R, Troxler S, Dac LH, *et al*. Changes in respiratory viruses in infancy during the SARS-CoV-2 pandemic: a prospective cohort study. *BMJ Open Respir Res* 2025;**12**:e003044. doi:10.1136/bmjresp-2024-003044

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjresp-2024-003044).

Received 22 November 2024
Accepted 19 February 2025

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ABSTRACT

Background Respiratory virus infections are a major cause of morbidity in early life. During the SARS-CoV-2 pandemic, non-pharmaceutical interventions (NPIs) lead to worldwide changes in respiratory virus epidemiology. However, evidence regarding virus circulation in the outpatient setting remains largely unknown. The aim of this study is to longitudinally assess respiratory viruses in healthy infants before and during the SARS-CoV-2 pandemic in Switzerland.

Methods In this prospective observational birth cohort study, we followed 34 infants throughout the first year of life before and during the SARS-CoV-2 pandemic. We analysed 648 biweekly nasal swabs for nine different respiratory viruses by Multiplex-PCR and assessed respiratory symptoms, COVID-19 infections of family members and childcare status in weekly interviews. 712 nasal swabs from 32 infants analysed before the pandemic and published previously served as control group.

Results During the period with strict NPIs (pandemic I), most common respiratory viruses were not detected, with a rebound (driven by Adenovirus and Parainfluenza virus) after most NPIs were relaxed (pandemic II): prepandemic: 27%, pandemic I: 19%, pandemic II: 33%; historic: 36% of collected swabs per period, p<0.001. Human rhinovirus (HRV) prevalence persisted during NPIs presence, mainly in the form of asymptomatic HRV detection: prepandemic=24%, pandemic I=19%, pandemic II=25%, historic: 25%, p=0.3. SARS-CoV-2 detection (asymptomatic and symptomatic) was low, and only present after NPIs were relaxed: pandemic II=2.4%. No severe COVID-19 infections were reported.

Discussion In our cohort, infants did not contribute largely to spread of SARS-CoV-2. The role of persisting asymptomatic HRV prevalence is still unclear, but it might help to maintain population immunity to prevent more severe infections. Our results underscore the importance of capturing asymptomatic viruses via longitudinal community-based data assessment to better understand virus transmission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Epidemiological data from emergency departments and hospitalised patients show that respiratory virus infection changed largely during the SARS-CoV-2 pandemic.

WHAT THIS STUDY ADDS

⇒ Longitudinal data from the outpatient setting suggest that NPIs had no effect on (asymptomatic) human rhinovirus prevalence in healthy infants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study underlines the importance of longitudinal and prospective data collection in the outpatient setting and in otherwise healthy infants in infection epidemiology monitoring.

INTRODUCTION

Respiratory virus infections are a major cause of mortality and morbidity in early life.[1] The SARS-CoV-2 and the non-pharmaceutical interventions (NPIs) (eg, social and physical distancing, travel barriers, extensive hygiene and closing of childcare facilities and schools) enacted to reduce the spread of SARS-CoV-2 have caused a large impact on epidemiology of common respiratory viruses and bacteria.[2–4]

During the initial phase of the pandemic, characterised by stringent NPIs, hospitalisations and emergency consultations for respiratory illnesses in infants and children were notably reduced.[5] For instance, there was a decline in cases of respiratory syncytial virus (RSV)-related bronchiolitis[6] and asthma exacerbations,[5] often triggered by virus infections such as human rhinovirus (HRV). Afterwards, a strong increase of respiratory tract infections (RTIs) in children with a predominance of HRV was reported in Germany,[7] with increasing HRV prevalence in paediatric intensive care patients in the UK.[8] Moreover, the seasonal pattern of respiratory viruses was disrupted, with notable increases in hospitalisations due to RSV, human metapneumovirus (MPV) or influenza virus.[9 10]

Although SARS-CoV-2 infection in children is frequently asymptomatic or mild,

characterised by upper respiratory tract symptoms, the consequences of asymptomatic carriage remain poorly understood.[11] Most epidemiological studies have relied on data from emergency departments or hospital records,[12] often analysed retrospectively,[13] thus limiting our understanding of virus occurrence in outpatient settings and among asymptomatic or mildly affected individuals.

Therefore, the objective of this study was to longitudinally investigate the detection of respiratory viruses in both asymptomatic and symptomatic otherwise healthy infants before and during the SARS-CoV-2 pandemic in Switzerland. We aim to provide insights into the dynamics of transmission and its implications on respiratory virus infections in children, in the context of the COVID-19 NPIs.

METHODS

Study design and studied cohort

This is a prospective, observational, community-based study among healthy infants from the Basel Bern Infant Lung Development (BILD) cohort (for more information, see online supplemental methods).[14 15] We included 34 healthy, unselected infants born between 2019 and 2022. We collected anterior nasal swabs for virus assessment biweekly throughout the first year of life, starting at the age of 5 until the age of 52 weeks. Study nurses performed weekly telephone interviews to assess respiratory health and changes in the environment. We assessed SARS-CoV-2 infection and vaccination status of infants and family members.

Nasal swabs and virus analyses

Nasal swabs (FLOQSwabs, in UTM-RT (Copan, Italia)) were taken biweekly by the parents after instruction by a study nurse and sent to the study centre in Bern. They were aliquoted and stored at −80°C until analysis. Virus analysis was performed via multiplex RT-PCR including SARS-CoV-2 (N/S gene, RdRP gene), influenza A virus (influenza A), influenza B virus (influenza B), human RSV, human MPV, human adenovirus (AdV), HRV, human parainfluenza virus (PIV) and internal controls (for more information, online supplemental methods). The RT-qPCR cycle threshold (Ct) values were reported for each analysed gene.

Respiratory symptoms and virus detection

We recorded respiratory symptoms, wheeze and/or cough in weekly standardised telephone interviews. We assessed rhinitis (runny or blocked nose) independently as the most common upper respiratory symptom. We defined mild respiratory symptoms if coughing with or without rhinitis was recorded. We defined severe respiratory symptoms as wheeze or breathing difficulties accompanied by upper respiratory tract symptoms or elevated temperature over more than 2 consecutive days.[16] We also combined mild and severe respiratory symptoms as well as rhinitis and defined these as 'any symptoms'.

We defined virus detection as swabs positive for any virus, irrespective of symptoms. We defined 'symptomatic virus detection' as swabs positive for any virus accompanied by respiratory symptoms occurring up to 7 days before and 7 days after the swab was taken and 'asymptomatic virus detection' as swabs positive for any virus but not accompanied by respiratory symptoms.[16] In addition, we assessed 'virus episodes' if the same virus was detected in consecutive swabs (interval between swabs <21 days) and 'symptomatic virus episode' if there was a symptomatic virus detection within the episode.

We defined age at first virus detection and age at first symptomatic virus detection, as the age of the infant in days at the initial observation of the specific event.

Assessment of different time periods

We assessed the current dataset in three groups following the regulations for NPIs in Switzerland: (1) before the pandemic ('prepandemic' July 2019–February 2020), (2) during mainly strict lockdown phases and when most NPIs were enacted ('pandemic I' March 2020–April 2021), (3) after most NPIs were relaxed in Switzerland ('pandemic II' May 2021–August 2022).[17] At the beginning of pandemic I, schools in Switzerland were closed (16 March 2020–10 May 2020) and the government recommended parents to stay at home with their children if possible. In addition, shops and public places were repeatedly closed, home office was recommended and public gatherings were restricted in pandemic I. People were supposed to wear facemasks in public places. In pandemic II, governmental NPIs were relaxed stepwise. Online supplemental figure 1 shows a timeline of NPIs in Switzerland (for further details, see online supplemental table 1 and figure 2). We compared the current dataset with 712 real-time PCR samples of 32 healthy infants collected in years 2010–2014 ('historic') and published previously.[16] Study design and setting were identical. The PCR kits were not identical. Thus, only the following respiratory viruses covered in both PCR methods were compared: HRV, AdV, PIV, MPV, RSV, FluA and FluB. SARS-CoV-2 was analysed separately.

Statistical analyses

We summarised all detected viruses per study phase among all infants (in %). We compared the three pandemic phases and the historic control group with Pearson's χ^2 test and Fisher's exact test (demographic data, virus detection (weeks) and virus episodes). In the next step, we used multivariate logistic regression, including a random effect to account for multiple measurements in the same individuals to assess the following outcome variables: (1) differences in any virus detection, (2) differences in symptomatic and asymptomatic virus detection and episodes, (3) differences in HRV detection and (4) differences in symptomatic and asymptomatic

HRV detection and episodes. The results of the unadjusted models are shown in online supplemental table 2. Next, we included the following predictors in the model: time period (three pandemic phases and historic), mode of delivery, childcare at time of swab, breastfeeding at time of swab, siblings, atopic disease of the mother, season, parental smoking, age in days (grouped into four age categories). Missing information was omitted in our analysis as it is default option for the *glmer* function. All statistical analyses were performed with R statistical software V.4.1.2[18] packages lme4 and gtsummary. Graphs were produced with ggplot2 and vistime packages in R.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study population

We analysed eight respiratory viruses in 648 biweekly assessed nasal swabs (prepandemic=94, pandemic I=215, pandemic II=339) from 34 infants (infants recruited per phase prepandemic=12, pandemic I=10, pandemic II=12). Respiratory virus analyses from 712 swabs from 32 infants assessed between 2010 and 2014 served as additional control group to increase power for prepandemic data assessment.[16] In the current dataset, we detected respiratory viruses in median in 26% of swabs per infant (range: 8%–71%). In the historic dataset, we detected respiratory viruses in median in 35% (15% to 68%) of swabs per infant. The median age of the first swab taken was 44 days (IQR=40–48) in the current dataset and 37 days (IQR=34–41) in the historic dataset. The median age of the first virus detection was 81 days (IQR=48–106) in the current dataset and 63 days (IQR=46–104) in the historic dataset. For details on the study population, see online supplemental table 3. The differences in childcare attendance between the different time phases were not statistically significant (historic=7 (22%); prepandemic: n=1 (11%), pandemic I: n=10 (36%), pandemic II: n=11 (37%) p=0.2). During the pandemic, childcare attendance was possible in Switzerland at almost any time point (online supplemental figure 1 and table 1, online supplemental figure 2).

Prevalence of respiratory viruses in the different time periods

Results of asymptomatic and symptomatic virus detection for the investigated time periods are displayed in table 1. Virus prevalence in infants was lower during the first lockdown phase (pandemic I) compared with prepandemic data and the historic data set. This was followed by a rebound of respiratory viruses after NPIs were relaxed (prepandemic: 27%, pandemic I: 19%, pandemic II: 33%; historic: 36% of collected swabs per period) (figure 1). Repeating analyses but investigating virus episodes (instead of positive swabs) did not change the results (table 1). This was confirmed in multivariable analyses with increased ORs compared with pandemic I (as baseline) (table 2): historic data set (OR 2.45), prepandemic (OR 1.96) and pandemic II (OR 2.04). Number of infants with siblings was higher in the historic data set (table 1), however, none of the investigated potential risk factors (sex, season, breastfeeding at swab, childcare at swab, caesarean section, siblings, maternal atopy and age category) was associated with virus detection (table 2).

During pandemic I, virus detection rates were not higher in infants attending childcare compared with infants staying at home (virus positive swabs in infants at home: 20%, in childcare: 18%, p=0.7). During school closing and reduced childcare offering at the beginning of pandemic I (online supplemental figure 1 and table 1), two children still attended childcare and virus prevalence was also 20% (number of swabs=5, virus positive=1).

Respiratory virus codetections did not differ between the investigated time periods but were only observed in pandemic II (2.4%) and the historic data (3.4%) (table 1). The increase in virus detection in pandemic II was mainly driven by PIV (p=0.006) and AdV (p=0.015) (table 1, figure 2A–B). Both viruses could not be detected during pandemic I. Due to low detection rates overall, we did not perform multivariate logistic regression for PIV and AdV. Compared with historic data, the observed rebound was likely a return to normal state (table 1).

Symptomatic respiratory virus detection

Symptomatic virus detection was lower in pandemic I (7%) compared with the other time periods (prepandemic (17%), pandemic II (16%), historic data (19%), p<0.001, table 1 and online supplemental table 4). The presence of virus infections with severe symptoms was low overall (n=27 (2.0%)) and differed between the investigated phases (table 1, p=0.038): in pandemic I, severe virus infections were not detected (0%), the highest number was counted in the historic data set (n=20 (2.8%)). The presence of virus infections with mild symptoms ranged between 3.2% (prepandemic) and 6.2% (pandemic II) with no statistic difference between groups (p=0.4). Virus detection with rhinitis was with 6% lower in pandemic I compared with 14%–16% in the other investigated time periods (table 1, p=0.003).

Investigation of symptomatic virus episodes showed similar results. We observed differences between the investigated time periods (p=0.004), with the lowest number of symptomatic episodes in Pandemic I (6.5%) (table 1).

Risk factors for symptomatic virus detection and symptomatic virus episodes were siblings, season, childcare attendance at time of swab and older age (online supplemental table 4 and 5). Symptomatic virus detection rates were not higher in infants attending childcare compared with infants staying at home (symptomatic virus positive

Table 1 Respiratory viruses and respiratory symptoms in different pandemic phases

Characteristic	Historic, N=712*	Prepandemic, N=94*	Pandemic I, N=215*	Pandemic II, N=339*	P value overall	P value† prepandemic/pandemic I	P value† prepandemic/pandemic II
HRV‡	177 (25%)	23 (24%)	41 (19%)	85 (25%)	0.3	0.078	>0.9
AdV§	43 (6.0%)	1 (1.1%)	1 (0.5%)	14 (4.1%)	<0.001	0.002	0.3
MPV§	5 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0.4	0.6	0.3
RSV§	17 (2.4%)	0 (0%)	1 (0.5%)	3 (0.9%)	0.10	0.14	0.15
Flu_A§	1 (0.1%)	1 (1.1%)	0 (0%)	0 (0%)	0.2	>0.9	>0.9
Flu_B§	2 (0.3%)	0 (0%)	0 (0%)	0 (0%)	>0.9	>0.9	>0.9
PIV§	35 (4.9%)	0 (0%)	0 (0%)	11 (3.2%)	<0.001	0.002	0.4
SARS-CoV-2§	NA	0 (0%)	0 (0%)	8 (2.4%)	0.022	NA	NA
Any virus detection‡¶**	256 (36%)	25 (27%)	41 (19%)	105 (31%)	<0.001	<0.001	0.2
Virus co-detection§	24 (3.4%)	0 (0%)	0 (0%)	8 (2.4%)	0.081	0.09	0.6
Symptomatic virus detection‡¶**	138 (19%)	16 (17%)	15 (7.0%)	53 (16%)	<0.001	<0.001	0.2
Severe symptoms§	20 (2.8%)	1 (1.1%)	0 (0%)	6 (1.8%)	0.038	0.012	0.4
Mild symptoms§	40 (5.6%)	3 (3.2%)	7 (3.3%)	21 (6.2%)	0.4	0.2	0.6
Rhinitis‡	113 (16%)	15 (16%)	13 (6.0%)	46 (14%)	0.003	<0.001	0.3
Asymptomatic virus detection‡¶**	118 (16%)	8 (8.6%)	26 (12%)	52 (15%)	0.13	0.2	0.9
Symptomatic HRV detection‡	75 (11%)	15 (16%)	15 (7.0%)	43 (13%)	0.065	0.072	0.5
Asymptomatic HRV detection‡	102 (14%)	7 (7.5%)	26 (12%)	42 (12%)	0.3	0.6	0.6
Virus episodes‡¶**	204 (29%)	23 (24%)	33 (15%)	87 (26%)	0.001	<0.001	0.4
Symptomatic virus episodes‡¶**	115 (16%)	15 (16%)	14 (6.5%)	46 (14%)	0.004	<0.001	0.3
HRV episodes‡	127 (18%)	21 (22%)	32 (15%)	67 (20%)	0.3	0.2	0.6
Symptomatic HRV episodes‡	71 (10%)	14 (15%)	14 (6.5%)	37 (11%)	0.13	0.076	0.9

*n (%).
†Historic and prepandemic were taken together and compared to the two pandemic phases.
‡Pearson's χ^2 test.
§Fisher's exact test.
¶Codetections with different viruses at the same time were counted once.
**Except SARS-CoV-2.
AdV, human adenovirus; Flu A, influenza A virus; Flu B, influenza B virus; HRV, human rhinovirus; IQR, interquartile range; MPV, human metapneumovirus; PIV, human parainfluenza virus; RSV, respiratory syncytial virus.

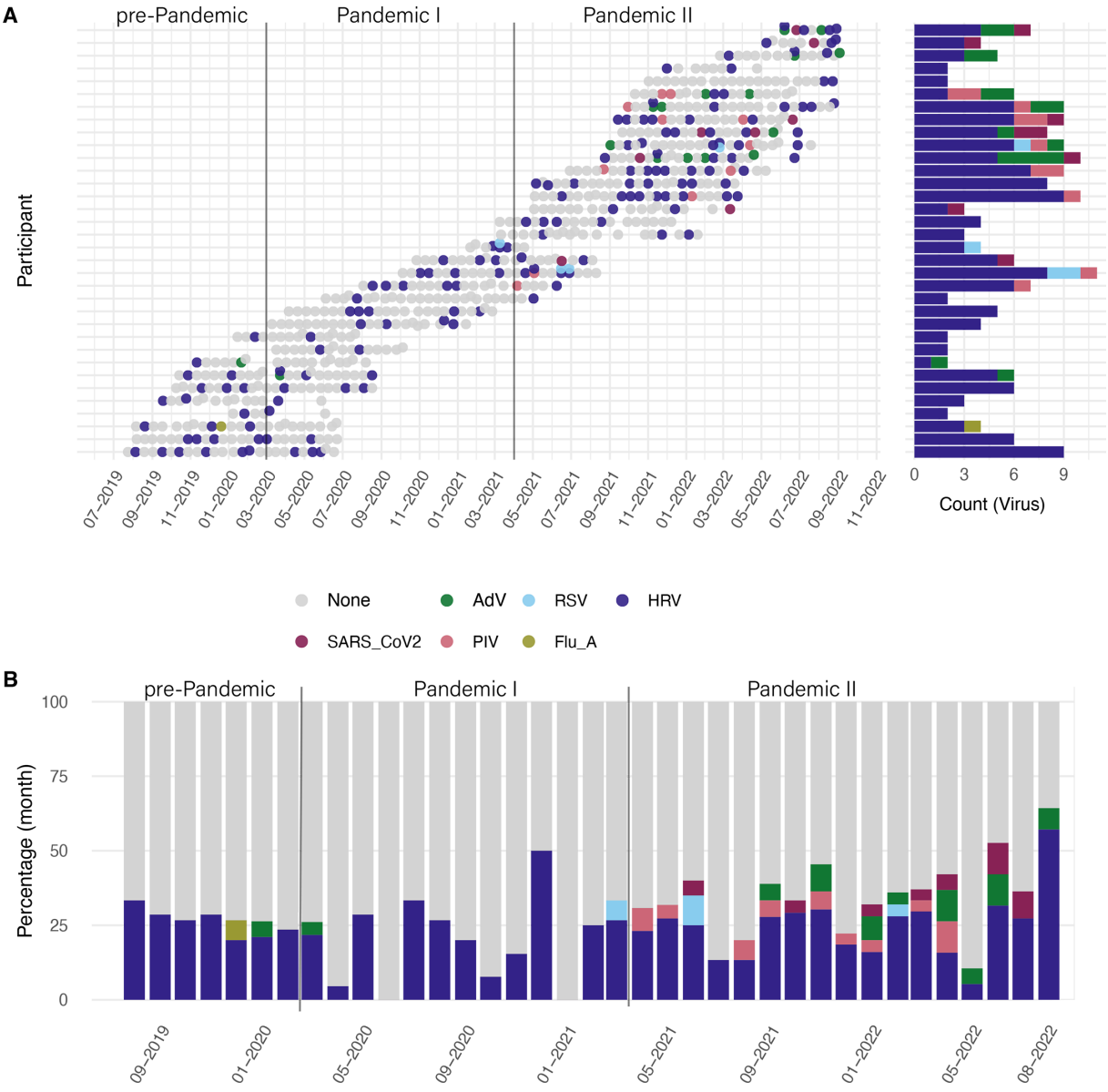

Figure 1 Respiratory virus detection throughout the SARS-CoV-2 pandemic. (A) The x-axis shows the monthly-analysed swabs in the study period. On the y-axis, each row reflects a study participant and each point a nasal swab. The colours display the detected viruses. The horizontal bar plot shows the absolute counts of each detected virus for each participant. (B) The monthly detection of respiratory viruses throughout the study period is displayed as bars. Time is shown on the x-axis and the percentage of detections in stacked bars on the y-axis. AdV, human adenovirus; Flu_A, influenza A virus; HRV, human rhinovirus; PIV, human parainfluenza virus; RSV, human respiratory syncytial virus.

swabs in infants at home: 8 (5.4%), in childcare: 7 (10%), p=0.2) in pandemic I, but numbers were low overall.

Age at first events

Age at first virus detection (symptomatic or overall) suggests a younger age of virus detection in pandemic II and an older age of symptomatic virus detection in pandemic I: virus detection: median (IQR) age (in days): historic=63 (46–104), prepandemic=85 (54–150), pandemic I=86 (72–100), pandemic II=48 (42–89), p=0.2; symptomatic virus detection: median (IQR) age (in days): historic=104 (83–150), prepandemic=146 (94–195), pandemic I=170 (107–228), pandemic II=92 (49–153), p=0.4). Lacking statistical significance could be due to the small sample sizes within the different groups. The age of first HRV detection did not differ between periods (historic=69 (48–130), prepandemic=85 (53–163), pandemic I=86 (70–105), pandemic II=66 (47–130), p=0.8).

Prevalence of HRV in the different time periods

In all time periods, the most frequently detected virus was HRV. In contrast to all other respiratory viruses, HRV persisted over the course of the pandemic (figure 2C). No difference of HRV prevalence could be seen throughout the time periods (historic=25%, prepandemic=24%,

Table 2 Multivariate logistic regression for virus detection

Variable	Category	OR	95% CI lower	95% CI upper	P value
Period					<0.01
	Historic	2.45	1.6	3.75	
	Prepandemic	1.96	1.02	3.78	
	Pandemic I	Ref			
	Pandemic II	2.04	1.26	3.29	
Season					0.49
	Spring	Ref			
	Summer	1.21	0.87	1.68	
	Autumn	1.08	0.77	1.52	
	Winter	0.96	0.68	1.34	
Caesarean section	Yes	0.94	0.68	1.29	0.69
Sex	Male	1.08	0.82	1.41	0.60
Siblings	Yes	1.17	0.85	1.59	0.34
Childcare at swab	Yes	1.13	0.8	1.6	0.49
Breastfeeding at swab	Yes	1.07	0.77	1.48	0.68
Atopic mother	Yes	1.2	0.9	1.59	0.22
Age (days, category)					0.25
	0–90	Ref			
	91–180	1.07	0.75	1.52	
	181–270	1.19	0.8	1.75	
	>270	1.52	0.98	2.36	

pandemic I=19%, pandemic II=25%, table 1 and online supplemental table 6). Results did not change investigating HRV episodes (table 1).

We assessed potential risk factors for HRV detection and observed a decreased risk for HRV detection in winter (compared with the reference category spring: OR 0.63, 95% CI 0.43 to 0.93, p=0.01, online supplemental table 6). None of the other investigated risk factors were associated with HRV detection. HRV detection was not higher among infants attending childcare compared with infants staying at home in pandemic I (18% vs 20%, p=0.7).

Symptomatic HRV detection

We observed a decrease in symptomatic HRV detection in pandemic I compared with the other time periods (historic=11%, prepandemic=16%, pandemic I=7%, pandemic II=13%, table 1 and online supplemental table 7). Risk factors for symptomatic HRV detection and symptomatic HRV episodes were season of swab (lowest OR in winter and highest OR in autumn) having siblings, childcare attendance at the time of swab and increasing age (online supplemental table7 and 8).

We aimed to better understand asymptomatic and symptomatic HRV detection and the association with the potential risk factors of having siblings and attending childcare during the different time periods. We tested the interaction between the environmental factors childcare attendance and the presence of siblings in relation to HRV detection (overall and symptomatic), but no interactions were identified (figure 3).

SARS-CoV-2

SARS-CoV-2 was only detected in pandemic II when NPIs were relaxed (table 1, figure 2D). SARS-CoV-2 was detected in eight swabs (2.4%) from seven infants. One infant was infected two times, but not in subsequent weeks. Four out of the seven infants with SARS-CoV-2 detection reported mild respiratory symptoms, none of the infected infants was severely ill (figure 2D). Ct values ranged from 17.6 to 38.5 (mean=26.2). None of the parents of the seven infants with SARS-CoV-2 detection reported respiratory symptoms for themselves 14 days before or after the positive swabs of their children. In our cohort, 11 parents reported to be tested positive for SARS-CoV-2, but in none of these cases, swabs of their children were detected positive for SARS-CoV-2 and no respiratory symptoms were reported.

DISCUSSION

This prospective longitudinal study investigated the effect of NPIs in Switzerland on the prevalence of common respiratory viruses in otherwise healthy infants in the outpatient setting during the SARS-CoV-2 pandemic.

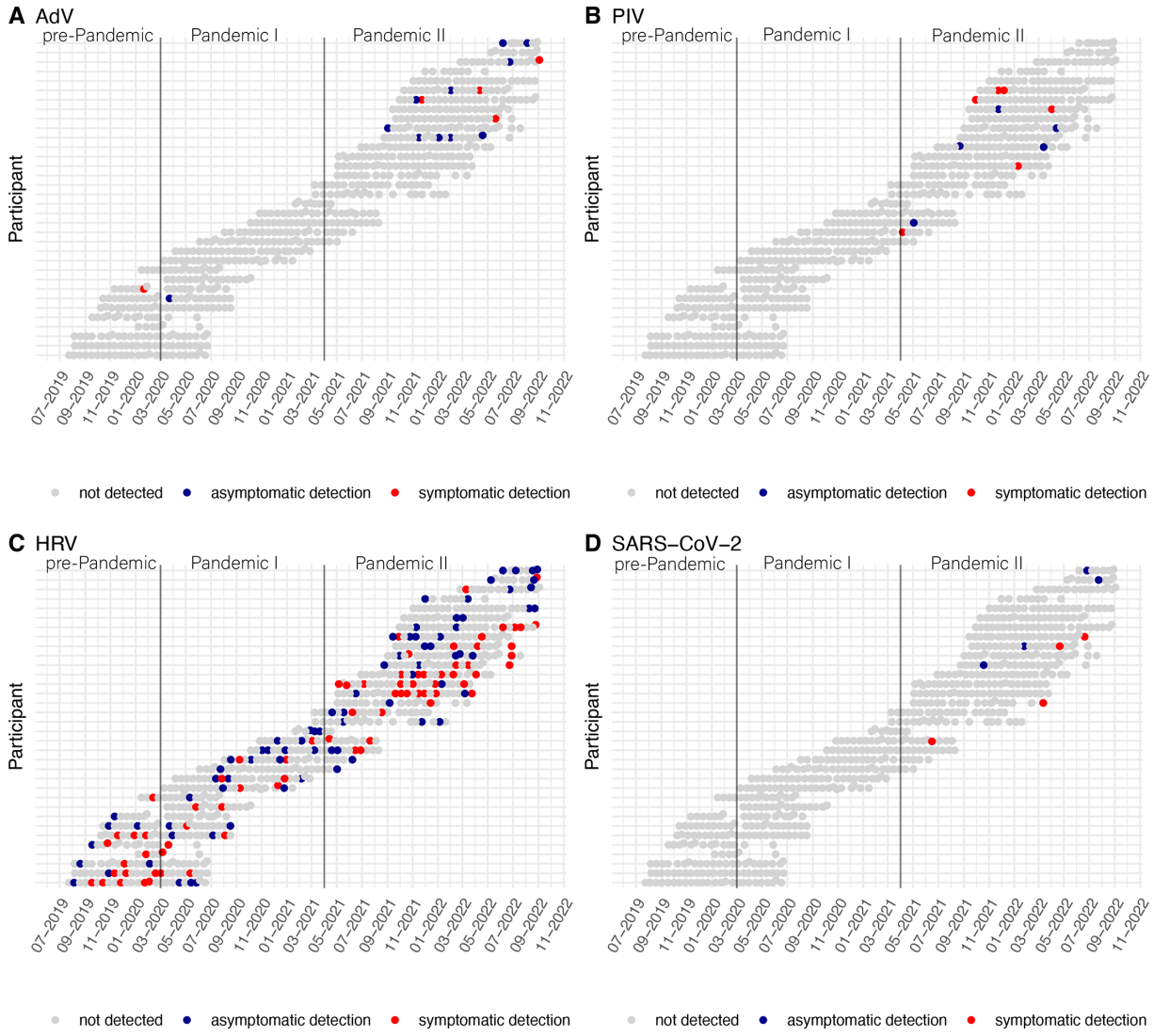

Figure 2 Symptomatic and asymptomatic detection of four different viruses. The x-axes show the monthly-analysed swabs in the study period. On the y-axes, each row reflects a study participant and each point a nasal swab. Red colour shows symptomatic detection, blue colour asymptomatic detection and grey colour no detection of the virus displayed. (A) PIV, (B) AdV, (C) HRV, (D) SARS-CoV-2. AdV, human adenovirus; HRV, human rhinovirus; PIV, human parainfluenza virus.

In line with data from hospitalised patients and emergency departments from different countries, NPIs lead to a decrease in respiratory virus prevalence.[5] HRV prevalence remained stable, mainly driven by asymptomatic episodes. We can report known risk factors for respiratory virus infection (siblings, childcare, older age, season) in our study,[19] however during strict lockdown, infants attending childcare were not at higher risk for asymptomatic or symptomatic virus detection, also age of first virus detection did not change. Severe virus infections were very low in the study population overall and could not be detected during stricter lockdown. In contrast to other countries, schools were closed only for a short time period and day care was always possible in Switzerland during the pandemic. Our data are in line with other studies from Switzerland reporting no negative effects from open schools and day care facilities.[17 20] High rates of asymptomatic or mildly symptomatic virus detection (non-medically attended) have been described in large studies before SARS-CoV-2.[21 22] Our findings from the outpatient setting (including asymptomatic virus episodes) can thus contribute to a better understanding for dynamics of respiratory virus transmission during the SARS-CoV-2 pandemic.

As expected, HRV was the most frequently detected virus.[21 22] Symptomatic HRV episodes decreased during (strict) NPIs; however, asymptomatic HRV detection was not affected by NPIs. Several studies from numerous countries report a decreased but persisting HRV prevalence despite NPIs—in contrast to other viruses like influenza or RSV.[23–26]

HRV are non-enveloped viruses, rendering them less sensitive to disinfection agents. They might thus be less susceptible to inactivation by handwashing.[27] Most other respiratory viruses are transmitted by aerosols. However, for HRV predominant, transmission is via direct contact

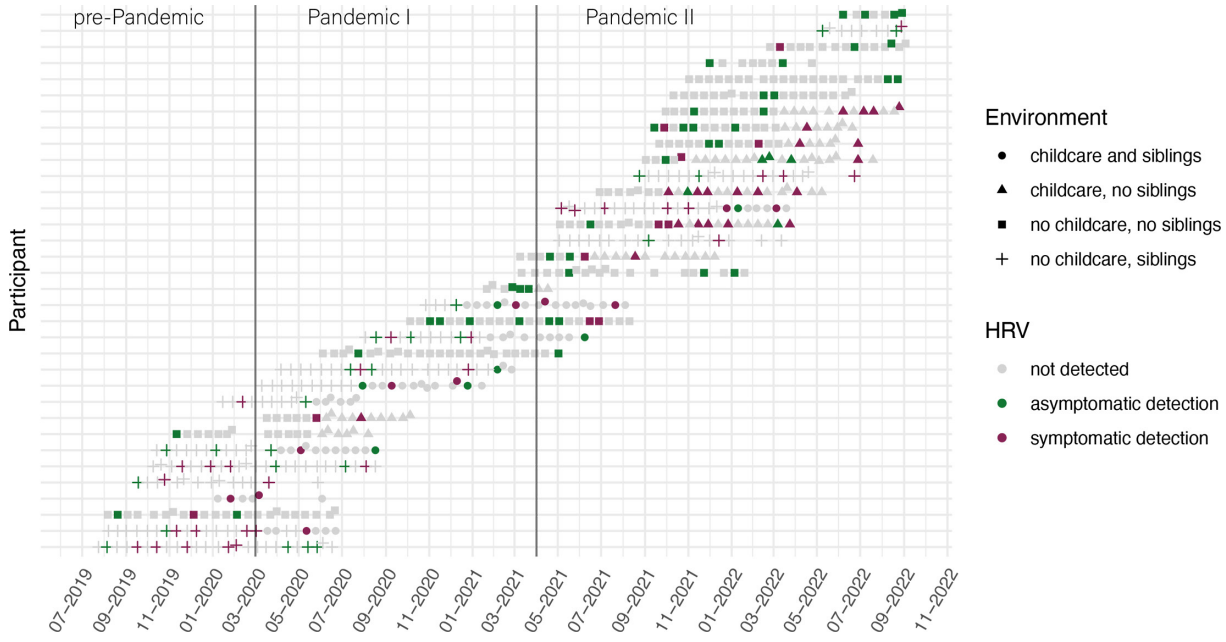

Figure 3 HRV detection and environment. (A) The x-axis shows the monthly-analysed swabs in the study period. On the y-axis, each row reflects a study participant and each symbol a nasal swab. Red colour shows symptomatic detection, green colour asymptomatic detection and grey colour no detection of HRV. Different symbols as explained in the legend show whether infants attended childcare or had siblings. HRV, human rhinovirus.

infection route and may therefore be less preventable by the use of facemasks.[28] In our study, day care attendance did not increase the risk of HRV infection, nor did we find a strong rebound of HRV at any time. We could not identify specific risk factors for HRV infection (eg, siblings, childcare and possible interactions, see figure 3) during strict lockdown or after. This is in line with a study from Finland, where reopening of schools and day care centres seemed to have no immediate impact on the incidences of respiratory pathogens.[29] However, others report rising HRV detection rates after school/day care attendance restarted.[30] Cross-serotype T-cell-mediated immunity to HRV has been described[31] and might require frequent boosting. A reduced HRV exposure could result in decreased population immunity and increased susceptibility to the virus especially in children, who are immunologically naïve to many HRV serotypes.[32] As day care was possible throughout the whole pandemic and schools closed only for a short time period in Switzerland, decreased herd immunity in the population might be less pronounced.[33] Larger studies are needed to investigate this matter further. The reason why especially asymptomatic HRV episodes persisted in our study cohort remain unclear. We can only speculate that changed virus patterns (eg, less influenza) and thus changed virus–virus interference[34] or altered immune responses due to changed exposition to other pathogens and/or a different host microbiota could contribute to this finding. A prepandemic longitudinal cohort study in healthy infants reported an association of asymptomatic HRV detection with a higher susceptibility towards RTIs later in life.[35] This underlines the relevance of this finding, and it should be examined in detail in future studies. In our cohort, a follow-up visit is always suggested at the age of 6 years[15]—this will help to better understand possible associations with later asthma and/or RTIs. A rebound of respiratory viruses could be detected after most NPIs were relaxed, mainly driven by increased numbers of ADV and PIV detection. In studies from hospitalised and severely ill patients, an increase of RSV and influenza was mainly reported.[7 27 36–38] Our results are in line with studies from outpatient surveillance from Germany and Finland, where ADV and PIV strongly increased.[7 24 38 39] In our cohort, it was likely a 'return to normal state' (as numbers are comparable to the historic data set) and not an overshoot of infections.

Due to our small study population and the low number of nasal swabs with SARS-CoV-2 detection, it is not possible to draw final conclusions on spreading mechanisms or disease burden of the virus. SARS-CoV-2 detection was only present when strict NPIs were relaxed, as reported by others before.[36 37] At this time, the dominant SARS-CoV-2 variants in Switzerland were the Delta and different Omicron variants (see online supplemental figure 1).[40] In line, these variants seemed to affect the paediatric population more than previous variants.[41] Surprisingly, we could not detect any SARS-CoV-2 in the initial phase of the pandemic. In addition, SARS-CoV-2 was not detected in two consecutive samples (or more) and no severe SARS-CoV-2 episodes were reported. This is in line with most paediatric studies; fortunately, SARS-CoV-2 infections especially in infancy are very rare.[34] Importantly, also asymptomatic SARS-CoV-2 detection was

very low in our cohort and independent of childcare attendance and having older siblings. Parents from infants positive for SARS-CoV-2 in our study did not report respiratory symptoms—vice versa infants from parents tested positive for SARS-CoV-2 were not infected. Thus, asymptomatic spread of SARS-CoV-2 through young children (either within families or within day care facilities) in our study cohort seems unlikely. However, the role of children in transmission of SARS-CoV-2 remains unclear and likely depends on different variables (such as sociodemographic factors, household characteristics, local policies or virus evolution).[42–44] These results are important regarding implementations of NPIs especially concerning day care and school closing, as by now numerous studies have described their negative socioeconomic and psychological impacts on children.[45]

A major strength of this study is the prospective and longitudinal study design with standardised, biweekly sampling not restricted to scheduled visits or periods of respiratory illness and a historic control group. Detailed information about sociodemographic factors and the weekly documentation of changes in environmental exposures allowed us to assess a number of possible confounders or risk factors. The longitudinal follow-up provides a comprehensive overall picture of the dynamics of virus detection—having not only a 'snap shot' of virus colonisation at a certain time point. A limitation of this study is the small number of study infants. To detect further differences in low prevalent viruses between the study periods, larger numbers are needed. This is also true for a better understanding of episodes of severe respiratory infection. Furthermore, sequencing and subtyping of HRV were not performed in our study, so HRV subgroups could not be analysed. Also in our multiplex PCR, some common viruses such as human coronavirus were not assessed. Nasal swabs from parents were not routinely performed, thus results of SARS-CoV-2 infections were not assessed regularly.

CONCLUSION

In this small study, we found no evidence that infants contribute largely to asymptomatic spread of SARS-CoV-2. In contrast to the other respiratory viruses, we report continuous prevalence of HRV in our study during all pandemic phases, and most interestingly especially of asymptomatic episodes. This could prevent strong rebounds of certain (severe) virus infections, but the role of asymptomatic HRV prevalence remains unclear. In our cohort, a follow-up visit is planned at the age of 6 years, including lung function measurements. This will hopefully contribute to a better understanding. Although this has to be investigated in larger studies, our findings clearly underscore the importance of longitudinal cohort studies also capturing asymptomatic viral prevalence to understand viral dynamics—especially in a pandemic situation. Time will show how the changed epidemiological picture of 'non-SARS-CoV-2' viral detection will affect virus prevalence in the future.

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Acknowledgements We express our gratitude to all study participants and their families from the BILD cohort. We also sincerely thank Sandra Lüscher, Fabienne Furrer and Sybille Thommen for their invaluable contributions in managing the cohort and collecting data.

Collaborators Not applicable.

Contributors RS, IK and PL designed the study. RS, IK, ST, LHD, A-CK and XB were involved in data acquisition. RS, ST and IK collected clinical and metadata. PB was responsible for virus PCR. RS and IK performed and interpreted statistics. RS, IK, PL, UF, CA and PA interpreted the results. RS and IK wrote the manuscript. The BILD study group (information in the online data supplement) contributed to data collection. Families and children participating in the BILD study contributed to the data presented in this work. All listed authors read and approved the final manuscript. IK is the guarantor of this work.

Funding RS: Young Investigator Grant, Cystic Fibrosis Switzerland. Swiss National Science Foundation (SNF 182871/1, Professor Urs Frey). IK: Stiftung KinderInsel Bern University Hospital; Nachwuchsförderungs-Grant für translationale Forschung: 'Protected Research time'.

Competing interests PL reports grants and honoraria from OM Pharma, Vifor, and Vertex, not related to this work. PL also reports participation in advisory or monitoring boards for Polyphor, Santhera (DMC), Vertex, OM Pharma, Vifor, Allecra, and Sanofi Aventis, none of which are related to this work. RS received grants from Cystic Fibrosis Switzerland, the Swiss National Science Foundation, and Vertex, unrelated to this work. IK received grants from Stiftung KinderInsel and the University of Bern related to this work, as well as honoraria from Vertex, outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Ethics Committee of Bern, Switzerland (project number 2019-01072). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. Please contact the corresponding author.

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