

**Decline in Pneumococcal Disease in Young Children during the COVID-19 Pandemic in Israel Associated with Suppression of seasonal Respiratory Viruses, despite Persistent Pneumococcal Carriage: A Prospective Cohort Study**

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**Summary:** During the COVID-19 pandemic, pneumococcal pneumonia and invasive infections were strongly reduced coinciding with reduced activity of RSV, influenza and hMPV. Notably, prevalence, serotype distribution and density of pneumococcal carriage were similar to previous seasons.

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## Abstract

**Background:** The incidence of invasive pneumococcal disease (IPD) declined during the COVID-19 pandemic. Previous studies hypothesized that this was due to reduced pneumococcal transmission resulting from non-pharmaceutical interventions. We used multiple ongoing cohort surveillance projects in children <5 years to test this hypothesis.

**Methods:** The first SARS-CoV-2 cases were detected in February-2020, resulting in a full lockdown, followed by several partial restrictions. Data from ongoing surveillance projects captured the incidence dynamics of community-acquired alveolar pneumonia (CAAP), non-alveolar lower respiratory infections necessitating chest X-rays (NA-LRI), nasopharyngeal pneumococcal carriage in non-respiratory visits, nasopharyngeal respiratory virus detection (by PCR), and nationwide invasive pneumococcal disease (IPD). Monthly rates (January-2020 through February-2021 vs. mean monthly rates 2016-2019 [expected rates]) adjusted for age and ethnicity, were compared.

**Results:** CAAP and bacteremic pneumococcal pneumonia were strongly reduced (incidence rate ratios, [IRRs] .07 and .19, respectively); NA-LRI and non-pneumonia IPD were also reduced, with a lesser magnitude (IRRs, .46 and .42, respectively). In contrast, pneumococcal carriage prevalence was only slightly reduced, and density of colonization and pneumococcal serotype distributions were similar to previous years. The decline in pneumococcus-associated disease was temporally associated with a full suppression of RSV, influenza viruses, and hMPV, often implicated as co-pathogens with pneumococcus. In contrast, adenovirus, rhinovirus, and parainfluenza activities were within or above expected levels.

**Conclusions:** Reductions in pneumococcal and pneumococcus-associated diseases occurring during the COVID-19 pandemic in Israel were not predominantly related to reduced pneumococcal carriage and density, but were strongly associated with the disappearance of specific respiratory viruses.

**Key words:** Pneumococcal pneumoniae; respiratory viruses; COVID-19; lower respiratory infections

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## Introduction

*Streptococcus pneumoniae* (pneumococcus) is a leading cause of acute respiratory and invasive infections in all ages [1]. Pneumococcal disease rates are influenced by the frequency of pneumococcal exposure (i.e., nasopharyngeal carriage prevalence among healthy children) and host susceptibility. Epidemiological, clinical, and experimental evidence suggests that certain viruses can increase the susceptibility to pneumococcal disease [1-3]. Since SARS-CoV-2 is a respiratory virus, concerns were raised that COVID-19 could increase susceptibility to pneumonia and invasive pneumococcal diseases (IPD). However, early reports during the pandemic demonstrated reduced IPD rates [4], and co-infections of these two pathogens were infrequent [5]. At the same time, non-pharmacological interventions (NPIs) such as social distancing and travel restrictions were associated with an unexpected global suppression of the activity of several seasonal respiratory viruses, often implicated as co-pathogens with pneumococcus. These include respiratory syncytial virus (RSV), influenza viruses, and human metapneumovirus (hMPV) [6, 7]. We hypothesized that the reduction in pneumococcal disease in children observed during the COVID-19 pandemic was due mainly to the reduction in the incidence of these seasonal respiratory viruses rather than to reductions in transmission of pneumococcus.

We took advantage of multiple ongoing prospective pediatric cohort surveillance projects in our region to assess the dynamics of various clinical presentations associated with pneumococcus during the COVID-19 pandemic period (January 2020 through February 2021). The pneumococcal disease rates during the pandemic were compared to those during 2016-2019 and to common seasonal respiratory virus dynamics. Uniquely, our data included information on clinical pneumococcal diseases, pneumococcal carriage among healthy

children, and the activity of specific respiratory viruses. These data provide an opportunity to understand the factors influencing the incidence of pneumococcal disease in children.

## Methods

### Setting

The Soroka University Medical Center (SUMC) is the only hospital in the Negev, southern Israel, providing primary health services to the entire population of the region. Over 95% of the children living in the region are served by the SUMC, enabling incidence calculations. Two ethnic populations reside in southern Israel: The Bedouin population, with infectious diseases epidemiology similar to lower-middle income countries; and the Jewish population whose epidemiology resembles higher-income Western countries. Higher rates of respiratory and invasive disease, and pneumococcal carriage were reported among Bedouin than among Jewish children [8]. In 2020, there were ~97,400 children <5 years in the Negev; ~50% were Bedouin [9].

Pneumococcal conjugate vaccines (PCVs) were introduced to the National Immunization Plan in 2009 (PCV7) and 2010 (PCV13); since 2013 ~90% of children have received three doses [10].

### COVID-19 in Israel

The first COVID-19 case occurred in Israel on February 21, 2020. Three official national lockdown periods, with variable degrees of stringency, were implemented thereafter (**Supplementary Figure 1**): April through Mid-May 2020; Mid-September to November 2020; and December to early February 2021. (For detailed **description see Supplementary Figure 1**). The numbers of new COVID-19 cases nationally increased from <50 by the end of the first lockdown to ~6,000, and ~4,000 before the second and third lockdowns,

respectively, reaching >8,000 daily new cases by January 2021. With increasing vaccination coverage, the rates declined towards mid-February.

### **Study design**

The study population for pneumonia and virological testing comprised all cohorts of children <5 years living in our region January 2016 -February 2021. For IPD, we included all children <5 years nationwide. For pneumococcal carriage, we included children <3 years in our region. Our data were derived from multiple ongoing, prospective long-standing cohort surveillance programs. Monthly incidence or prevalence rates during 2020-2021 were compared to mean monthly rates during 2016-2019. The total numbers for each database and the comparison of demographic characteristics, during 2016-2019 and January 2020-February 2021 are presented in **Table 1** (for detailed description, see (**Supplementary Material**)). The following outcomes were assessed:

- 1) *Community-acquired alveolar pneumonia (CAAP)*: Since November 2001, all children <5 years visiting the Pediatric Emergency Room (PER) or hospitalized requiring chest radiography were included. CAAP was defined as per the World Health Organization (WHO) Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children [12].
- 2) *Non-alveolar lower respiratory infections (NA-LRI)*: All children <5 years visiting PER or hospitalized for LRIs requiring chest radiography, excluding those with CAAP [13].

- 3) *Invasive pneumococcal diseases (IPD)*: This is an ongoing, nationwide prospective, active surveillance, initiated in 1989. All IPD cases in children <5 years were reported monthly by local investigators in all 27 medical centers where blood and CSF cultures were obtained, accounting for >95% all IPD cases. A bacteremic pneumonia episode was defined as an episode diagnosed as pneumonia by the treating physician during which *S. pneumoniae* was isolated from blood [14]. A non-pneumonia IPD episode was defined as an IPD episode excluding bacteremic pneumonia.
- 4) *Nasopharyngeal pneumococcal carriage*:
- a) *Children visiting the SUMC*: Since November 2009, each working day nasopharyngeal cultures have been obtained from the first eight children <5 years seen at the PER or within 48 hours, if hospitalized. Children <3 years without respiratory infections were included in the current analysis. Positive cultures were assessed by semi-quantitative methodology [15].
- b) *Healthy children*: Since 2011, nasopharyngeal cultures have been obtained from healthy children <3 years, presenting for vaccination [16]. The detailed methodology was previously described [10].
- 5) *Nasopharyngeal detection of respiratory viruses in hospitalized children*: Respiratory virus samples were obtained as per clinical indication and sent to the SUMC virology laboratory for detection of RSV, influenza A and B viruses, parainfluenza virus, adenovirus, hMPV and rhinovirus (rhinovirus was added since February 2019), as previously described [17] (**Supplementary Table 1**).



- 6) *All pediatric PER visits and hospitalizations*: Data were collected from the SUMC computerized records.
  
- 7) *Hospital visits for all-cause trauma*: PER visits with trauma diagnosis were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge codes.

All the above projects, as well as the overall current study were approved by the SUMC Ethics Committee.

### **Statistical analysis**

Demographical characteristics were compared between the pre-COVID-19 years (2016-2019) and the COVID-19 period (2020-2021) using the Pearson  $\chi^2$  test or Student's *t*-test, as appropriate. Monthly incidence rates for all end-points were calculated by age (<2, 2-4 years) and ethnicity (Bedouin, Jewish). The monthly proportions of positive pneumococcal nasopharyngeal cultures were calculated out of all samples for children <1 and 2-3 years, except during April-May 2020 (the strict lockdown) due to disruptions in sample collection. No difference in the age distribution of the population <5 was observed during the study years. Rate ratios of incidences and proportions were calculated to compare COVID-19 and pre-COVID-19 periods. All rate ratios were adjusted for ethnicity and age using the Cochran-Mantel-Haenszel method.

The statistical significance threshold was  $P < .05$ . Data were analyzed using R 4.0.2 [18].

## Results

The first COVID-19 case was identified on February 21, 2020. All NPIs that followed, along with the dynamics of new daily nationwide COVID-19 cases, are described in **Supplementary Figure 1**. Until February 28, 2021, 777,155 COVID-19 cases were documented.

### *The COVID-19 pandemic was associated with reduced rates of IPD*

During October 2020 through February 2021, there was a marked reduction in IPD rates vs. expected (IRR .47; 95% CI: .32 - .70) (**Supplementary Tables 2, 3; Supplementary Figure 2**). However, while bacteremic pneumonia declined by 81% compared to the pre-COVID period, non-pneumonia IPD declined only by 42% (**Figure 1A-D**).

### *The COVID-19 pandemic was associated with reduced CAAP rates, and to a lesser magnitude, reduced NA-LRI rates*

Overall LRI rates were reduced during fall and winter 2020-2021 (**Supplementary Figure 3**): IRR vs. 2016-2019, .47 (95% CI .44 – .50)

*Community-acquired alveolar pneumonia:* During 2016-2019, a clear seasonality of CAAP, typically thought to be of bacterial etiology, was seen, peaking during December through February and a nadir during June through August (**Figure 1E, 1F; Supplementary Tables 2, 4**). In the first quarter of 2020, the dynamics of CAAP were similar to those in previous years. During the second quarter, the rates were strongly reduced, coinciding with the strict first lockdown. During the summer months, CAAP rates caught up with the expected seasonal rates, but in October 2020 through February 2021 the rates were extremely low (IRR vs. 2016-2019: .07; 95% CI .05-.10).

*Non-alveolar LRIs (NA-LRI):* As with CAAP dynamics, in 2016-2019, NA-LRIs incidence peaked during December through February with a nadir in June through August (**Figure 1G, 1H; Supplementary Tables 2, 5**). However, the variations between seasons were of a lesser magnitude compared to CAAP. As observed for CAAP, during the first quarter of 2020 the dynamics were not affected, and the second quarter was affected mainly by the first strict lockdown. However, unlike CAAP rates, NA-LRIs rates increased again following the first lockdown to reach the expected seasonal rate in July-September. The reduction during October 2020 to February 2021 vs. the rates in 2016-2019 was only half compared to that of CAAP (46%, 95% CI 43-50%; vs. 93%, 95% CI 90-95%, respectively).

*Nasopharyngeal pneumococcal carriage was not significantly affected during COVID-19 pandemic*

During 2016-2019, the mean proportion of children <3 years old carrying pneumococcus was  $44.3 \pm 1.9\%$ , ranging from 33.8% (August) to 53.8% (December) (**Figure 2; Supplementary Table 6**). Nasopharyngeal testing was temporarily interrupted during the months April-May 2020. Although carriage rates were somewhat reduced in October-December 2020, the rates during January-February 2021 were not significantly different than those in previous years (**Supplementary Table 6**). Furthermore, using a semi-quantitative method, the mean bacterial density was within the ranges of the previous years. Additionally, no notable difference in pneumococcal serotype distribution between the COVID-19 and the pre-COVID period was seen (**Supplementary Table 7**).

***The COVID-19 pandemic was associated with a marked suppression of RSV, influenza viruses, and hMPV circulation***

The detection of respiratory viruses in children during the four years preceding 2020 showed typical dynamics of temperate zone seasonality [19] (**Figures 3, 4; Supplementary Table 8**). Apart from rhinovirus, which was common throughout the year, the most prevalent virus was RSV. Fall to early-spring seasonality was seen for RSV, influenza viruses, and hMPV; adenovirus was perennial with some decrease in the summer months; parainfluenza was lower in winter and spring compared to summer and fall. From January through March 2020, the detection of respiratory viruses was within that expected for the season. During the first (strict) lockdown, very few samples were obtained for viruses, due to reductions in all hospital visits. However, thereafter, several important observations were noted: 1) Parainfluenza was undetected from April to November, but sharply increased in December 2020 through February 2021, to levels markedly higher than those seen since 2016; 2) RSV, influenza viruses, and hMPV first decreased during April, to non-detectable levels, as expected seasonally (except for two RSV-detections, in August and September [one in each month]). However, unexpectedly, a complete suppression continued through February 2021; 3) after the first lockdown (March-April 2020), adenovirus and rhinovirus activity resumed to levels observed in previous years (for rhinovirus, only activity since February 2019 was available for comparison).

***The dynamics of pneumococcus-associated disease rates were temporally associated with the dynamics of RSV, influenza viruses, and hMPV activity***

Throughout the study duration, excluding the first strict lockdown period, the dynamics of pneumococcus-associated disease closely followed those of RSV, influenza viruses, and hMPV. This was most striking with bacteremic pneumonia (**Supplementary Figure 4**) and

CAAP. For NA-LRI and non-pneumonia IPD, the association was less apparent. However, the peak that would typically occur during winter, coinciding with epidemics of RSV, influenza viruses, and hMPV did not occur (**Supplementary Figure 5**).

### ***Hospital visit rates for trauma vs non-trauma***

We evaluated trends in hospital visits for trauma, since they are essentially independent of respiratory infections, to examine whether some of the observed reductions in the reporting of LRIs will be related to lower detection rates during the COVID-19 epidemic (**Supplementary Figure 6**). As expected, trauma visits peaked in the warm months, in contrast to the non-trauma visits, peaking during fall and winter. For both, a reduction during the first strict lockdown period was seen, but the trauma visit returned to close-to-normal rates, while the overall visits failed to show the expected fall and winter spike.

### **Discussion**

This prospective cohort study demonstrates a marked reduction of hospital visit rates in southern Israel for both LRI and pneumococcal disease in children <5 year old during winter 2020-2021, coinciding with the peak of the COVID-19 pandemic. This reduction was closely associated with an extreme suppression of the circulation of specific respiratory viruses: RSV, influenza viruses, and hMPV. The most dramatic reductions were seen in CAAP and bacteremic pneumonia, but NA-LRI and non-pneumonia IPD were also reduced. In contrast, during the same period, pneumococcal nasopharyngeal carriage prevalence was only slightly reduced, and density of colonization and pneumococcal serotype distribution were similar to those in previous years. This was a surprising finding because carriage is a prerequisite for pneumococcal disease.

In most published reports, NPIs were suggested to be responsible for reduced pneumococcal carriage, circulation, and transmission, resulting in reduced pneumococcal disease [20-25]. Our findings lead to the hypothesis that the reduction in pneumococcus-associated disease during fall-winter 2020-2021 resulted mainly from the complete suppression of specific respiratory viruses rather than reduced transmissibility or serotype selection of *S. pneumoniae* in the community. These viruses, especially RSV and influenza are epidemiologically associated with both increased pneumococcal bacteremic pneumonia and non-bacteremic CAAP [14, 26]. Furthermore, the most frequently detected virus during IPD and alveolar pneumonia is RSV, followed by influenza viruses and hMPV [3, 27]. The strong association of these viruses with pneumonia might explain why the reduction during fall-winter 2020-2021 was of a higher magnitude in the case of bacteremic pneumonia and CAAP than in non-pneumonia IPD and NA-LRIs.

While, by definition, *S. pneumoniae* is the causative agent for IPD, the extent of pneumococcal involvement in CAAP and NA-LRI is still not fully clarified. This cannot be directly answered, since often pathogens cannot be isolated in young children, and detection of bacteria or viruses in the respiratory tract does not necessarily imply their causative role. However, measuring pneumococcal PCV impact on CAAP and LRI (the vaccine probe approach) provides a powerful tool for inference on the likely causative role of *S. pneumoniae* in these clinical outcomes [28]. Studies from Israel and elsewhere, have demonstrated a ~50% reduction in CAAP in young children following PCV implementation [13, 29], thus strongly suggesting an extensive causative role of *S. pneumoniae* in CAAP during the pre-PCV era.

Our NA-LRI cases were severe enough to warrant a chest radiography, but per definition, those with CAAP were excluded. Studies have shown that in such cases, a rate reduction of

$\geq 25\%$  was observed in young children post PCV implementation, including a 34% reduction in our region [13]. Using a similar logic as per CAAP, it is plausible that vaccine-serotype pneumococci also played an important role in NA-LRI, although of a lesser magnitude. The similarity in dynamics between CAAP and IPD, in particular bacteremic pneumonia is therefore not surprising.

Animal and human models have demonstrated that viral infections predispose not only to post-viral pneumococcal diseases, but frequently true respiratory viral-bacterial co-infections [1]. This explains why PCVs reduced hospitalization for viral infections, including viral pneumonia [3, 30]. Multiple mechanisms by which viruses enhance virulence or invasiveness of *S. pneumoniae* were described, mainly with RSV and influenza viruses [31, 32]. It is therefore not surprising that the seasonality of IPD and pneumonia overlap, especially regarding CAAP and bacteremic pneumonia [14]. It is also plausible that the suppression of CAAP and IPD (and bacteremic pneumonia in particular) is deeper than that of NA-LRI diseases for which a lower causative role of *S. pneumoniae* is assumed.

The dynamics of NA-LRIs were similar, but not identical to those of CAAP. After the initial rate reduction during the strict first lockdown, the rates returned to those seasonally expected and observed in 2016-2019. Despite this, the expected late-fall and winter increases did not occur, presumably due to the absence of RSV, influenza viruses, and hMPV. Yet, the rates were not reduced as much as those of CAAP, but rather showed the same magnitude as those in summer. The NA-LRI pattern in 2020-21 suggests that viruses such as parainfluenza and adenovirus, and potentially also rhinovirus and others could play a relative greater role for this entity than for CAAP.

It is not clear why adenovirus, and rhinovirus rates were not significantly decreased during 2020-2021, in contrast to RSV, hMPV, and influenza virus. While adenovirus can be carried

for long periods, rhinoviruses are carried only for short periods [33, 34], and thus its high prevalence suggests frequent infections.

Multiple reports showed off-season re-emergence of RSV and hMPV worldwide, mostly in spring and summer 2021. In Germany, re-emergence of IPD was speculated to be linked to viral re-emergence. In Israel, the Ministry of Health reported re-emergence of hMPV and RSV in spring and summer with parallel re-emergence of hospital visits for pneumonia in children <5 years [35]. Preliminary results by our study group suggest co-re-emergence of RSV, hMPV, and pneumococcal-associated diseases (Data not shown). Further detailed analysis is planned.

The main strength of our study is its prospective conduct, using multiple ongoing cohort surveillance programs in the same population, enabling to compare dynamics during the pandemic to those during previous years, on the one hand, and different outcomes, on the other, with appropriate adjustments for time, age and ethnicity. The main weakness of the current study was the inability to determine with certainty the causative agents in the CAAP and NA-LRI cases, a difficulty inherent to all studies on LRI in infants and young children. An additional weakness was that we did not attempt to diagnose all potential viral pathogens including non-COVID-19 corona viruses.

In conclusion, the reductions in pneumococcal disease in children during the COVID-19 pandemic were not predominantly related to reduced or modified pneumococcal carriage, prevalence, or density. Instead, reductions could be related to the unprecedented suppression of the activity of specific viruses, capable of increasing the virulence of *S. pneumoniae* in children. The relative contribution of facial masking and social distancing to the observed findings still remains to be determined.



## Notes

### Conflict of Interest

**Shalom Ben-Shimol** has received grant/research support, honorarium for scientific consultancy, speaker bureau and participation in advisory committees from Pfizer Inc.; honorarium for scientific consultancy, speaker bureau and participation in advisory committees from MSD; speaker bureau from GlaxoSmithkline.

**David Greenberg** has received honorarium for scientific consultancy and speaker bureau from Pfizer, Inc.; grant/research support, honorarium for scientific consultancy a speaker bureau from MSD; honorarium for scientific consultancy and speaker bureau from GlaxoSmithkline.

**Daniel M. Weinberger** has received consulting fees from Pfizer, Merck, and Affinivax for work unrelated to this manuscript and is Principal Investigator on research grants from Pfizer and Merck to Yale University.

**Ron Dagan** has received grant/research support, honorarium for scientific consultancy, payment for expert testimony, speaker bureau and participation in advisory committees from Pfizer Inc.; grant/research support, honorarium for scientific consultancy, speaker bureau and participation in advisory committees from MSD; grant/research support from MedImmune, Speaker bureau from Sanofi Pasteur; honorarium for educational activities from GSK; participation on DSMB/Advisory Board for Biondvax; consulting fees from Memed.

**All the other authors** have no financial interest to declare.

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**Table 1. Demographics of the study population**

	<b>Total</b>	<b>2016-2019</b>	<b>2020-2021</b>	<b>P value<sup>a</sup></b>
<b>Viruses</b>				
Cases	24,088	19,448	4,640	
Age; months (mean±SD)	14.2±14.8	14.0±14.7	14.7±15.2	.005 <sup>b</sup>
Ethnicity; n (%)				
Jewish	8,454 (35.1%)	7,016 (36.1%)	1,438 (31.0%)	<.001 <sup>c</sup>
Bedouin	15,634 (64.9%)	12,432 (63.9%)	3,202 (69.0%)	
<b>ER Visits</b>				
Cases	121,606	99,090	22,516	
Age; months (mean±SD)	20.9±16.7	20.8±16.7	21.3±17.0	<.001 <sup>b</sup>
Ethnicity <sup>d</sup> ; n (%)				
Jewish	55,388 (45.6%)	45,637 (46.1%)	9,751 (43.3%)	<.001 <sup>c</sup>
Bedouin	66,105 (54.4%)	53,352 (53.9%)	12,753 (56.7%)	
<b>Trauma</b>				
Cases	17,585	14,165	3,420	
Age; months (mean±SD)	28.9±16.1	28.9±16.1	29.0±16.1	.748 <sup>b</sup>
Ethnicity <sup>e</sup> ; n (%)				
Jewish	8,006 (45.5%)	6,473 (45.7%)	1,533 (44.8%)	.345 <sup>c</sup>
Bedouin	9,572 (54.5%)	7,685 (54.3%)	1,887 (55.2%)	

**Carriage**

Cases	9,330	7,922	1,408	
Age; months (mean±SD)	11.2±9.3	11.3±9.3	10.7±9.1	.017 <sup>b</sup>
Ethnicity; n (%)				
Jewish	4,202 (45.0%)	3,616 (45.6%)	586 (41.6%)	
Bedouin	5,128 (55.0%)	4,306 (54.4%)	822 (58.4%)	.005 <sup>c</sup>

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**CAAP**

Cases	2,684	2,307	377	
Age; months (mean±SD)	17.1±14.6	17.2±14.6	16.9±14.6	.724 <sup>b</sup>
Ethnicity; n (%)				
Jewish	1,020 (38.0%)	881 (38.2%)	139 (36.9%)	
Bedouin	1,664 (62.0%)	1,426 (61.8%)	238 (63.1%)	.625 <sup>c</sup>

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**Non-CAAP LRI**

Cases	22,597	18,277	4,320	
Age; months (mean ±SD)	17.3±14.8	17.2±14.7	17.8±15.3	.019 <sup>b</sup>
Ethnicity; n (%)				
Jewish	9,150 (40.5%)	7,613 (41.7%)	1,537 (35.6%)	
Bedouin	13,447 (59.5%)	10,664 (58.3%)	2,783 (64.4%)	<.001 <sup>c</sup>

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**IPD**

Cases	704	592	112	
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Age; months (mean $\pm$ SD)	17.1 $\pm$ 12.7	17.4 $\pm$ 12.7	15.8 $\pm$ 12.4	.233 <sup>b</sup>
Ethnicity; n (%)				
Jewish	574 (81.5%)	487 (82.3%)	87 (77.7%)	.251 <sup>c</sup>
Non-Jewish	130 (18.5%)	105 (17.7%)	25 (22.3%)	

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<sup>a</sup> *P* value 2020-2021 vs. 2016-2019

<sup>b</sup> *P* value calculated using Student's *t*-test

<sup>c</sup> *P* value calculated using the Pearson  $\chi^2$  test

<sup>d</sup> 113 cases without data on ethnicity

<sup>e</sup> 7 cases without data on ethnicity

Abbreviations: SD, standard deviation; ER, Emergency Room; CAAP, community-acquired alveolar pneumonia; LRI, lower respiratory tract infection; IPD, invasive pneumococcal disease

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## Legends to Figures

### Figure 1:

Monthly dynamics of IPD and LRI incidence in children <5 years of age, January 2016 through February 2021; and the numbers of nationally reported new COVID-19 cases (all ages).

A- Bacteremic pneumonia

C- Non pneumonia IPD

E- CAAP

G- NA-LRIs

Incidence rate ratios (IRRS) by period, January 2020 through February 2021 vs 2016-2019.

B-Bacteremic pneumonia

D- Non-pneumonia LRI

F- CAAP

H- NA-LRIs

### Figure 2:

A. Monthly dynamics of the proportions of all tested nasopharyngeal swabs that were positive for *S. pneumoniae* in children <3 years of age, and the monthly number of newly nationally reported COVID-19 (all ages).

B. Dynamics of monthly density of positive nasopharyngeal samples of *S. pneumoniae*, measured by semiquantitative methods, and monthly number of newly nationally reported COVID-19 (all ages).

min = Minimum

max = Maximum

Note: During the months of April and May 2000 no samples were collected.

**Figure 3:**

A. Mean monthly virus-positive nasal wash samples in children <5 years of age, by specific virus, 2016 through 2019.

\*Rhinovirus PCR testing was initiated in February 2019; thus, for rhinovirus the graph depicts only the year 2019

† Since rhinovirus testing was not done in January 2019, we depicted for January 2019 the result in January 2020 instead

B. Monthly virus-positive nasal wash samples in children <5 years of age, by specific virus, January 2020 through February 2021.

**Figure 4**

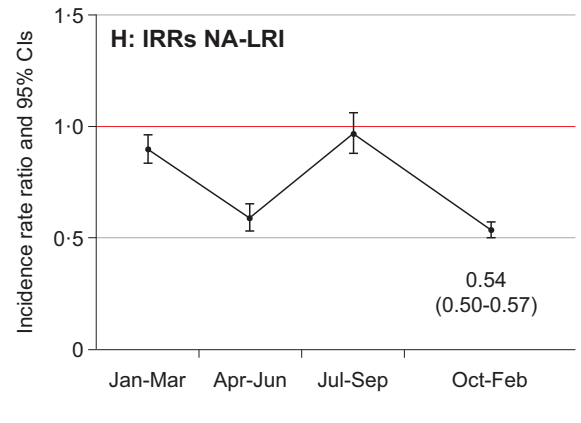
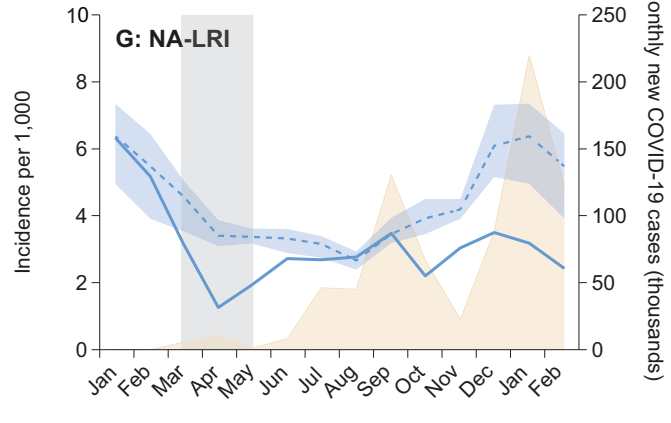
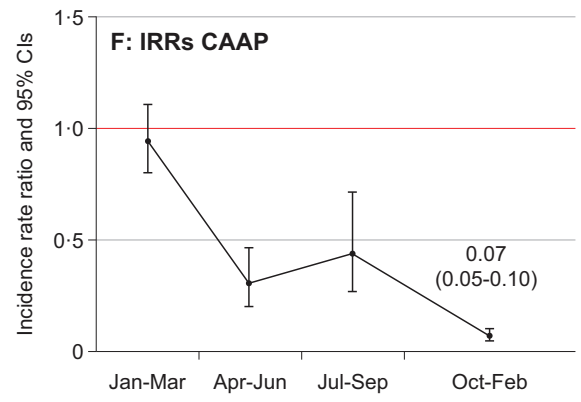
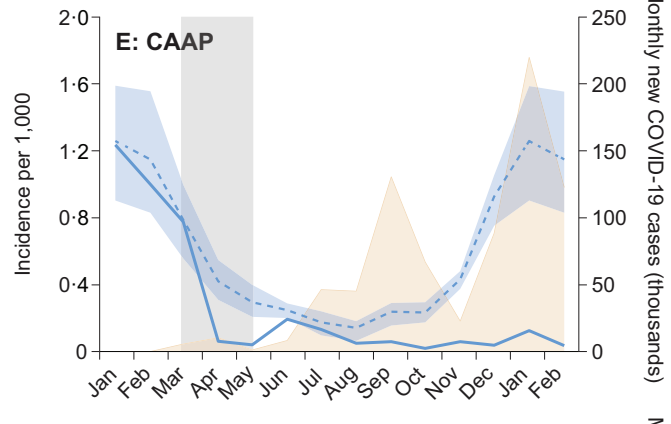
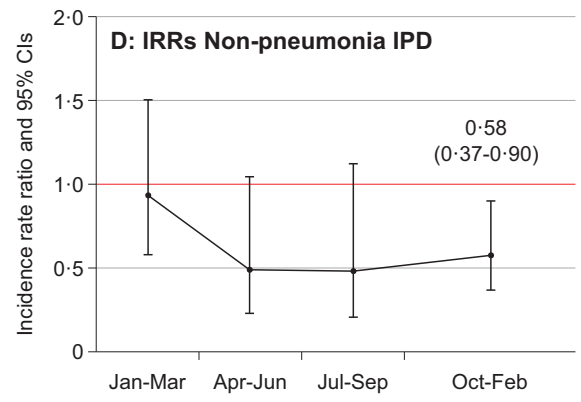
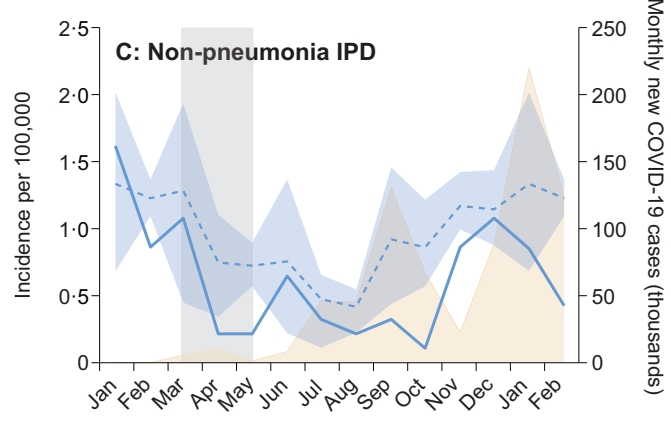
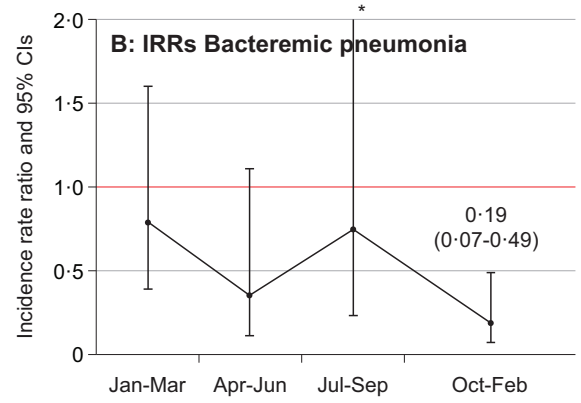
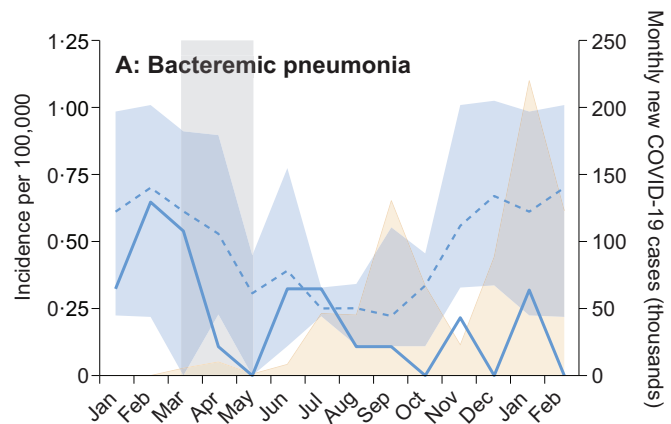
Dynamics of monthly numbers of virus-positive nasal wash samples of specific viruses, January 2016 through February 2021, in children <5 years of age

\*Rhinovirus PCV usage was initiated in February 2019

min = Minimum

max = Maximum

— Monthly incidence 2020-2021      ■ Monthly new COVID-19 cases  
- - - Mean monthly incidence 2016-2019      ■ Min - Max Incidence 2016-2019      ■ First lockdown period

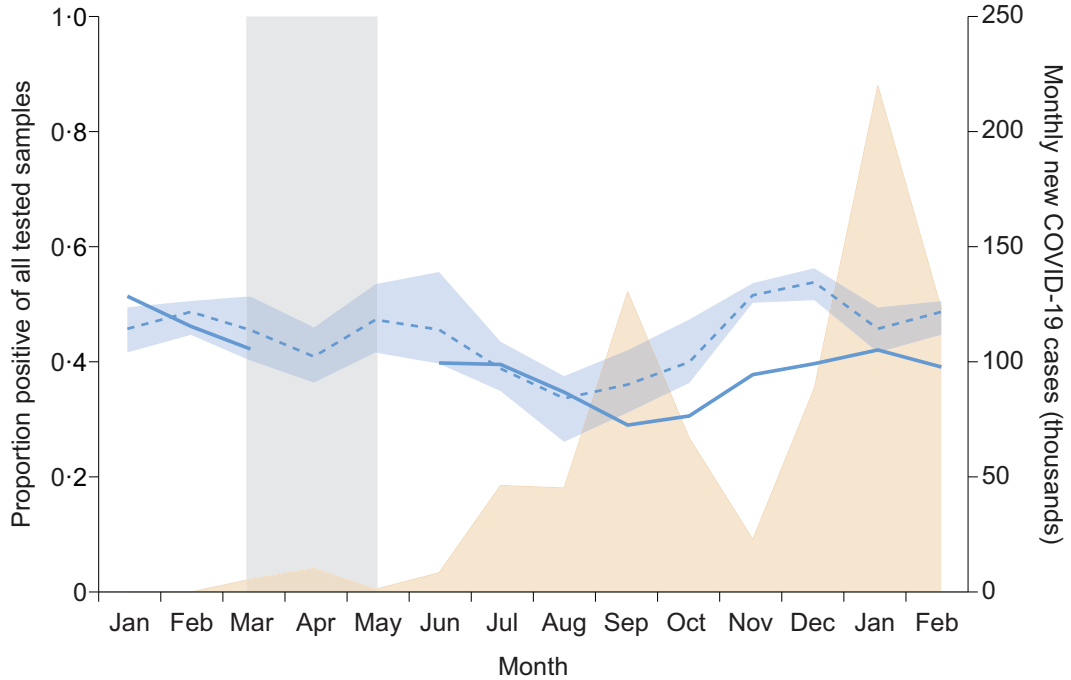


Month

Period

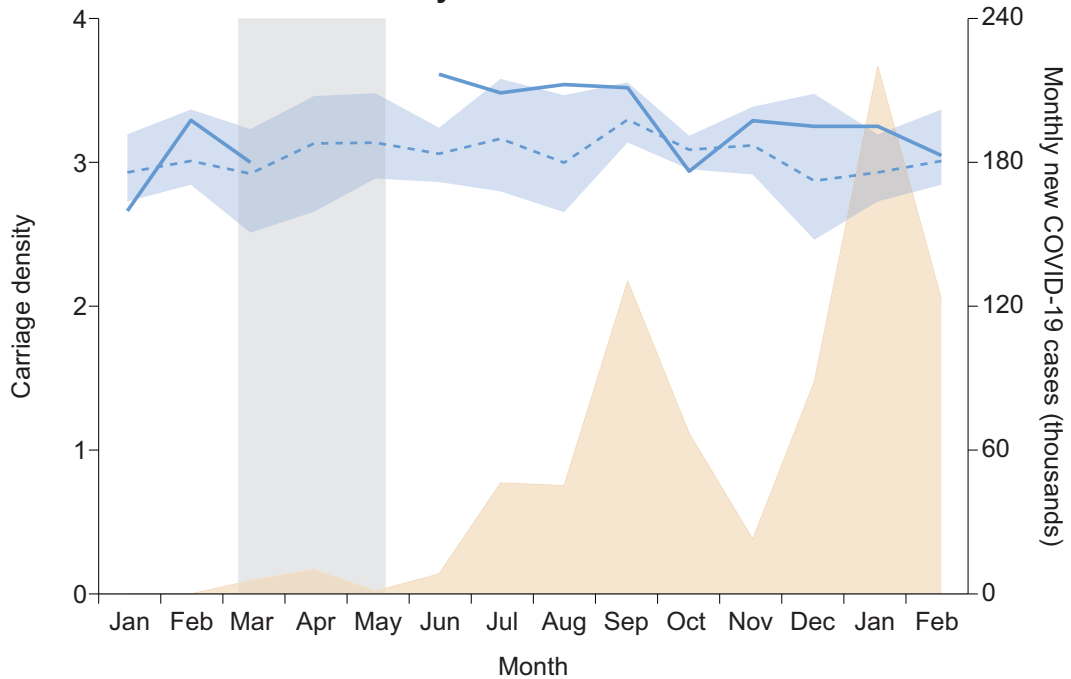
- Monthly carriage 2020-2021
- Mean monthly carriage 2016-2019
- Min - Max Carriage 2016-2019
- Monthly new COVID-19 cases
- First lockdown period

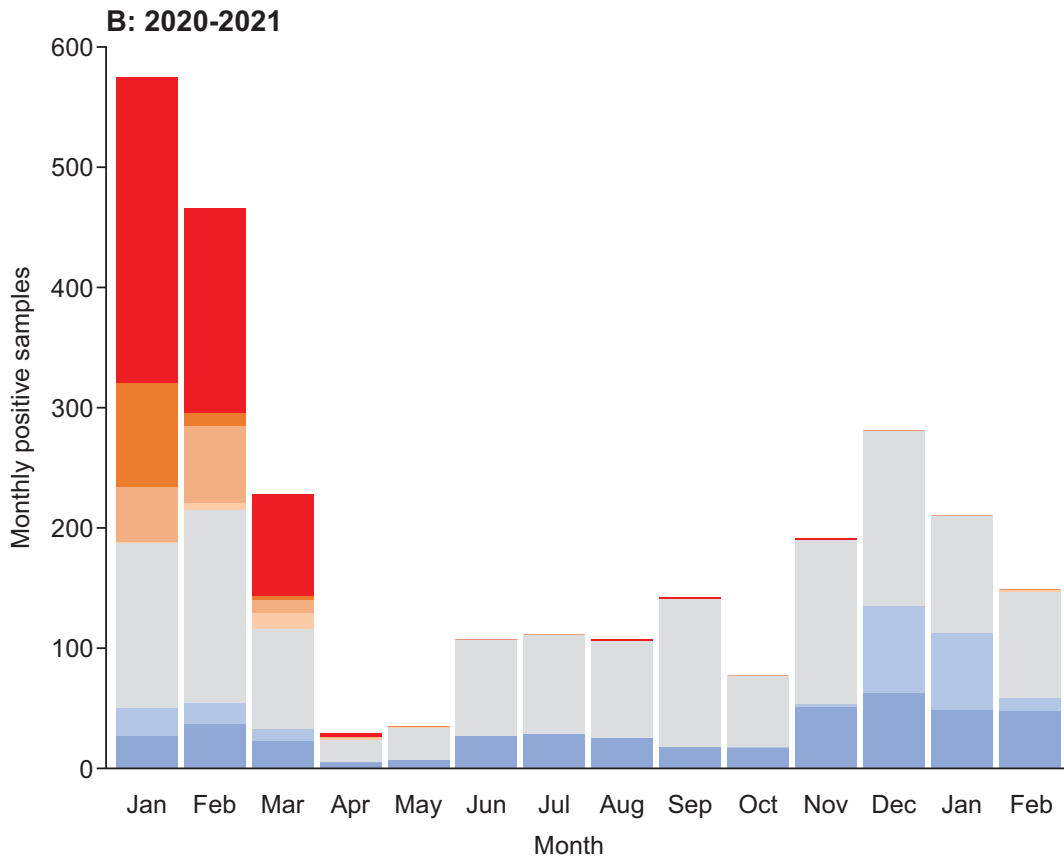
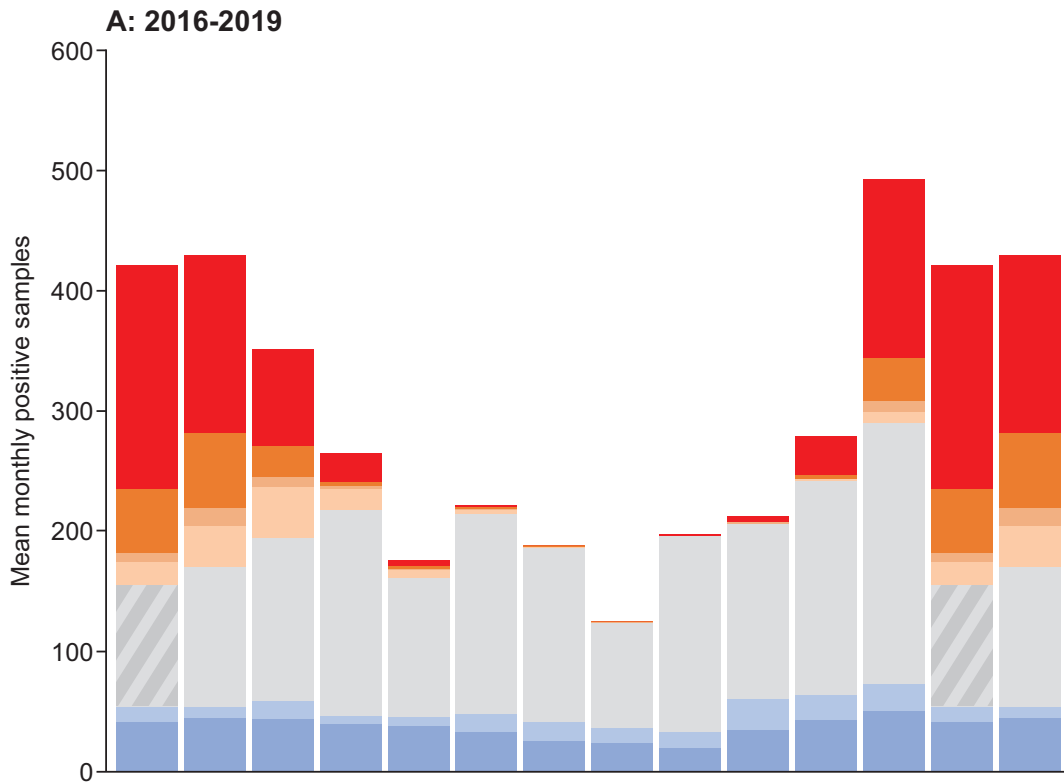
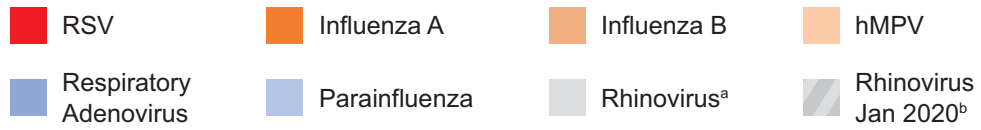
**A: Pneumococcal carriage**



- Mean monthly pneumococcal density 2016-2019
- Min - Max density 2016-2019
- First lockdown period
- Monthly pneumococcal density 2020-2021
- Monthly new COVID-19 cases

**B: Pneumococcal density**





— Monthly virus positive 2020-2021    - - - Mean monthly virus positive 2016-2019    Min-max virus positive 2016-2019

