Potential Causative Association between Respiratory Viruses and Pneumococcus-Associated Disease in Young Children in Israel: Lessons from the COVID-19 Pandemic

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Background

- In young children, rates of community-acquired alveolar pneumonia (CAAP) and invasive pneumococcal disease (IPD) have been associated with respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza (flu), and parainfluenza (PIV) (collectively termed here as pneumococcal disease-associated viruses [PDA-viruses])
- However, their contribution to the pathogenesis of pneumococcal-associated disease has not yet been elucidated
- The COVID-19 pandemic provided a unique opportunity to examine the question

Methods and population studied

- This prospective study comprised all children <5 years, born and living in southern Israel, during 2016 through 2021
- The data were derived from multiple ongoing prospective cohort surveillance programs[1] and included:
  - hospital visits for CAAP
  - IPD episodes with a diagnosis of pneumonia (IPD-pneumonia)*
  - Nasopharyngeal pneumococcal carriage (<3 years of age without a respiratory disease)
  - Respiratory virus activity
  - Nationwide all ages COVID-19 episodes[2]
- A hierarchical negative binominal regressive model was developed to estimate the proportion of the clinical outcomes attributable to each of the viruses
  - For each outcome, time series of incidence by month, stratified by age and ethnicity was applied
  - The covariates showed a linear trend over time, 12-month harmonic variables to capture unexplained seasonal variations, and the proportions of tests positive for each virus in that month
  - The model was fit into a Bayesian framework with minimally informative prions, using rjags
- The study was approved by the Local Ethics Committee

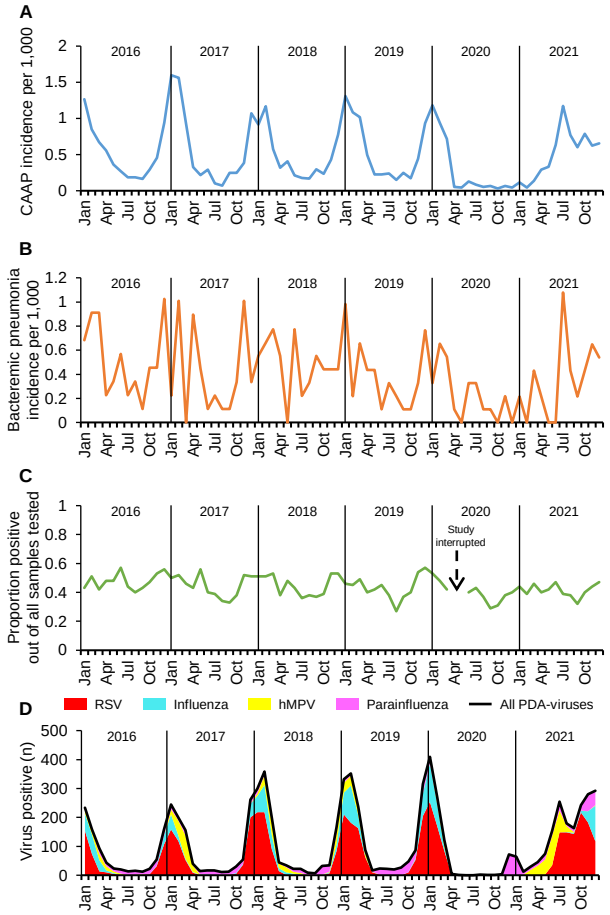
* Data derived form Nationwide surveillance
[1]Danino D. et al. Clin Infect Dis. 2022, https://doi.org/10.1093/cid/ciab1014
[2]https://datadashboard.health.gov.il/COVID-19/general

Results

Descriptive results

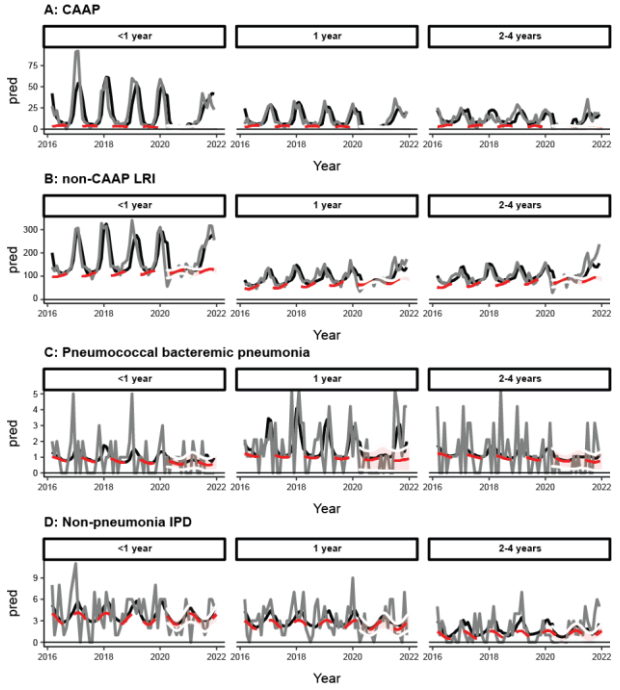
- During 2016 through December 2021, 3,204 CAAP and 257 pneumonia IPD episodes were recorded (Figure 1)
- Abrupt and significant declines in the rates of the 2 disease outcomes were observed starting in April 2020, lasting to March 2021. However, starting in spring 2021, an off-season, abrupt surge was observed with unexpectedly high rates, reaching a magnitude similar to those observed during 2016-2019
- A total of 7,921, 1,190, and 1,323 nasopharyngeal samples for pneumococcal culture and serotyping were obtained in 2016-2019, 2020, and 2021, respectively. No overall trend in carriage rates was observed, and changes in carriage prevalence did not correlate with changes in the disease outcomes in a multivariate regression

Figure 1: Dynamics of CAAP (A) and IPD-Pneumonia (B) incidence rates in children < 5 years; prevalence of nasopharyngeal pneumococcal carriage in children <3 years (C); and all virus-positive nasopharyngeal swabs in children <5 years ("Viral activity"), 2016-2021 (D)



- A total of, 17,555; 3,444; and 6,143 nasopharyngeal samples were obtained for virus detection in 2016-2019, 2020, and 2021, respectively. Of these, 41.7%, 58.0%, and 63.4%, respectively, were positive for ≥1 virus: RSV 4,024, AdV 3,049, PIV 1,143, flu A 1,026, hMPV 883, flu B 308. Testing for RhV was only initiated in February 2019 with 4,845 positive samples. Co-detection of ≥2 viruses was common, especially starting in February 2019, when RhV testing was added. However, a co-detection of any PDA-virus with another PDA-virus was rare (1.3%)
- From April 2020 through October 2020, none of the PDA-viruses were detected. However, since November 2020, an off-season sequential re-emergence of the PDA-viruses was observed, each with a peak reaching an equal or higher magnitude compared to the pre-pandemic seasonal peaks. Nevertheless, flu B was not detected from March 2020 throughout the study
- In contrast, although RhV and AdV had a short nadir during the time of the first lockdown (April-May 2020), they were frequently detected throughout the study (RhV was tested only since February 2019)

Figure 2: Observed (dark gray lines) and model-fitted values (black line) for the number of cases of CAAP and IPD-pneumonia, based on a model fit to the entire data set. the red dashed line and shaded area represent the estimate for how many cases there would have been in the absence of viruses +/- 95% CI



Modelling to estimate the proportion of the disease outcomes attributable to each of the viruses

- The viruses included in the model were RSV, hMPV, flu, PIV and AdV. RhV was not included since testing for this virus was initiated only in February 2019. however multi-regression analysis for the period of February 2020 to December 2021 showed no correlation of RhV activity to the 2 disease outcomes
- Model fit to the pre-pandemic period correctly captured the re-emergence of CAAP in <12m old, but underestimates the increase in older children
- To better disentangle the contribution of the viruses to the burden of pneumonia, we leveraged the different timing of the re-emergence of the different viruses in 2020-21 and refit the models to the entire dataset (Figure 2)
- We estimated that 82% of CAAP episodes and 31% of IPD-pneumonia episodes could be attributed to the common respiratory viruses (Table)

Table: Percent of disease outcomes attributable to RSV, hMPV, Flu, AdV, PIV (adjusted for ethnicity), stratified by age

		Virus	CAAP	IPD-pneumonia
All children <5 years		Any	82 (75,88)*	29 (11,54)
		RSV	49 (43,55)	18 (6,30)
		hMPV	13 (10,17)	0 (0,7)
		Flu	7 (1,13)	3 (0,12)
		AdV	0 (0,4)	0 (0,22)
		PIV	11 (7,15)	0 (0,12)
<1 year		Any	87 (80,93)	21 (0,45)
		RSV	62 (50,71)	15 (0,33)
		hMPV	11 (6,17)	0 (0,4)
		Flu	7 (0,18)	1 (0,11)
		AdV	0 (0,5)	0 (0,15)
		PIV	5 (1,9)	0 (0,9)
1 year		Any	80 (70,88)	40 (13,81)
		RSV	49 (41,57)	29 (6,48)
		hMPV	14 (8,19)	0 (0,9)
		Flu	5 (0,11)	1 (0,15)
		AdV	0 (0,5)	0 (0,42)
		PIV	10 (4,16)	0 (0,12)
2-4 years		Any	76 (62,87)	19 (0,50)
		RSV	29 (20,38)	5 (0,21)
		hMPV	17 (10,23)	0 (0,14)
		Flu	6 (0,13)	2 (0,22)
		AdV	0 (0,6)	0 (0,17)
		PIV	22 (11,31)	0 (0,26)

Conclusions

- **CAAP and IPD-pneumonia rates were markedly reduced during the first months of the COVID-19 pandemic, re-remerging off-season, in the presence of still ongoing COVID-19 pandemic**
- **The disease dynamics were not associated with pneumococcal nasopharyngeal carriage rate, which was largely unchanged, strongly suggesting the continuous circulation of S. pneumonia**
- **The disease dynamics were associated with the dynamics of the PDA-viruses, but not with rhinoviruses and adenoviruses**
- **RSV was by far the most important virus associated with both bacteremic and non-bacteremic respiratory disease**
- **hMPV contributed mainly to CAAP**
- **The attributable role of influenza and parainfluenza viruses was only modest**