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Did the resurgence of childhood lower respiratory infections offset the initial benefit of COVID-19-related non-pharmaceutical interventions in children? A time-series analysis

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Abstract

Background Following non-pharmaceutical interventions (NPI) lifting in 2021, an important surge in childhood lower respiratory tract infections (LRTI) was reported in several countries, raising major concerns about the middle-term consequences of such interventions. Whether this recent upsurge overwhelms the initial benefit of NPI remains unknown.

Methods We conducted an interrupted time-series analysis based on exhaustive national surveillance systems. All hospitalisations from January 2015 to March 2023 and all ambulatory visits for LRTI from a network of 110 paediatricians from June 2017 to March 2023 were included. The main outcome was the monthly incidence of children hospitalised for LRTI per 100,000 over time, assessed by a seasonally adjusted quasi-Poisson regression model.

Results We included 845,047 hospitalisations. The incidence of hospitalisation for LRTI significantly decreased during the NPI period (−61.7%, 95% CI −98.4 to −24.9) and rebounded following NPI lifting, exceeding the pre-NPI baseline trend (+12.8%, 95% CI 6.7 to 19.0). We observed similar trends for hospitalisation due to bronchiolitis, pneumonia and pneumonia with pleural effusion, along with ambulatory LRTI. Overall, despite the recent rebound, 31,777 (95% CI, 25,375 to 38,179) hospitalisations for paediatric LRTI were averted since NPI implementation up to 2023.

Conclusions Three years after their implementation, despite an increase in LRTI incidence, the middle-term impact of NPI remains highly beneficial in preventing overall paediatric LRTI. The implementation of some societally acceptable NPI, particularly during epidemics, may be considered in the future to further reduce the burden of paediatric LRTI.

Keywords COVID-19 pandemic, Lower respiratory tract infections, Respiratory pathogens, Time-series analysis

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Background

Lower respiratory tract infections (LRTI) are the leading cause of death of children under 5 years of age worldwide, accounting for 650,000 deaths annually. These infections are also responsible for five million hospital admissions each year globally, resulting in a major health care consumption [1].

LRTI epidemiology has been strongly influenced by the unprecedented coronavirus disease 2019 (COVID-19)-related non-pharmaceutical interventions (NPI) implemented worldwide to reduce the spread of SARS-CoV-2. Indeed, the implementation of these NPI affected the transmission of other respiratory pathogens, resulting in a major decrease in both paediatric emergency department visits and hospital admissions for viral and bacterial LRTI [2–5]. However, following the NPI lifting, many countries reported a large increase in the incidence of seasonal infections, notably those related to respiratory syncytial virus (RSV) and influenza, as well as *Streptococcus pneumoniae* and *Streptococcus pyogenes*, exceeding the pre-pandemic rates [6–9]. This unusual upsurge may have been related to an increased proportion of the population that was naïve to respiratory pathogens, leading to the "immune debt" concept [10, 11]. These reports raised major concerns regarding the middle-term public health benefit of implementing NPI. To date, whether this increase overwhelmed the initial benefit of NPI on the burden of LRTI is still unclear.

The aim of this study was to estimate the middle-term impact of NPI on the incidence of childhood LRTI.

Methods

Study design

We conducted an interrupted time-series analysis using both hospital and ambulatory-based French national surveillances of LRTI in children over 8 years (1 January 2015 to 31 March 2023). The data collection was approved by the National Commission on Information and Liberty. Because this study used anonymous aggregated data, it did not require ethical committee approval or written informed consent.

Data collection

Inpatient data were obtained from the French Medicalization of Information Systems Program (PMSI), which is an exhaustive national database that includes all hospital discharge records for public and private hospitals in France, as previously published [12, 13]. Ambulatory visit data were collected via the Paediatric and Ambulatory Research in Infectious diseases (PARI) network, a national surveillance network that involves 110 paediatricians located across the French territory and trained in the diagnosis and management of infectious diseases [14, 15]. For both the hospital and ambulatory-based surveillance systems, the diagnoses were recorded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

Inclusion criteria

We included all children younger than 18 years of age hospitalised for an LRTI between January 2015 and March 2023, in France. An LRTI was defined as bronchitis, bronchiolitis, pneumonia or pneumonia with pleural effusion (the details of the ICD-10 diagnosis codes are presented in Additional file 1: eTable1). The following data were recorded for each inpatient stay: age, sex, date and duration of hospitalisation, transfer to an intensive care unit (ICU) and in-hospital death.

For the ambulatory-visit data, we included all children < 16 years of age visiting a paediatrician of the PARI network for bronchiolitis or pneumonia from June 2017 to March 2023.

Study periods

Data on NPI implemented in France over time were collected using open data on national response measures to COVID-19 from the European Centre for Disease Prevention and Control (ECDC). As defined by the ECDC [16], they were individual-level (physical distancing, respiratory hygiene, i.e. covering the mouth and nose when coughing and sneezing, hand hygiene and the wearing of face masks), environmental-level (cleaning of frequently touched surfaces in healthcare facilities and ventilation for an increased rate of air exchange) and population-level (limiting close physical inter-personal interactions by isolation of symptomatic cases not requiring hospitalisation, quarantining of contacts, medically and sociably shielding the vulnerable population, limiting the size of gatherings, teleworking, closure of non-essential businesses, school closures, curfew, lockdown and travel-related measures, such as domestic travel restrictions, border closures, travel advice, screening at points of entry at national borders and the quarantine of passengers).

A stringency index was developed after NPI implementation, to estimate the degree of proximity among individuals [17]. According to this stringency index and as previously published, we defined three time periods: the "pre-NPI period" from January 2015 to March 2020, the "NPI period" from April 2020 to March 2021 and the "NPI-lifting period" from April 2021 to March 2023 [13, 18].

Outcomes

The main outcome was the monthly national incidence of hospitalisation for LRTI per 100,000 children aged under 18 years. To calculate the incidence per 100,000 children, we used age-specific French population data for each year of the study provided by the National Institute for Statistics and Economical studies as the denominator and the number of hospitalisations for LRTI as the numerator [19]. Secondary outcomes were the monthly incidence of hospitalisation for LRTI by age group (< 1 year, 1 to < 2 years, 2 to < 5 years and 5 to < 18 years), clinical presentation (bronchitis, bronchiolitis, pneumonia or pneumonia with pleural effusion), severity (clinical observation unit or intensive care unit hospitalisation) and infectious agent. For the ambulatory-visit data, we analysed the monthly rate of bronchiolitis and pneumonia per 1000 visits.

To explore the potential bias due to hidden cointerventions, the evolution of the national incidence of hospitalisation for urinary tract infections (UTI) for children aged < 18 years over the same period was analysed as a control outcome [12].

Statistical analysis

Outcomes were analysed using a quasi-Poisson regression model, accounting for seasonality by including harmonic terms (sines and cosines with 12-, 6- and 3-month periods), with the time unit set to 1 month [20–22].

First, the observed monthly incidence of hospitalisation for LRTI was fitted by the model for each time-point of the study period, with the NPI implementation and lifting included as explanatory variables. Then, according to the pre-NPI trend and seasonality, and setting the intervention terms to zero, the model enabled us estimate the expected values of the outcome without NPI. Based on this model, we estimated changes in the incidence of hospitalisation for LRTI following NPI implementation and NPI lifting, compared to the expected values of the outcome based on the pre-NPI trend.

Combining changes during both the NPI-implementation and NPI-lifting periods, such modelling allowed us to estimate the overall number of averted LRTI hospitalisations since NPI implementation. The validity of the quasi-Poisson regression models was assessed by visual inspection of correlograms and residuals analysis.

To assess the robustness of the study findings, we performed six sensitivity analyses for the main outcome: (1) a quasi-Poisson regression model including harmonic terms with only 12-month periods, (2) a segmented linear regression model including a combination of harmonic terms (sines and cosines) with 12-month periods, (3) and 12-, 6- and 3-month periods to explore different seasonal patterns, (4) a segmented linear regression using an additive model to remove seasonality, (5) a negative binomial regression model, (6) and a quasi-Poisson regression model adjusted for the control outcome (incidence of UTI over the same period) to explore the possibility that potential changes observed in the incidence of LRTI may have been related to another intervention.

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using R version 4.2.2 (www.R-project.org).

Results

General characteristics of hospitalised children

In total, 845,047 children aged < 18 years were included between 1 January 2015 and 31 March 2023. The median [IQR] age was 0.6 [0.2–2.0] year, with 450,866 (53.4%) boys and 394,181 (46.6%) girls. Bronchiolitis accounted for 422,036 (49.9%) cases, pneumonia for 188,319 (22.3%) cases, pneumonia with pleural effusion for 4682 (0.6%) cases, other LRTI for 60,968 (7.2%) cases, and UTI for 173,724 (20.6%) cases. The characteristics of hospitalised patients are presented in Table 1.

Association of NPI with the incidence of hospitalisation for LRTI

NPI implementation in March 2020 was associated with a significant decrease in the incidence of LRTI (estimated cumulative change; −61.7%, 95% CI −98.4 to −24.9, $p = 0.0014$), and a significant increase following NPI lifting, that exceeded the pre-NPI baseline trend (estimated cumulative change; 12.8%, 95% CI 6.7 to 19.0, $p < 0.0001$; Table 2, Fig. 1), relative to the forecasted pre-NPI trend. Correlograms and residuals analyses indicated a satisfactory quality of the final model (Additional file 2: eFigure 1) and sensitivity analyses provided similar results (Table 2). By contrast, the incidence of UTI did not significantly change over the study period (Table 2 and Additional file 3: eFigure 2 in the supplement).

Association of NPI with the rate of ambulatory LRTI

In total, 5,425,855 paediatric ambulatory visits for children aged < 16 years were included between 1 June 2017 and 31 March 2023. Bronchiolitis accounted for 28,005 cases (0.5%) and pneumonia for 2831 cases (0.05%).

The characteristics of the paediatric ambulatory visits are presented in Table 3.

NPI implementation in March 2020 was associated with a decreased rate of ambulatory visits for bronchiolitis (estimated cumulative change; −76.2%, 95% CI −100.0 to −49.0, $p < 0.0001$), as well as pneumonia (estimated cumulative change; −85.8%, 95% CI −100.0 to −65.6, $p < 0.0001$). Following NPI lifting, the rate of ambulatory bronchiolitis visits remained under the pre-NPI baseline trend (estimated cumulative change; −20.7%, 95% CI −28.7 to −12.8, $p < 0.0001$), as well as that of ambulatory pneumonia visits (estimated cumulative change; −44.4%, 95% CI −57.8 to −31.0, $p < 0.0001$)

Table 1 Baseline characteristics of children aged < 18 years hospitalised between January 2015 and March 2023 in France

Characteristics	Children, no. (%)			
	Pre-NPI period	NPI period	NPI-lifting period	All study periods
No. of cases	567,737 (67.2)	52,306 (6.2)	225,004 (26.6)	845,047
Age, median (IQR), y	0.6 (0.2–2.0)	0.8 (0.3–3.0)	0.5 (0.2–1.0)	0.6 (0.2–2.0)
LRTI	451,908 (67.3)	32,045 (4.8)	187,370 (27.9)	671,323
Bronchiolitis	277,642 (65.8)	18,250 (4.3)	126,144 (29.9)	422,036
Pneumonia	130,603 (69.4)	9999 (5.3)	47,717 (25.3)	188,319
Pneumonia with pleural effusion	3159 (67.5)	323 (6.9)	1200 (25.6)	4682
Other LRTI[a]	43,663 (71.6)	3796 (6.2)	13,509 (22.2)	60,968
UTI	115,829 (66.7)	20,261 (11.7)	37,634 (21.7)	173,724
Age groups[b]				
0–1 years	342,800 (65.8)	28,355 (5.4)	149,758 (28.8)	520,913
1–2 years	72,381 (69.5)	7123 (6.8)	24,620 (23.7)	104,124
2–4 years	73,121 (68.1)	7053 (6.6)	27,224 (25.3)	107,398
5–17 years	77,462 (70.7)	9482 (8.7)	22,620 (20.6)	109,564
Sex				
Male	302,335 (67.0)	26,969 (6.0)	121,562 (27.0)	450,866
Female	265,402 (67.3)	25,337 (6.5)	103,442 (26.2)	394,181
Outcome				
Duration of stay, median (IQR), d	3.0 (1.0–5.0)	3.0 (1.0–4.0)	3.0 (1.0–5.0)	3.0 (1.0–5.0)
ICU admission	23,529 (61.0)	2502 (6.5)	12,531 (32.5)	38,562
Death	1222 (63.6)	171 (8.9)	527 (27.5)	1920

Qualitative data are presented as numbers (%), and quantitative data (age, duration of stay) as medians (IQR)

[a] Other LRTI include acute bronchitis and bronchopneumonia

[b] Missing values for age groups were 1973 (0.3%) for the pre-NPI period, 293 (0.6%) for the NPI period and 782 (0.3%) for the NPI-lifting period

Abbreviations: *LRTI* Lower respiratory tract infection, *ICU* Intensive care unit, *UTI* Urinary tract infection, *NPI* Non-pharmaceutical interventions

compared to the forecasted pre-NPI baseline trend (Additional file 4 and 5: eTable 3, eFigure 3).

Incidence of hospitalisation for LRTI by clinical presentation, severity and age group

The patterns were similar within clinical presentations, although the greatest increase was observed for bronchiolitis (Table 2, Fig. 2). The incidence for LRTI decreased among all age groups during the NPI period, whereas it increased mainly in children < 1 year of age after NPI lifting (estimated cumulative change; 19%, 95% CI 8.8 to 29.1, $p = 0.0004$; Table 2, Additional file 6: eFigure 4).

The incidence of LRTI requiring ICU admission decreased during the NPI period (estimated cumulative change; − 26.4%, 95% CI − 50.7 to − 2.2, $p = 0.035$), followed by a marked increase after NPI lifting (estimated cumulative change; 27.9%, 95% CI 14.0 to 41.9, $p = 0.0002$; Table 2, Fig. 3). The median age decreased from 0.9 [0.2–5.0] years during the NPI period to 0.3 [0.1–1.0] years during the NPI-lifting period, and the proportion of bronchiolitis cases increased over the same period (32.2 to 50.4%; additional file 7: eTable 4).

Incidence of hospitalisation for LRTI by infectious agent over time

During the NPI period, the incidence of LRTI decreased significantly for RSV, influenza, adenovirus, metapneumovirus, enterovirus, rhinovirus and all bacterial agents, except *Chlamydia pneumoniae.* After NPI lifting, the magnitude of change varied substantially depending on the infectious agents, ranging from − 9.5% (95% CI − 17.0 to − 2.1, $p = 0.01$) for influenza to + 112.4% (95% CI 54.5 to 170.2, $p = 0.0003$) for adenovirus and + 141% (95% CI 116.4 to 165.8, $p < 0.0001$) for *Streptococcus pyogenes*. The incidence of pneumococcal pneumonia decreased during both periods (Additional files 8, 9 and 10: eTable 5, eTable 6 and eFigure 5).

During the NPI-lifting period, there was a decrease in the proportion of undocumented bronchiolitis cases (estimated cumulative change; − 29.4%, 95% CI − 54.2 to − 4.6, $p = 0.0224$), as well as those for undocumented pneumonia (estimated cumulative change; − 3.3%, 95% CI − 4.8 to − 1.8, $p < 0.0001$; Additional files 9 and 11: eTable 6, eFigure 6).

Table 2 Association of NPI implementation and lifting with the monthly incidence of children hospitalised for LRTI in France and estimated averted hospitalisations

Outcome	NPI period		NPI-lifting period		Overall estimated averted hospitalisations since NPI, no. (95% CI)[d]
	Estimated cumulative change in incidence, % (95% CI)	*p* value	Estimated cumulative change in incidence, % (95% CI)	*p* value	
LRTI[a,b]	−61.7% (−98.4 to −24.9)	0.0014	+12.8% (6.7 to 19.0)	<0.0001	31,777 (25,375 to 38,179)
Bronchiolitis	−65.8% (−100.0 to −12.7)	0.017	+19.3% (7.4 to 31.2)	0.0020	16,093 (10,961 to 21,224)
Pneumonia	−58.8% (−39.4 to −78.2)	<0.0001	−1.1% (−1.4 to −0.8)	<0.0001	15,274 (13,327 to 17,221)
Pneumonia with pleural effusion	−52.6% (−65.2 to −40.0)	<0.0001	−17.3% (−21.3 to −13.3)	<0.0001	624 (521 to 727)
Other LRTI[c]	−46.3% (−72.1 to −20.6)	0.0007	+6.5% (3.3 to 9.6)	0.0001	2959 (2716 to 3201)
Sensitivity analyses[a]					
Quasi-Poisson regression (12 m)	−61.7% (−100.0 to −16.6)	0.0087	+12.2% (4.8 to 19.5)	0.0016	32,973 (26,886 to 39,060)
Segmented linear regression with trigonometric function (12 m)	−43% (−87.4 to 1.3)	0.060	+10.1% (2.1 to 18.0)	0.014	28,695 (25,388 to 32,002)
Segmented linear regression with trigonometric function (3–6-12 month)	−43.5% (−78.5 to −8.4)	0.017	+9.1% (2.1 to 14.6)	0.0022	31,631 (28,877 to 34,385)
Segmented linear regression without trigonometric function	−52.2% (−90.1 to −14.1)	0.0084	+13.4% (3.4 to 23.4)	0.010	22,365 (1558 to 29,149)
Quasi-Poisson regression adjusted for the monthly incidence of UTI	−61.7% (−97.5 to −26.0)	0.0011	+11.5% (5.7 to 17.4)	0.0002	31,777 (25,376 to 38,179)
Negative binomial regression (3–6-12 m)	−56.9% (−100.0 to −13.0)	0.0111	+18.5% (7.2 to 29.8)	0.0013	11,511 (9330 to 13,693)
Secondary outcomes					
LRTI by age group[a,b]					
0–1 years	−67.0% (−100.0 to −19.3)	0.0072	+19.0% (8.8 to 29.1)	0.0004	16,657 (11,640 to 21,674)
1–2 years	−53.1% (−91.3 to −15.0)	0.0076	+2.3% (0.3 to 4.3)	0.026	5080 (4276 to 5884)
2–4 years	−58.5% (−88.5 to −28.5)	0.0002	+8.4% (4.8 to 12.0)	0.0001	4556 (3785 to 5327)
5–17 years	−43.6% (−56.2 to −31.1)	0.0001	−12.1% (−15.6 to −8.6)	<0.0001	5928 (5312 to 6545)
LRTI with ICU admission[a,b]	−26.4% (−50.7 to −2.2)	0.035	+27.9% (14.0 to 41.9)	0.0002	+284 (+140 to +428)
LRTI without ICU admission[a,b]	−62.3% (−33.7 to −91.0)	0.0001	+12.7% (7.1 to 18.3)	0.0001	32,105 (25,780 to 38,431)
Control outcome					
UTI[a,b]	−2.6% (−6.1 to 0.8)	0.14	−4.3% (−11.2 to 2.6)	0.23	

[a] Expressed as the monthly incidence per 100,000 children

[b] Analysis using a quasi-Poisson regression model with 12-, 6- and 3-month periods

[c] Other LRTI included acute bronchitis and bronchopneumonia

[d] The overall number of averted hospitalisations was calculated as the difference between the observed values fitted by the regression model and the expected values assuming no intervention had occurred during the NPI and NPI-lifting periods

Abbreviations: *LRTI* Lower respiratory tract infection, *ICU* Intensive care unit, *UTI* Urinary tract infection, *NPI* Non-pharmaceutical intervention

Estimated averted hospitalisations after NPI implementation

We estimated that 51,905 (95% CI 44,064 to 59,746) hospitalisations for LRTI were averted during the NPI period, whereas 20,128 (95% CI 18,689 to 21,567) excess hospitalisations for LRTI occurred during the NPI-lifting period. Overall, this led to an estimated 31,777 averted hospitalisations for LRTI (95% CI 25,375 to 38,179) from NPI implementation to March 2023. By contrast, there was no significant benefit for LRTI requiring ICU hospitalisation (Table 2, Additional file 12: eTable 7).

Discussion

Taking advantage of both hospital and ambulatory-based national surveillance systems, this study shows that the incidence of paediatric LRTI declined sharply during the COVID-19-related NPI period and returned after NPI lifting in April 2021, compared to the pre-NPI

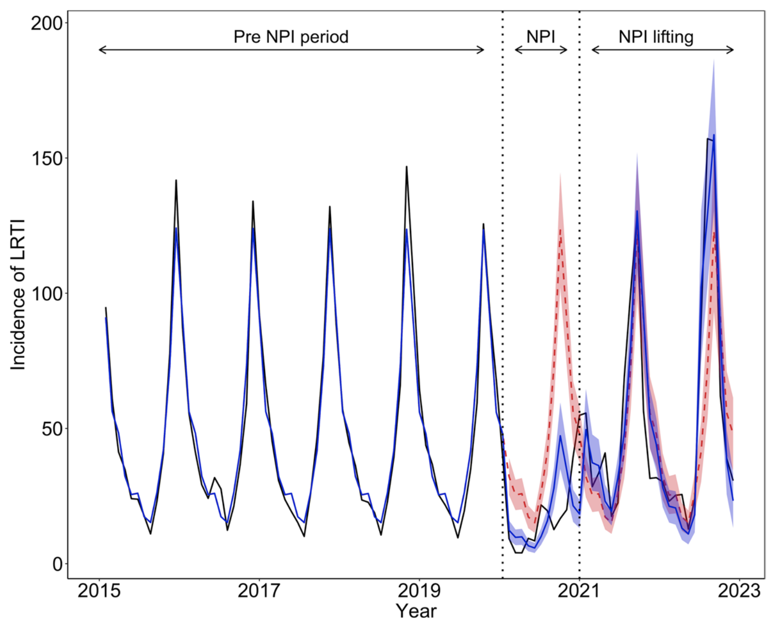

Fig. 1 Overall impact of non-pharmaceutical interventions on the monthly incidence of lower respiratory tract infections of children < 18 years requiring hospitalisation from January 2015 to March 2023 in France (*N* = 671,323). Incidence is expressed as the number of hospitalisations per 100,000 children per month. The black line shows the observed data. The blue line shows the model estimates based on observed data using the quasi-Poisson regression. The dashed red line shows the expected values assuming the NPI were not implemented using the same quasi-Poisson model. The blue and red shading indicates the 95% confidence intervals. Vertical dashed lines indicate NPI implementation and lifting. Pre-NPI period: 1 January 2015 to 31 March 2020. NPI period: 1 April 2020 to 31 March 2021. NPI-lifting period: 1 April 2021 to 31 March 2023. Abbreviations: NPI, non-pharmaceutical intervention; LRTI, lower respiratory tract infection

Table 3 Baseline characteristics of ambulatory bronchiolitis and pneumonia cases of children aged < 16 years between June 2017 and March 2023 in France

Characteristics	Children, no. (%)			
	Pre-NPI period	**NPI period**	**NPI-lifting period**	**All study periods**
Bronchiolitis				
No. of cases	12,813 (45.8)	2826 (10.1)	12,366 (44.2)	28,005
Sex ratio (H/F)	1.85	2.19	1.83	1.96
Age, median (IQR), y	0.7 (0.5–1.3)	0.8 (0.5–1.3)	0.7 (0.5–1.3)	0.73 (0.5–1.3)
Pneumonia				
No. of cases	1671 (59.0)	196 (6.9)	964 (34.1)	2831
Sex ratio (H/F)	1.22	1.36	1.29	1.29
Age, median (IQR), y	3.2 (1.9–4.8)	2.5 (1.3–3.8)	3.2 (2.0–4.5)	3.0 (1.7–4.4)
No. of visits	1,843,442	1,195,849	2,386,564	5,425,855

Qualitative data are presented as numbers (%), and quantitative data (age, duration of stay) as medians (IQR)

Pre-NPI period: 1 June 2017 to 31 March 2020

NPI period: 1 April 2020 to 31 March 2021

NPI-lifting period: 1 April 2021 to 31 March 2023

Abbreviations: *NPI* Non-pharmaceutical intervention

baseline trend. Despite this substantial upsurge, the overall middle-term impact of NPI remained beneficial, with more than 31,000 averted hospitalisations up to March 2023 estimated by the model.

The recent increase in hospitalisations for LRTI found in this study, exceeding the expected incidence without NPI, is consistent with reports from other countries [23, 24] and supports the "immune debt" theory

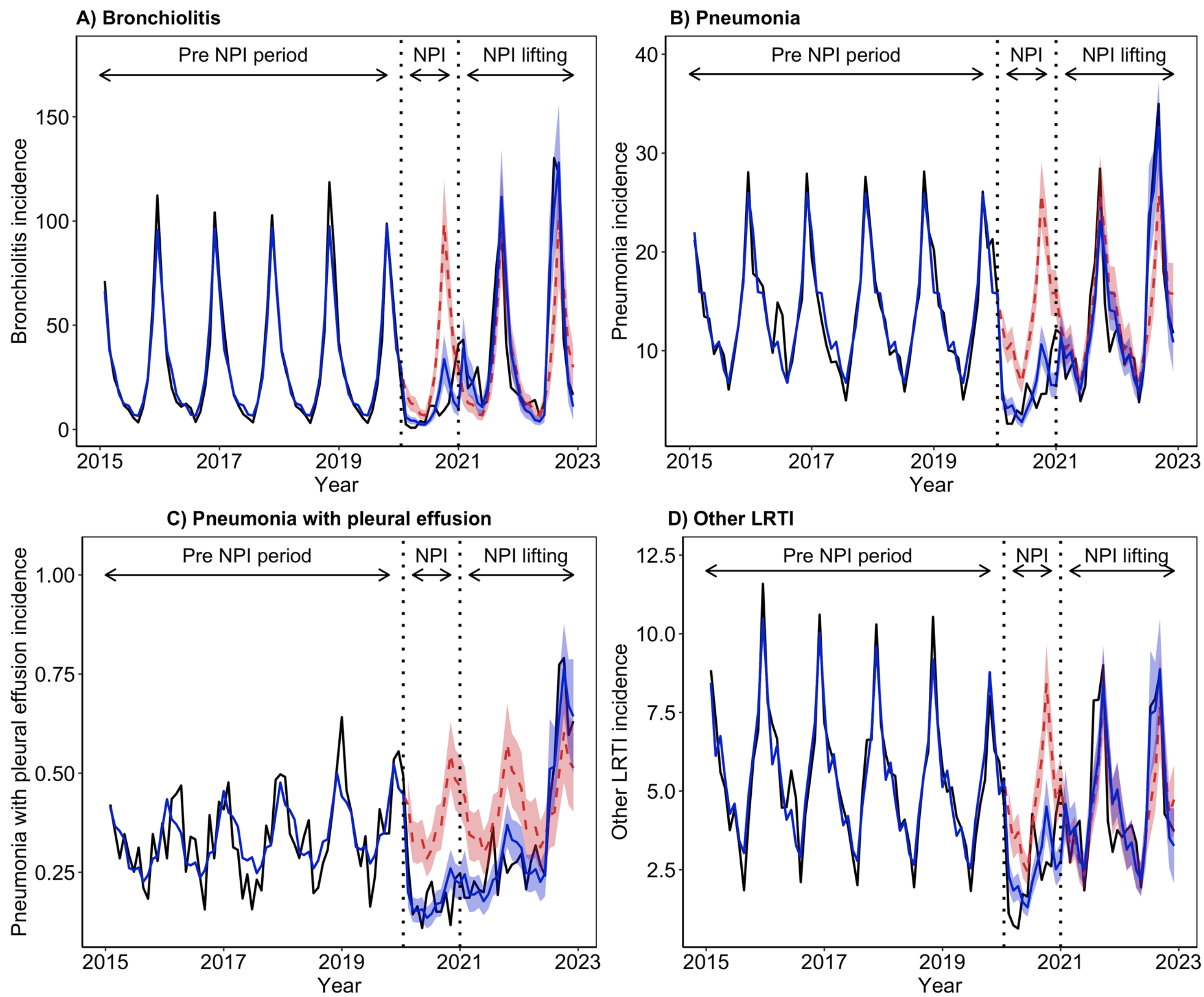

Fig. 2 Impact of non-pharmaceutical interventions on the monthly incidence of hospitalisation for **A** bronchiolitis (*N* = 422,036), **B** pneumonia (*N* = 188,319), **C** pneumonia with pleural effusion (*N* = 4682) and **D** other LRTI (*N* = 60,968) for children aged < 18 years from January 2015 to March 2023 in France. Incidence is expressed as the number of hospitalisations per 100,000 children per month. The black line shows the observed data. The blue line shows the model estimates based on observed data using the quasi-Poisson regression. The dashed red line shows the expected values assuming the NPI were not implemented using the same quasi-Poisson model. The blue and red shading indicates the 95% confidence intervals. Vertical dashed lines indicate NPI implementation and lifting. Pre-NPI period: 1 January 2015 to 31 March 2020. NPI period: 1 April 2020 to 31 March 2021. NPI-lifting period: 1 April 2021 to 31 March 2023. Abbreviations: NPI, non-pharmaceutical intervention; LRTI, lower respiratory tract infection

[10, 11]. Indeed, the decreased exposure of the population to infectious agents during the NPI period may have increased the proportion of individuals susceptible to these pathogens, leading to major outbreaks after NPI lifting [18, 25–27]. In addition, the higher incidence of hospitalisation for LRTI during the NPI-lifting period observed in this study involved mainly children < 1 year of age. This can be explained by decreased maternal exposure and immunity to viruses during the NPI period, resulting in lower transmission of protective antibodies during pregnancy and breastfeeding [28, 29].

We observed a marked increase in the incidence of LRTI requiring ICU admission during the NPI-lifting period. The observed higher severity may be the consequence of an elective involvement of young infants, as they are at higher risk of severe disease. Sub-group analyses showing a lower median age, together with an increased proportion of bronchiolitis cases among LRTI with ICU admission, tend to support this hypothesis.

Of note, hospitalisation for bronchiolitis with a detected pathogen showed a highly marked increase relative to overall hospitalisation for bronchiolitis. This

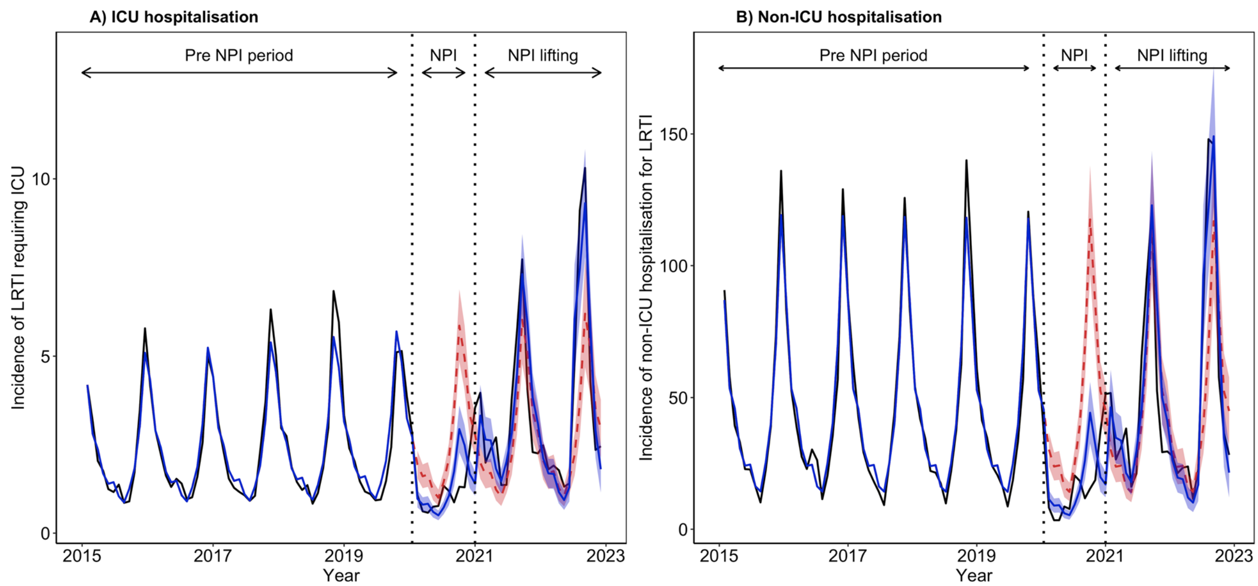

Fig. 3 Impact of non-pharmaceutical interventions on the monthly incidence of lower respiratory tract infections: **A** with ICU admission (N=36,948) and **B** without ICU admission (N=634,375) for children aged < 18 years from January 2015 to March 2023 in France. Incidence is expressed as the number of hospitalisations per 100,000 children per month. The black line shows the observed data. The blue line shows the model estimates based on observed data using the quasi-Poisson regression. The dashed red line shows the expected values assuming the NPI were not implemented using the same quasi-Poisson model. The blue and red shading indicates the 95% confidence intervals. Vertical dashed lines indicate NPI implementation and lifting. Pre-NPI period: 1 January 2015 to 31 March 2020. NPI period: 1 April 2020 to 31 March 2021. NPI-lifting period: 1 April 2021 to 31 March 2023. Abbreviations: ICU, intensive care unit; NPI, non-pharmaceutical intervention; LRTI, lower respiratory tract infection

is consistent with the major surge of pathogen-specific bronchiolitis cases, in particular RSV-positive bronchiolitis, observed in other countries following the progressive lifting of NPI in 2021 [30, 31]. These findings should be considered in the context of the decreased proportion of undocumented bronchiolitis, suggesting an increase in viral testing, which may have led to an overestimation of the increase in pathogen-related bronchiolitis. Thus, analyses focusing on the evolution of bronchiolitis with identified pathogens should be interpreted with caution. Overall respiratory diseases, independently of identified pathogens, may be a better outcome for analysing the changing burden of LRTI since the implementation of COVID-19-related NPI.

Our study had several limitations. First, as for any observational study relying on temporal associations, a causal relationship between NPI and the evolution of the incidence of hospitalisation for LRTI cannot be assumed. Second, the number of averted hospitalisations was estimated 2 years after the lifting of NPI. The benefit of NPI on the burden of childhood LRTI needs to be confirmed by a longer-term surveillance. Indeed, it is possible that reducing exposure to the agents responsible for respiratory infections secondary to NPI may have longer-term consequences for some pathogens. The intensity of the ongoing *Mycoplasma pneumoniae* and *Bordetella pertussis* epidemics in many countries may bear witness to this [32, 33]. Third, we considered the overall NPI to analyse the LRTI trends. As the various NPI largely overlapped, we could not detangle the specific role of each in the changing evolution of LRTI over time. However, a recent European study suggested that certain specific NPI, including facial masking and teleworking, were particularly effective in reducing the incidence of LRTI in children [34]. As the societal consequences of these measures might be more acceptable than others, these specific interventions may be considered to further reduce the burden of LRTI in children in the future. Fourth, the proportion of patients tested for respiratory pathogens was not provided, as testing results were reported only in the case of positivity. Fifth, other changes beyond NPI could be associated with the observed dynamics. Epidemiological changes (secular year-to-year variability, change in virus seasonality and in types of influenza viruses) and behavioural changes may have also partially change LRTI epidemiology. Sixth, we cannot rule out potential changes in coding practices or hospital admission capacity during the COVID-19 pandemic. However, the incidence of UTI analysed as a control outcome did not significantly change over the study period, limiting the risk of bias related to these potential confounders.

Conclusions

Three years after their implementation, the impact of NPI appears to still be beneficial for childhood LRTI. The use of some societally acceptable NPI may be considered as a public health measure to reduce the burden of LRTI in the future, particularly during epidemics and/or for the more susceptible population.

Abbreviations

COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICU	Intensive care unit
LRTI	Lower respiratory tract infections
NPI	Non-pharmaceutical interventions
PARI	Paediatric and Ambulatory Research in Infectious diseases
PMSI	Medicalization of Information Systems Program
RSV	Respiratory syncytial virus
UTI	Urinary tract infections

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03885-7.

Additional file 1: eTable 1 Clinical diagnoses defined by ICD-10 code combinations.

Additional file 2: eFigure 1 Correlograms and residuals analysis of the quasi-Poisson regression model for the monthly incidence of hospitalised LRTI per 100,000 children in France.

Additional file 3: eFigure 2 Impact of NPI on the monthly incidence of urinary tract infections (UTI) in children hospitalised in France from January 2015 to March 2023.

Additional file 4: eTable 3 Association of NPI with the monthly rates of ambulatory bronchiolitis ($N = 28{,}005$) and ambulatory pneumonia ($N = 2831$) among children aged < 16 years in France ($N = 5{,}425{,}855$).

Additional file 5: eFigure 3 Impact of NPI on the monthly rate of ambulatory bronchiolitis and pneumonia, among ambulatory visits in France from June 2017 to March 2023.

Additional file 6: eFigure 4 Impact of NPI on the monthly incidence of hospitalised LRTI by age group.

Additional file 7: eTable 4 Characteristics of LRTI requiring ICU admission in France, January 2015 to March 2023.

Additional file 8: eTable 5 Number of hospitalised lower respiratory tract infections (LRTI) by infectious agent, January 2015 to March 2023.

Additional file 9: eTable 6 Association of non-pharmaceutical interventions (NPI) with the monthly incidence of hospitalised LRTI in children by infectious agent, and the proportion of undocumented bronchiolitis and pneumonia.

Additional file 10: eFigure 5 Impact of NPI on the monthly incidence of hospitalised LRTI by infectious agent.

Additional file 11: eFigure 6 Impact of NPI on the proportion of A) undocumented bronchiolitis and B) undocumented pneumonia in children < 18 years hospitalised in France between January 2015 and March 2023.

Additional file 12: eTable 7 Estimated averted hospitalisations for LRTI between March 2020 and March 2023 in France.

Additional file 13: Number of children < 18 years of age living in France over time.

Additional file 14: Correlograms and residuals analysis of the sensitivity analyses.

Additional file 15: Correlograms and residuals analysis of the quasi-Poisson regression model for the monthly rate of bronchiolitis and pneumonia per 1000 ambulatory visits in France.

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Authors' contributions

NO and ZA take responsibility for the content of the manuscript, including the integrity of the data and the accuracy of the data analysis. IF, ZA, RB and NO made substantial contributions to the conception or design of the work. IF, ZA and NO drafted the manuscript. IF, ZA, LL, ZV, FK, CA, AB, AR, SB, CL, RC, BF, AW, FA, RB and NO were involved in the acquisition, analysis, or interpretation of data. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate.

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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References

1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18(11):1191–210.
2. Kruizinga MD, Peeters D, van Veen M, et al. The impact of lockdown on pediatric ED visits and hospital admissions during the COVID19 pandemic: a multicenter analysis and review of the literature. Eur J Pediatr. juill 2021;180(7):2271-9.
3. Angoulvant F, Ouldali N, Yang DD, et al. Coronavirus disease 2019 pandemic: impact caused by school closure and national lockdown on pediatric visits and admissions for viral and nonviral infections-a time series analysis. Clin Infect Dis. 2021;72(2):319–22.
4. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. Lancet Digit Health. juin 2021;3(6):e360-70.
5. Danino D, Ben-Shimol S, van der Beek BA, et al. Decline in pneumococcal disease in young children during the coronavirus disease 2019 (COVID-19) pandemic in Israel associated with suppression of seasonal respiratory viruses, despite persistent pneumococcal carriage: a prospective cohort study. Clin Infect Dis. 24 août 2022;75(1):e1154-64.
6. Hatter L, Eathorne A, Hills T, et al. Respiratory syncytial virus: paying the immunity debt with interest. Lancet Child Adolesc Health déc. 2021;5(12):e44-5.
7. Foley DA, Yeoh DK, Minney-Smith CA, et al. The interseasonal resurgence of respiratory syncytial virus in Australian children following the reduction of coronavirus disease 2019-related public health measures. Clin Infect Dis. 2021;73(9):e2829-30.
8. Ouldali N, Deceuninck G, Lefebvre B, et al. Increase of invasive pneumococcal disease in children temporally associated with RSV outbreak in Quebec: a time-series analysis. Lancet Reg Health Am mars. 2023;19: 100448.
9. Shaw D, Abad R, Amin-Chowdhury Z, et al. Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium. Lancet Digit Health sept. 2023;5(9):e582-93.
10. Cohen R, Ashman M, Taha MK, et al. Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap? Infect Dis Now août. 2021;51(5):418–23.
11. Cohen R, Levy C, Rybak A, et al. Immune debt: recrudescence of disease and confirmation of a contested concept. Infect Dis Now mars. 2023;53(2): 104638.
12. Assad Z, Michel M, Valtuille Z, et al. Incidence of acute chest syndrome in children with sickle cell disease following implementation of the 13-valent pneumococcal conjugate vaccine in France. JAMA Netw Open. 2022;5(8):e2225141.
13. Assad Z, Valtuille Z, Rybak A, et al. Unique changes in the incidence of acute chest syndrome in children with sickle cell disease unravel the role of respiratory pathogens: a time series analysis. Chest. 5 août 2023;S0012–3692(23)05256-X.
14. Levy C, Vie le Sage F, Varon E, et al. Pediatric ambulatory and hospital networks for surveillance and clinical epidemiology of community-acquired infections. J Pediatr. mars 2018;194:269–270.e2.
15. Cohen R, Béchet S, Gelbert N, et al. New approach to the surveillance of pediatric infectious diseases from ambulatory pediatricians in the digital era. The Pediatric Infectious Disease Journal juill. 2021;40(7):674.
16. Data on country response measures to COVID-19, https://www.ecdc.europa.eu/en/publications-data/download-data-response-measures-covid-19
17. Mathieu E, Ritchie H, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). https://ourworldindata.org/covid-stringency-index
18. Lassoued Y, Assad Z, Ouldali N, et al. Unexpected increase in invasive group A streptococcal infections in children after respiratory viruses outbreak in France: a 15-year time-series analysis. Open Forum Infect Dis. 2023;10(5):ofad188.
19. Accueil - Insee - Institut national de la statistique et des études économiques, https://www.insee.fr/fr/accueil
20. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther août. 2002;27(4):299–309.
21. Jandoc R, Burden AM, Mamdani M, et al. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. J Clin Epidemiol août. 2015;68(8):950–6.
22. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol févr. 2017;46(1):348–55.
23. Methi F, Størdal K, Telle K, et al. Hospital admissions for respiratory tract infections in children aged 0–5 years for 2017/2023. Front Pediatr. 2021;9: 822985.
24. Izu A, Nunes MC, Solomon F, et al. All-cause and pathogen-specific lower respiratory tract infection hospital admissions in children younger than 5 years during the COVID-19 pandemic (2020–22) compared with the pre-pandemic period (2015–19) in South Africa: an observational study. The Lancet Infectious Diseases sept. 2023;23(9):1031–41.
25. Foley DA, Sikazwe CT, Minney-Smith CA, et al. An unusual resurgence of human metapneumovirus in Western Australia following the reduction of non-pharmaceutical interventions to prevent SARS-CoV-2 transmission. Viruses. 2022;14(10):2135.
26. Munkstrup C, Lomholt FK, Emborg HD, et al. Early and intense epidemic of respiratory syncytial virus (RSV) in Denmark, August to December 2022. Euro Surveill. 2023;28(1):2200937.
27. Delestrain C, Danis K, Hau I, et al. Impact of COVID-19 social distancing on viral infection in France: a delayed outbreak of RSV. Pediatr Pulmonol déc. 2021;56(12):3669–73.
28. Størdal K, Lundeby KM, Brantsæter AL, et al. Breast-feeding and infant hospitalization for infections: large cohort and sibling analysis. J Pediatr Gastroenterol Nutr août. 2017;65(2):225–31.
29. Glezen WP. Effect of maternal antibodies on the infant immune response. Vaccine. 2003;21(24):3389–92.
30. Intensified circulation of respiratory syncytial virus (RSV) and associated hospital burden in the EU/EEA. 2022, https://www.ecdc.europa.eu/en/publications-data/intensified-circulation-respiratory-syncytial-virus-rsv-and-associated-hospital
31. Cong BM, Dina et al. Changes in the global hospitalisation burden of respiratory syncytial virus in young children during the COVID-19 pandemic: a systematic analysisLancet. Infect Dis 2023;24(4):361-74
32. Meyer S, MPereyre M, Sabine et al. Mycoplasma pneumoniae: delayed re-emergence after COVID-19 pandemic restrictions. The Lancet Microbe. 2023;5(2)e100-e101.
33. Rodrigues C, Bouchez V, Soares A, et al. Resurgence of Bordetella pertussis, including one macrolide-resistant isolate, France, 2024. Euro Surveill août. 2024;29(31):2400459.
34. Lenglart L, Ouldali N, Honeyford K, et al. Respective role of non-pharmaceutical interventions on bronchiolitis outbreaks, an interrupted time series analysis based on a multinational surveillance system. Eur Respir J. 2022;61:2201172.

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