ORIGINAL ARTICLES

Surge of Pediatric Respiratory Tract Infections after the COVID-19 Pandemic and the Concept of "Immune Debt"

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Objective To investigate a dose-response relationship between the magnitude of decrease in pediatric respiratory tract infections (RTIs) during the 2020 implementation of nonpharmaceutical interventions (NPIs) and the increase thereafter during NPI lifting.

Study design We conducted an interrupted, time-series analysis based on a multinational surveillance system. All patients <16 years of age coming to medical attention with various symptoms and signs of RTI at 25 pediatric emergency departments from 13 European countries between January 2018 and June 2022 were included. We used generalized additive models to correlate the magnitude of decrease of each RTI during NPI (such as social distancing) implementation and its subsequent increase during NPI lifting. Urinary tract infections served as control outcome.

Results In total, 528 055 patients were included. We observed reductions in cases during the NPI period, from −76% (95% CI −113 to −53 in pneumonia) to −65% (95% CI −100 to −39 for tonsillitis/pharyngitis), followed by strong increases during NPI lifting, from +83% (95% CI 29-150 for tonsillitis/pharyngitis) to +329% (95% CI 149-517 for bronchiolitis). For each RTI, we found a significant association between the magnitude of decrease during NPI implementation and the increase during NPI lifting. Urinary tract infection cases remained stable.

Conclusions The magnitude of increase in RTI observed after NPI lifting was directly correlated to the magnitude of case reduction during NPI implementation, suggesting a "dose-response" relationship from an "immune debt" phenomenon. The likely rebound in RTIs should be expected when implementing and lifting NPI in the future. *(J Pediatr 2025;284:114420)*.

AOM	Acute otitis media
EDF	Effective degree of freedom
GAM	Generalized additive model
NPI	Nonpharmaceutical intervention
PED	Pediatric emergency department
PICU	Pediatric intensive care unit
RTI	Respiratory tract infection
UTI	Urinary tract infection

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Respiratory tract infections (RTIs) are the leading cause of death in young children globally,[1] responsible for 650 000 deaths annually in children younger than 5 years. Moreover, they are the leading cause of pediatric emergency department (PED) visits, especially during winter, and estimated to be responsible for 5 million hospital admissions every year in the US.[2]

Since 2020, the unprecedented implementation of various nonpharmaceutical interventions (NPIs),[3,4] such as personal protective equipment, social distancing, closures, and quarantines, to contain the COVID-19 pandemic strongly reduced the incidence of community-acquired pediatric RTI[5-9] of viral or bacterial origins such as acute otitis media (AOM), pharyngitis, tonsillitis, laryngitis, bronchiolitis, or pneumonia.[5,10-13] However, concerns have been raised regarding the risk of disproportionally high communicable disease outbreaks after NPI lifting. Indeed, strong outbreaks of respiratory pathogens have been reported after the relaxing of NPI in several countries.[6-9,14-16] Several explanations have been proposed to this resurgence, including changes in vaccine uptake, in population's behaviors, usual year-to-year variations of these diseases, or the "immune debt"[17]/"shortage"[18] theory, a consequence of the increased proportion of the population naïve to these pathogens. To date, the exact reasons underlying these resurgences remain unclear, and the immune debt theory remains a debated concept. Understanding factors that drive immune debt are important.

We hypothesized that if the immune debt drove the recent dynamics of RTI in children, the magnitude of the rebound would be correlated to the magnitude of the previous decrease of RTI during the implementation of NPI. To investigate a "dose-response" relationship[19] between the level of decrease of a disease and its subsequent dynamic, multinational scale data and analyses, which have not been conducted to date, are required. Relying on an already-established European PED network,[11,20,21] the aim of this study was to correlate the magnitude of the decrease of 5 pediatric RTIs during the NPI implementation period with their subsequent dynamics after NPI lifting in 13 European countries.

Methods

Study Design and Sample

We conducted a quasi-experimental interrupted time-series analysis on the basis of data from the EPISODES multinational study network. Twenty-five PEDs (**Appendix 1**, online; available at www.jpeds.com) in 13 European countries (Austria, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Sweden, Switzerland, Turkey, and United Kingdom) participated in the study. All children <16 years of age presenting to 1 of the participating sites between January 1, 2018, and June 30, 2022, and diagnosed with AOM, croup or laryngitis, tonsillitis or pharyngitis, bronchiolitis (<1 year-old only), or pneumonia were included in this study. All urinary tract infection (UTI) cases in children aged <16 years were included in the study and served as a control outcome. As previously published,[11,20] the identification of patients was determined by the *International Classification of Diseases, Tenth Revision*, coding system (**Appendix 2**, online; available at www.jpeds.com) or on the diagnosis provided by the PED physician in the health record of the case.

Data Collection and Period Definition

We retrospectively collected monthly aggregated and anonymized data for each participating center through a clinical report form, including total number of patients presenting to the PED, age category and sex, diagnosis (AOM, tonsillitis/pharyngitis, laryngitis/croup, bronchiolitis, pneumonia and UTI), and clinical management (discharged to home or hospitalization to short stay unit, ward or pediatric intensive care unit [PICU]). All data were stored into secure and validated REDCap electronic data capture tools.[22]

As previously published,[11,23] according to European Center for Disease Control reports, we used a total of 14 NPIs from 4 categories (individual protection, social distancing/lockdowns, "test, trace and isolate," and travel bans) to define 3 time periods as follows: pre-NPI period (from January 1, 2018, to March 31, 2020), NPI period (from April 1, 2020, to March 31, 2021), and NPI-lifting period (from April 1, 2021, to June 30, 2022) (**Appendix 3**, online; available at www.jpeds.com).

Outcome Measures

The main outcome of the study was the percentage of change in the monthly number of cases diagnosed with AOM, tonsillitis/pharyngitis, laryngitis/croup, bronchiolitis, and pneumonia in each participating country during the NPI period and the NPI-lifting period compared with previous periods, assessed by interrupted time series analysis models at a national level.

The secondary outcomes of the study were the percentage of change in the monthly number of cases (1) by group of pathologies (upper RTI and lower RTI), (2) by type of infection (suspected viral: laryngitis/croup and bronchiolitis; and suspected viral or bacterial: AOM, tonsillitis/pharyngitis and pneumonia), and (3) by severity of cases (hospitalized or nonhospitalized cases and percentage of PICU hospitalizations for lower RTI). UTI cases were used as a control outcome, as they were not expected to be influenced by NPI.[23,24]

Statistical Analysis

The main analysis focused on modeling the correlation between the magnitude of decrease in the monthly number of cases of the 5 RTIs within the 13 participating countries during the NPI period and their dynamics during the NPI-lifting period by using generalized additive models (GAMs). The dynamic of each of the 5 RTI diagnoses during the NPI period and the NPI-lifting period was first assessed by interrupted time series analysis models for each of the 13 participating countries. For each of the 5 RTIs, the evolution of the monthly number of cases was analyzed using a quasi-Poisson regression accounting for seasonality, overdispersion of data, and secular trend during the pre-NPI, NPI, and NPI-lifting periods.[25-27] Seasonality was taken into account by including harmonic

Table I. General characteristics of the sample, n = 528 055

Characteristics	Pre-NPI period January 1, 2018, to March 31, 2020	NPI period April 1, 2020, to March 31, 2021	NPI-lifting period April 1, 2021, to June 30, 2022	Total period January 1, 2018, to June 30, 2022
AOM				
Total number	67 918	8877	26 144	102 939
Age*				
<3 mo	464/52 325 (0.9)	166/6278 (2.6)	124/20 269 (0.6)	754/78 872 (0.9)
3 mo to 1 y	6758/52 325 (12.9)	1113/6278 (17.7)	2456/20 269 (12.1)	10 327/78 872 (13.1)
1-16 y	55 084/66 676 (82.6)	6815/8731 (78.0)	21 732/25 258 (86.0)	83 631/100 665 (83.1)
Croup/laryngitis				
Total number	29 525	4892	16 380	50 797
Age*				
<3 mo	309/23 615 (1.3)	38/3400 (1.1)	67/13 349 (0.5)	414/40 364 (1.0)
3 mo to 1 y	4016/23 615 (17.0)	597/3400 (17.6)	2085/13 349 (15.6)	6698/40 364 (16.6)
1-16 y	23 966/29 525 (81.2)	3943/4892 (80.6)	13 566/16 380 (82.8)	41 475/50 797 (81.6)
Severity†				
Nonhospitalized	22 142/26 170 (84.6)	4042/4502 (89.8)	12 902/14 445 (89.3)	39 086/45 117 (86.6)
Hospitalized	4028/26 170 (15.4)	460/4502 (10.2)	1543/14 445 (10.7)	6031/45 117 (13.4)
Tonsillitis/pharyngitis				
Total number	174 477	27 185	70 536	272 198
Age*				
<3 mo	2280/124 537 (1.8)	193/15 482 (1.2)	701/44 870 (1.6)	3174/184 889 (1.7)
3 mo to 1 y	14 513/124 537 (11.6)	2486/15 482 (16.1)	5273/44 870 (11.7)	22 272/184 889 (12.0)
1-16 y	141 797/174 477 (81.3)	20 429/27 185 (75.1)	57 105/70 536 (81.2)	219 331/272 198 (80.5)
Bronchiolitis				
Total number	36 715	3869	17 576	58 160
Age				
<14 d	950/24 991 (3.8)	31/1392 (2.2)	253/12 705 (2.4)	1234/39 088 (3.3)
14 d to 3 mo	8055/24 991 (32.3)	362/1392 (26.0)	4327/12 705 (34.0)	12 744/39 088 (32.6)
3 mo to 1 y	15 978/24 991 (63.9)	1000/1392 (71.8)	8087/12 705 (63.6)	25 065/39 088 (64.1)
Severity				
Nonhospitalized	18 419/29 961 (61.5)	2537/3640 (69.7)	11 183/16 154 (69.2)	32 139/49 755 (64.6)
Hospitalized†	11 542/29 961 (38.5)	1103/3640 (30.3)	4971/16 154 (30.8)	17 616/49 755 (35.4)
Pneumonia				
Total number	32 481	2353	9127	43 961
Age*				
<3 mo	397/28 152 (1.4)	44/1772 (2.4)	98/7940 (1.2)	539/37 864 (1.4)
3 mo to 1 y	2236/28 152 (7.9)	146/1772 (8.2)	571/7940 (7.2)	2953/37 864 (7.8)
1-16 y	29 034/32 481 (89.4)	2043/2353 (86.8)	8279/9127 (90.7)	39 356/43 961 (89.5)
Severity				
Nonhospitalized	15 643/23 963 (65.3)	1193/2069 (57.7)	4895/7797 (62.8)	21 731/33 829 (64.2)
Hospitalized†	8320/23 963 (34.7)	876/2069 (42.3)	2902/7797 (37.2)	12 098/33 829 (35.8)
All RTIs				
Total number	341 116	47 176	139 763	528 055
Age*				
<3 mo	12 455/253 620 (4.9)	834/28 324 (2.9)	5570/99 133 (5.6)	18 859/381 077 (4.9)
3 mo to 1 y	43 501/253 620 (17.1)	5342/28 324 (18.8)	18 472/99 133 (18.6)	67 315/381 077 (17.6)
1-16 y	239 601/303 159 (78.8)	33 230/44 553 (74.6)	100 682/134 006 (75.1)	383 723/511 582 (75.0)
Severity				
Nonhospitalized	56 204/80 094 (70.2)	7772/10 211 (76.1)	28 980/38 396 (75.5)	92 956/128 701 (72.2)
Hospitalized†	23 890/80 094 (29.8)	2439/10 211 (23.9)	9416/38 396 (24.5)	35 745/128 701 (27.8)

Variables are reported as number/number of available data for the variable and percentage.
*France was only able to provide age-categories in year; this explains the difference of denominator for monthly and yearly age-categories.
†Hospitalized cases include short-stay unit, ward, and PICU admissions.

terms (sines and cosines), with 12- and 6-month periods to adjust for seasonal patterns.[27] The chosen time unit was 1 month. Two dummy variables accounted for the NPI period and NPI-lifting period.[25,26] A quasi-Poisson distribution allows accounting for overdispersion better than a Poisson distribution. The validity of the regression was assessed by visual inspection of correlograms and residual analysis.[27]

For each studied RTI, in each country, we calculated the changes associated to the 2 interventions (NPI implementation and NPI lifting) by estimating the fitted value of the number of observed cases during the 2 different intervention time periods compared with the expected value on the basis of the model parameters for each time point. Changes during the NPI period were determined by the expected values estimated via the pre-NPI period trend, and changes during the NPI-lifting period were determined by the expected values estimated via the NPI period trend. For the 5 RTIs, we finally estimated the correlation between the changes in each of the 13 participating countries during the NPI period and the subsequent changes during the NPI-lifting period using GAMs.[28] GAMs have multiple advantages for dynamic time-series data, including when suspecting a possible

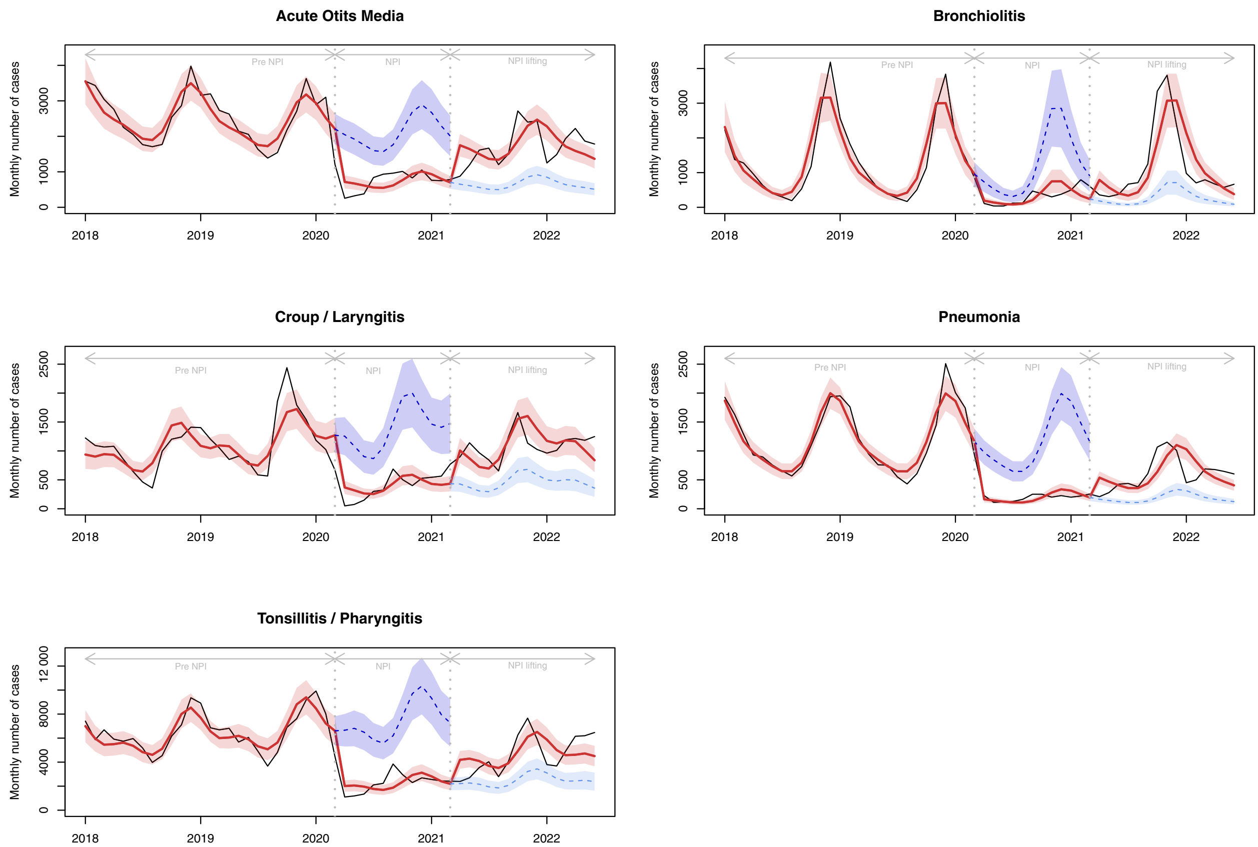

Figure 1. Evolution of the monthly number of AOM (A, n = 102 939), croup/laryngitis (C, n = 50 797), tonsillitis/pharyngitis (E, n = 272 198), bronchiolitis (B, n = 58 160), pneumonia (D, n = 43 961), and UTI (F, n = 37 083) during the pre-NPI, NPI, and NPI-lifting periods for the 13 participating countries. The *black line* shows the observed data. The *solid red line* shows the model estimates based on observed data (quasi-Poisson regression modeling) and is associated to its 95% CI in *transparent red*. The *dashed dark blue line* shows the expected values without NPIs in the NPI period (quasi-Poisson regression modeling) and is associated to its 95% CI in *transparent dark blue*. The *light blue line* shows the expected values without NPIs lifting during the NPI-lifting period (quasi-Poisson regression modeling) and is associated to its 95% CI in *transparent light blue*. The implementation of NPIs is indicated by the first *vertical dashed line* and their lifting by the second. Pre-NPI period: January 1, 2018, to March 31, 2021. NPI period: April 1, 2020, to March 31, 2021. NPI-lifting period: April 1, 2021, to June 30, 2022.

nonlinear relationship across time, the ability to model nonconstant correlations between repeated measurements, and to accommodate incomplete observations and unbalanced data. To account for the heterogeneity in the number of included cases in each participating country, we used weighted GAMs.[29] The weight of each country was calculated as the proportion of patients visiting the participating PED of each country divided by the total number of patients visiting all the participating PED over the total study period (**Appendix 4**, online; available at www.jpeds.com). When analyzing GAMs results, figures as well as the effective degree of freedom (EDF) and *P* values are presented.[30] EDF represent a proxy of the degree of nonlinearity of the relationship tested in the analysis but does not inform on the direction (positive or negative) of the correlation. An EDF of 1 is equivalent to a linear relationship, an EDF >2 is a highly nonlinear relationship.[31]

The following sensitivity analyzes were performed: (1) a correlation analysis using a weighted Pearson correlation coefficient, (2) an analysis including only 12-month periods instead of 12- and 6-month periods to adjust for seasonal patterns in the interrupted time series model, (3) a linear segmented regression analysis including additive model to adjust for seasonality instead of quasi-Poisson in the interrupted time series model, (4) an analysis estimating the changes during the NPI-lifting period on the basis of the expected values estimated via the pre-NPI period trend instead of the NPI period trend, and (5) a correlation analysis using a polynomial weighted model instead of the weighted GAMs.

All secondary outcomes were analyzed using the previously described methodology. All statistical tests were 2-sided, with $P < .05$ considered statistically significant. All analyzes were performed using R statistical software, version 4.1.1 (http://www.R-project.org).

Table II. Cumulative changes in AOM, croup/laryngitis, tonsillitis/pharyngitis, bronchiolitis, and pneumonia cases during the NPI and NPI-lifting period in the 13 participating centers, n = 102 939 (AOM), n = 50 797 (croup/laryngitis), n = 272 198 (tonsillitis/pharyngitis), n = 58 160 (bronchiolitis), and n = 43 961 (pneumonia)

	Acute otitis media				Croup / Laryngitis				Tonsillitis / Pharyngitis			
	Cumulative change NPI period*		Cumulative change NPI lifting period*		Cumulative change NPI period*		Cumulative change NPI lifting period*		Cumulative change NPI period*		Cumulative change NPI lifting period*	
	95%CI	p-value	95%CI	p-value	95%CI	p-value	95%CI	p-value	95%CI	p-value	95%CI	p-value
Austria	-89% [-113; -65]	<0.001	+147% [47;249]	<0.001	-88% [-121;-55]	<0.001	+111% [64;158]	<0.001	-87% [-121;-52]	<0.001	+113% [64;163]	0.010
France	-60% [-100;-19]	<0.001	+73% [1;144]	0.001	-64% [-121;-7]	<0.001	+24% [-61;+108]	0.355	-53% [-94;-12]	<0.001	+68% [3;134]	0.001
Germany	-73% [-132;-13]	<0.001	+285% [+96;476]	<0.001	-74% [-131;-17]	0.001	+489% [+170;809]	<0.001	-72% [-130;-15]	<0.001	-58% [-110;-6]	0.016
Ireland	-64% [-112;-17]	<0.001	+196% [84;308]	<0.001	-83% [-136;-29]	<0.001	+235% [75;396]	<0.001	-69% [-108;-30]	<0.001	+150% [62;239]	<0.001
Italy	-66% [-121;-11]	<0.001	+155% [30;280]	<0.001	-63% [-113;-14]	<0.001	+180% [69;291]	<0.001	-42% [-127;+43]	0.084	+79% [21;137]	0.039
Latvia	-77% [-112;-41]	<0.001	+202% [70;335]	<0.001	-73% [-129;-17]	<0.001	+280% [105;456]	<0.001	-57% [-100;-14]	<0.001	+111% [25;197]	<0.001
Lithuania	-78% [-139;-17]	<0.001	+320% [119;520]	<0.001	-89% [-139;-27]	<0.001	+569% [269;820]	<0.001	-63% [-111;-6]	<0.001	+190 [60;289]	<0.001
Netherland	-57% [-107;-7]	0.029	+196% [126;266]	0.002	-55% [-99;-11]	0.021	+43% [-85;+170]	0.261	-82% [-182;+18]	0.004	-27% [-201;148]	0.597
Portugal	-62% [-103;-21]	<0.001	+174% [79;270]	<0.001	-69% [-127;-11]	<0.001	+222% [74;375]	<0.001	-75% [-112;-38]	<0.001	+149% [56;242]	<0.001
Sweden	-64% [-107;-21]	<0.001	+209% [106;312]	<0.001	-56% [-107;-6]	<0.001	+72% [33;109]	0.005	-38% [-74;-3]	<0.001	-8% [-49;+32]	0.457
Switzerland	-58% [-111;-5]	<0.001	+393% [226;559]	<0.001	-64% [-117;-11]	<0.001	+66% [23;109]	0.017	-43% [-91;+5]	0.003	+105% [25;184]	<0.001
Turkey	-92% [-139;-44]	<0.001	+420% [159;682]	<0.001	-92% [-170;-14]	<0.001	+99% [-153;351]	0.257	-97% [-142;-53]	<0.001	+180% [88;272]	0.033
United Kingdom	-75% [-111;-39]	<0.001	+184% [88;281]	<0.001	-78% [-146;-9]	<0.001	+149% [82;215]	0.006	-76% [-104;-47]	<0.001	+165% [94;236]	<0.001
All countries	-65% [-98;-32]	<0.001	+168% [91;247]	<0.001	-66% [-110;-31]	<0.001	+130% [49;222]	<0.001	-65% [-100;-39]	<0.001	+83% [29;150]	<0.001

(*continued*)

Results

A total of 528 055 patients with RTI were included during the study period (102 939 AOM, 50 797 laryngitis/croup, 272 198 tonsillitis/pharyngitis, 58 160 bronchiolitis and 43 961 pneumonias) (**Table I**). Of all RTI cases, 5% (18 859/381 077) were children aged younger than 3 months, and 18% (67 315/381 077) were aged between 3 and 12 months. Overall, 28% (35 745/128 701) of the cases were hospitalized: 13% (6031/45 117) of laryngitis/croup, 35% (17 616/49 755) of bronchiolitis, and 36% (12 098/33 829) of pneumonia.

We observed a significant reduction in cases for each RTI during the NPI period, ranging from −76% (95% CI −113 to −53) for pneumonia to −65% for AOM (95% CI − 98 to −32) as well as tonsillitis/pharyngitis (95% CI −100 to −39), followed by an increase during the NPI-lifting period, ranging from +83% (95% CI 29-150) for tonsillitis/pharyngitis to +329% (95% CI 149-517) for bronchiolitis. Cumulative changes during NPI and NPI-lifting period varied widely across the different countries (**Figure 1** and **Table II**). In total, 37 083 UTIs were included during the study period. The number of UTIs (ie, the control sample) diagnosed in the participating centers remained stable during the NPI and NPI-lifting periods, without significant rebound during the NPI-lifting period (**Figure 1**, **Appendix 5**, online; available at www.jpeds.com).

For each of the 5 studied RTIs, we found a statistically significant correlation between the magnitude of the decrease of the disease during the NPI period and its subsequent increase during the NPI-lifting period (**Figure 2** and **Table III**). Most

Table II. Continued

	Bronchiolitis				Pneumonia			
	Cumulative change NPI period*		Cumulative change NPI lifting period*		Cumulative change NPI period*		Cumulative change NPI lifting period*	
	95%CI	p-value	95%CI	p-value	95%CI	p-value	95%CI	p-value
Austria	-94% [-169;-18]	**0.002**	+907% [34;1780]	**0.011**	-77% [-108;-47]	**<0.001**	+142% [56;228]	**<0.001**
France	-56% [-100;-12]	**0.016**	+70% [-60;+199]	0.08	-74% [-115;-32]	**<0.001**	+55% [16;93]	**0.030**
Germany	-96% [-223;+30]	0.079	+9965% [3031;1689	**0.015**	-39% [-49;-29]	**0.040**	+38% [-50;+127]	0.135
Ireland	-85% [-152;-18]	**<0.001**	+760% [361;1158]	**<0.001**	-90% [-129;-50]	**<0.001**	+543% [310;777]	**<0.001**
Italy	-90% [-170;-10]	**0.001**	+1711% [696;2726]	**<0.001**	-86% [-141;-32]	**<0.001**	+253% [49;457]	**<0.001**
Latvia	-90% [-179%;-1]	**<0.001**	+1817% [597;3036]	**<0.001**	-81% [-124;-38]	**<0.001**	+335% [167;503]	**<0.001**
Lithuania	-83% [-187;+41]	**0.021**	+1814% [642;2962]	**<0.001**	-88% [-135;-25]	**<0.001**	+389% [143;609]	**<0.001**
Netherland	-96% [-180;-12]	**0.026**	+1138% [-90;+2565]	0.071	-71% [-137;-4]	**<0.001**	+120% [60;178]	**0.008**
Portugal	-82% [-138;-26]	**<0.001**	+498% [224;772]	**<0.001**	-88% [-139;-37]	**<0.001**	+309% [79;539]	**<0.001**
Sweden	-91% [-229;+47]	0.084	+4590% [998;8182]	**0.005**	-81% [-131;-32]	**<0.001**	+213% [69;356]	**<0.001**
Switzerland	-91% [-171;10]	**<0.001**	+1694% [487;2900]	**<0.001**	-79% [-118;-40]	**<0.001**	+341% [198;485]	**<0.001**
Turkey	-87% [-189;+14]	0.072	+193% [73;312]	**0.001**	-90% [-153;-27]	**<0.001**	+83% [-132;+298]	0.252
United Kingdom	-84% [-149;-20]	**<0.001**	+438% [165;712]	**<0.001**	-87% [-128;-47]	**<0.001**	+309% [153;464]	**<0.001**
All countries	-69% [-129;-19]	**<0.001**	+329% [149;517]	**<0.001**	-76% [-113;-53]	**<0.001**	+220% [127;330]	**<0.001**

P values <.05 are shown in bold.
Changes during the NPI period (April 1, 2020, to March 31, 2021) were based on the expected values estimated via the pre-NPI period (January 1, 2018, to March 31, 2020) trend.
Changes during the NPI-lifting period (April 1, 2021, to June 30, 2022) were based on the expected values estimated via the NPI period trend.
*For each studied RTI, in each country, we calculated the changes related to the NPI and NPI-lifting period by estimating the fitted value of the number of observed cases for the 2 intervention time periods compared with the expected value based on the model parameters for each time point, using interrupted time series analysis.

relationships were linear (EDF = 1). All sensitivity analyzes found similar results, including the weighted Pearson correlation analysis (**Table III** and **Appendix 6**, online; available at www.jpeds.com).

For all secondary analyzes (upper RTI, lower RTI, viral pathologies, viral or bacterial pathologies, hospitalized cases and nonhospitalized cases), there was a statistically significant correlation between the magnitude of the decrease during the NPI period and their subsequent increase during the NPI-lifting period (**Table III**, **Figure 3**). However, there was no change in the percentage of PICU hospitalization for LRTIs during the NPI implementation and NPI-lifting periods.

Discussion

This multinational quasi-experimental interrupted time-series analysis found significant correlations between the magnitude of decrease in cases of 5 RTIs (AOM, croup/laryngitis, tonsillitis/pharyngitis, bronchiolitis, and pneumonia) in PEDs during the NPI period and their subsequent increase during the NPI-lifting period, meaning that, at a country

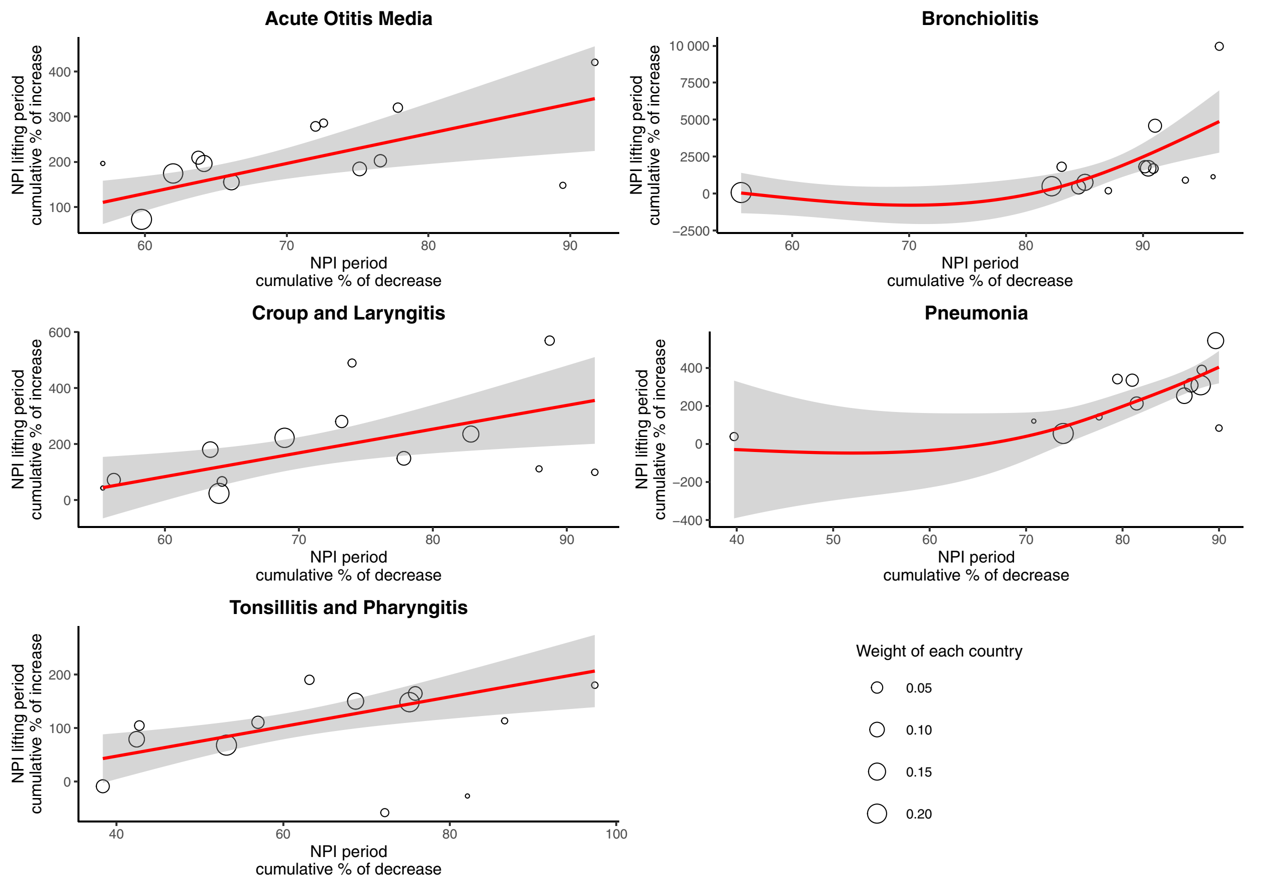

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Figure 2. Correlation between the magnitude of decrease during the NPI period and the dynamic during the NPI-lifting period in each country for AOM (A, n = 102 939), croup/laryngitis (C, n = 50 797), tonsillitis/pharyngitis (E, n = 272 198), bronchiolitis (B, n = 58 160), and pneumonia (D, n = 43 961). All figures represent the correlation between the magnitude of decrease during the NPI period and the dynamic during the NPI-lifting period in each country-weighted GAM model. The weight of each country was calculated as the proportion of patients visiting the PED of participating centers of each country over the study period divided by the total number of patients visiting the PED of all participating centers over the study period. NPI period: April 1, 2020, to March 31, 2021. NPI-lifting period: April 1, 2021, to June 30, 2022.

level, the greater the reduction during the NPI period, the greater the rebound during the NPI-lifting period.

These results could be keys to better understand the immune debt phenomenon, a consequence of the implementation of NPIs, as we observed a possible "dose-response" relationship between the dynamics of 5 RTI during NPI implementation and lifting. This effect was not observed for the control outcome, UTI, and, hence, likely not attributable to overall changes in care seeking patterns during and after the pandemic.

In this study, we did not observe the same level of rebound in RTI cases after NPI lifting in every country, with some not reaching the pre-NPI period number of cases. This is in line with many other reports.[8,16,32-34] To date, several hypotheses have been proposed to explain the changes in RTI dynamics observed after the beginning of the SARS-CoV-2 pandemic. First, this increase could be explained by an increase in social contacts after NPI lifting. However, the stringency index,[35] a composite measure calculated by the Oxford Coronavirus Government Response Tracker, reflective of the level of 9 NPI implemented[36] and correlated to the social mixing within a population,[37,38] remained non-negligible in Europe during the NPI-lifting period. Thus, the evolution of social mixing patterns over time could not explain the observed correlation between the dynamics during the NPI period and the NPI-lifting period. Second, the secular year-to-year variability of RTI have been suggested. However, in this case, no correlation would have been found between the decrease in RTI during the NPI period and the increase during the NPI-lifting period across countries. Third, the competition between SARS-CoV-2 and other viruses, including respiratory syncytial virus, in the nasopharynx has been proposed as a reason for the strong decrease in RTI during the NPI period.[39,40] Yet, Winter 2021-2022 was marked with a major SARS-CoV-2 Omicron variant circulation, and still, we observed an increase in RTI cases. Finally, the immune debt concept[17] that relies on (1) the increased proportion of the naïve population to various respiratory

Table III. Correlation between the magnitude of decrease during the NPI period and the dynamic during the NPI-lifting period in each country for AOM, croup/laryngitis, tonsillitis/pharyngitis, bronchiolitis, pneumonia, and secondary analyzes, n = 102 939 (AOM), n = 50 797 (croup/laryngitis), n = 272 198 (tonsillitis/pharyngitis), n = 58 160 (bronchiolitis), and n = 43 961 (pneumonia)

	Main analysis		Sensitivity analysis	
Outcomes	EDF*	*P* value	Rho†	*P* value
AOM	1.01	**.012**	0.67	**.011**
Croup/laryngitis	1.00	**.027**	0.61	**.026**
Tonsillitis/pharyngitis	1.00	**.009**	0.69	**.009**
Bronchiolitis	1.88	**.011**	0.53	.064
Pneumonia	1.99	**.004**	0.72	**.005**
Secondary analyses	EDF*			
URTI‡	1.00	**.001**		
LRTI§	1.00	**.028**		
Suspected viral pathologies¶	1.00	**.019**		
Suspected viral or bacterial pathologies**	1.00	.053		
Hospitalized cases††	1.00	**.004**		
Non-hospitalized cases	1.00	**.009**		

LRTI, lower respiratory tract infection; *URTI*, upper respiratory tract infection.
P values <.05 are shown in bold.
NPI period: April 1, 2020, to March 31, 2021. NPI-lifting period: April 1, 2021, to June 30, 2022.
*EDF represents a proxy of the degree of nonlinearity of the relationship tested in the analysis, but does not inform on the direction of the correlation. An EDF of 1 is equivalent to a linear relationship, an EDF >2 is a highly nonlinear relationship.[29]
†This is the result of one of the sensitivity analyses, the weighted Pearson correlation analysis.
‡URTIs include AOM, croup/laryngitis and tonsillitis/pharyngitis, n = 425 934.
§LRTIs include bronchiolitis and pneumonia, n = 102 121.
¶Viral pathologies include croup/laryngitis and bronchiolitis, n = 108 957.
**Viral or bacterial pathologies include AOM, tonsillitis/pharyngitis, pneumonia, n = 419 098.
††Hospitalized cases include hospitalization to short stay unit, ward, or pediatric intensive care unit, n = 92 956. Nonhospitalized cases: n = 383 723.

pathogens and (2) the reduction of the trained immunity[41] seems the most plausible. Although this was initially suggested by modeling studies,[42] a recent study from South Africa[43,44] showed that, in a country where NPIs were only partially implemented and quickly lifted, the reduction in RTI was low compared with other countries. Thus, the circulation of respiratory pathogens was not completely disturbed, and no major increase was observed during the 2021-2022 season. Our findings are concordant with the South African study and confirm the significance of NPI implementation scheme in impacting RTI dynamics in the short and middle run.[11] In this case, the smaller the reduction of cases during the NPI period, the smaller the increase during the NPI-lifting period. In this context, our study, taking advantage of a multinational surveillance system, supports the immune debt phenomenon as the main driver for the recent RTI surges in children.

Furthermore, as for today, no study has been able to conclude which types of pathogens were most affected by the immune debt. Indeed, at first, the alerts of an increase in RTI concerned bronchiolitis and respiratory syncytial virus mainly,[7,33,45-47] but then unprecedent outbreaks of other respiratory viruses,[12] intestinal viruses,[48,49] and hand, foot, and mouth disease[50] were also reported, as well as *Streptococcus pneumoniae*[13,16,51,52] and Group A *Streptococcus*.[8,9] The secondary analysis in our study suggests that the correlation between the dynamic of decrease during NPI period and the dynamic of increase during the NPI-lifting period concern pathologies from both viral and bacterial suspected origins.

Our findings provide information on the consequences of the drastic, yet temporary, reduction of RTI cases in the pediatric population following the implementation of NPI. This suggests that, in the future, the implementation and lifting of NPI should take into account the risk of congestion of the health care systems due to the substantial rebound correlated to the level of the previous reduction of circulation of respiratory pathogens.

Nonetheless, this study has some limitations. First, as this study is observational, a definitive causal relationship between the magnitude of decrease in the 5 RTIs during the NPI period and their subsequent increase during the NPI-lifting period cannot be established. Further studies are required to confirm these findings. Second, we did not include laboratory testing and, therefore, did not have access to the identified viral or bacterial pathogens. Although it would have added some precision to the study, our study is determined by clinical definition of cases seen at the PED, which allows the report of a real world-like view of the evolution of RTI in children during the COVID-19 pandemic, as most of cases are not routinely tested in PEDs. Moreover, the drastic changes in testing practices during the COVID-19 pandemic have provided highly biased data.[53] Third, the definition of the NPI and NPI-lifting periods was determined on the basis of European Center for Disease Control reports and considered all NPIs together rather than analyzing each of them separately. This approach does not allow identifying which NPI specifically drove the epidemiology of RTIs. Further studies are required to explore this question. Fourth, the identification of cases was determined on the basis of

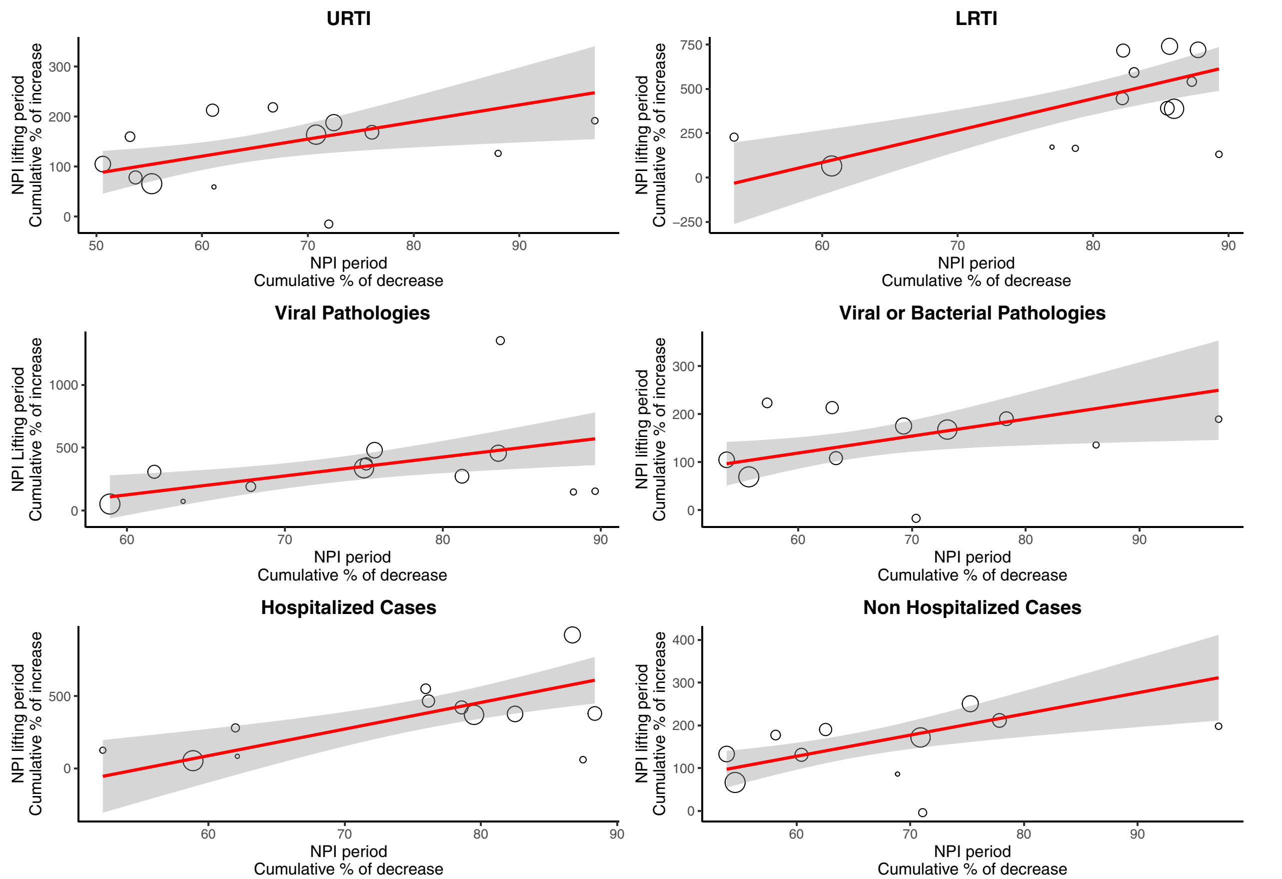

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Figure 3. Correlation between the magnitude of decrease during the NPI period and the dynamic during the NPI-lifting period in each country for secondary outcomes: upper RTI (n = 425 934), lower RTI (n = 102 121), viral pathologies (n = 108 957), viral or bacterial pathologies (n = 419 098), hospitalized cases (n = 92 956), and nonhospitalized cases (n = 383 723). **A,** Upper RTIs include AOM, croup/laryngitis, and tonsillitis/pharyngitis. **B,** Lower RTIs include bronchiolitis and pneumonia. **C,** Viral pathologies include croup/laryngitis and bronchiolitis. **D,** Viral or bacterial pathologies include AOM, tonsillitis/pharyngitis, and pneumonia. **E,** Hospitalized cases include hospitalization to short-stay unit, ward, or pediatric intensive care unit. The weight of each country was calculated as the proportion of patients visiting the PED of participating centers of each country over the study period divided by the total number of patients visiting the PED of all participating centers over the study period. NPI period: April 1, 2020, to March 31, 2021. NPI-lifting period: April 1, 2021, to June 30, 2022.

International Classification of Diseases, *Tenth Revision*, coding,[54] and cases were not reviewed manually to ensure the accuracy of the diagnoses or consistency in coding. However, a survey performed in the same multinational network[11,21] using the same methodology, did not identify changes in clinical diagnosis and management practices of pediatric RTI in the participating centers during the study period. Furthermore, the surveillance system was determined on the basis of a diagnostic coding system and a data extraction methodology that remained unchanged throughout the study period. Fifth, some changes in health care–seeking behaviors, such as the fear of contracting SARS-CoV-2 in the PED, or changes in health status of children such as comorbidities or incomplete immunizations schedules could not be captured by our methodology and we cannot exclude that they could have had an impact on consultation patterns of PED and thus on our results. Still, we did not observe an increase in the proportion of severe cases, and we did not observe significant variations in the monthly number of cases of UTI, used as a control outcome, suggesting that patterns of consultation may not have changed as substantially as often is hypothesized during the NPI and NPI-lifting periods. ■

CRediT authorship contribution statement

Lea Lenglart: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Luigi Titomanlio:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Zsolt Bognar:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Silvia Bressan:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Danilo Buonsenso:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Tisham De:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Ruth Farrugia:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Kate Honeyford:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Ian K. Maconochie:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Henriette A. Moll:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Rianne Oostenbrink:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Niccolo Parri:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Damian Roland:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Esra Akyüz Özkan:** Writing – review & editing, Methodology, Investigation. **Laura Almeida:** Writing – review & editing, Methodology, Investigation. **Ilaria Alberti:** Writing – review & editing, Methodology, Investigation. **François Angoulvant:** Writing – review & editing, Methodology, Investigation. **Zein Assad:** Writing – review & editing, Software, Methodology, Formal analysis. **Camille Aupiais:** Writing – review & editing, Methodology, Investigation. **Michael Barrett:** Writing – review & editing, Methodology, Investigation. **Romain Basmaci:** Writing – review & editing, Methodology, Investigation. **Dorine Borensztajn:** Writing – review & editing, Methodology, Investigation. **Susana Castanhinha:** Writing – review & editing, Methodology, Investigation. **Antonio Chiaretti:** Writing – review & editing, Methodology, Investigation. **Robert Cohen:** Writing – review & editing, Validation, Methodology. **Sheena Durnin:** Writing – review & editing, Methodology, Investigation. **Patrick Fitzpatrick:** Writing – review & editing, Methodology, Investigation. **Susanne Greber-Platzer:** Writing – review & editing, Methodology, Investigation. **Romain Guedj:** Writing – review & editing, Methodology, Investigation. **Florian Hey:** Writing – review & editing, Methodology, Investigation. **Lina Jankauskaite:** Writing – review & editing, Methodology, Investigation. **Kristina Keitel:** Writing – review & editing, Methodology, Investigation. **Ines Mascarenhas:** Writing – review & editing, Methodology, Investigation. **Gregorio P. Milani:** Writing – review & editing, Methodology, Investigation. **Anna Maria Musolino:** Writing – review & editing, Methodology, Investigation. **Zanda Pučuka:** Writing – review & editing, Methodology, Investigation. **Malin Ryd Rinder:** Writing – review & editing, Methodology, Investigation. **Maria Chiara Supino:** Writing – review & editing, Methodology, Investigation. **Francesca Tirelli:** Writing – review & editing, Methodology, Investigation. **Ruud G. Nijman:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Naim Ouldali:** Writing – original draft, Visualization, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

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