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Early View

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Respective role of non-pharmaceutical interventions on bronchiolitis outbreaks, an interrupted time series analysis based on a multinational surveillance system

Lea Lenglart, Naim Ouldali, Kate Honeyford, Zsolt Bognar, Silvia Bressan, Danilo Buonsenso, Liviana Da Dalt, Tisham De, Ruth Farrugia, Ian K Maconochie, Henriette A Moll, Rianne Oostenbrink, Niccolo Parri, Damian Roland, Katy Rose, Esra Akyüz Özkan, François Angoulvant, Camille Aupiais, Clarissa Barber, Michael Barrett, Romain Basmaci, Susana Castanhinha, Antonio Chiaretti, Sheena Durnin, Patrick Fitzpatrick, Laszlo Fodor, Borja Gomez, Susanne Greber-Platzer, Romain Guedj, Florian Hey, Lina Jankauskaite, Daniela Kohlfuerst, Ines Mascarenhas, Anna Maria Musolino, Zanda Pučuka, Sofia Reis, Alexis Rybak, Petra Salamon, Matthias Schaffert, Keren Shahar-Nissan, Maria Chiara Supino, Ozlem Teksam, Caner Turan, Roberto Velasco, Ruud G Nijman, Luigi Titomanlio and the EPISODES Study Group

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Respective role of non-pharmaceutical interventions on bronchiolitis outbreaks, an interrupted time series analysis based on a multinational surveillance system

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Abbreviations:

RSV: respiratory syncytial virus
ALRI: acute lower respiratory infection
NPI: non-pharmaceutical intervention
PED: paediatric emergency department
ECDC: European Centre for Disease Prevention and Control
PICU: paediatric intensive care unit

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Abstract

Background: Bronchiolitis is a major source of morbimortality among young children worldwide. Non-pharmaceutical interventions (NPIs) implemented to reduce the spread of SARS-CoV-2 may have had an important impact on bronchiolitis outbreaks, as well as major societal consequences. Discriminating between their respective impacts would help define optimal public health strategies against bronchiolitis. We aimed to assess the respective impact of each NPI on bronchiolitis outbreaks in 14 European countries.

Methods: We conducted a quasi-experimental interrupted time-series analysis based on a multicentre international study. All children diagnosed with bronchiolitis presenting to the paediatric emergency department of one of the 27 centres from January 2018 to March 2021 were included. We assessed the association between each NPI and change in the bronchiolitis trend over time by seasonally adjusted multivariable quasi-Poisson regression modelling.

Results: In total, 42,916 children were included. We observed an overall cumulative 78% reduction (95%CI [-100;-54], p<0.0001) in bronchiolitis cases following NPI implementation. The decrease varied between countries from -97% (95%CI [-100;-47], p=0.0005) to -36% (95%CI [-79;+07], p=0.105). Full lockdown (IRR 0.21, 95%CI [0.14;0.30], p<0.001), secondary-school closure (IRR 0.33, 95%CI [0.20;0.52], p<0.0001), wearing a mask indoors (IRR 0.49, 95%CI [0.25;0.94], p=0.034), and teleworking (IRR 0.55, 95%CI [0.31;0.97], p=0.038) were independently associated with reducing bronchiolitis.

Conclusion: Several NPIs were associated with a reduction of bronchiolitis outbreaks, including full lockdown, school closure, teleworking and facial masking. Some of these public health interventions may be considered to further reduce the global burden of bronchiolitis.

Introduction

Bronchiolitis is the most common hospitalised acute lower respiratory tract infection (ALRI) in children in western countries[1]. In Europe, bronchiolitis is responsible for 80 paediatric intensive care unit admissions per 100.000 children each year[2]. Respiratory syncytial virus (RSV) is a leading causative agent of bronchiolitis, detected in 62 to 87% of hospitalised cases[3]. Worldwide, RSV infections in children aged < 5 years were responsible for 33.1 million cases of ALRI in 2015 and 3.2 million hospitalisations[4].

Transmission of RSV occurs through large droplets and contact with contaminated surfaces and all children have encountered the virus by the age of 3 years[5]. There are currently no easily available curative or preventive therapeutics for the general population. Indeed, passive immunization with palivizumab, a monoclonal antibody, the only preventive therapy currently available, is limited to high-risk children in their first year of life[6] in most high income countries. The absence of preventive therapeutics available to the general population highlights the importance of further pharmaceutical research on new therapeutics[7] and of the evaluation of non-pharmaceutical interventions to reduce the yearly burden of bronchiolitis.

Since the beginning of the SARS-CoV-2 pandemic, unprecedented non-pharmaceutical interventions (NPIs) have been implemented worldwide to reduce the spread of the virus. Multiple NPIs were implemented, and differed across European countries. They also varied in time as the different waves occurred: from wearing face masks only in enclosed spaces to complete lockdown, with the closure of non-essential businesses and schools. The first goal of NPIs was to prevent the transmission of SARS-Cov-2, but they had a drastic impact on many airborne transmitted viruses among the child[8,9] and adult populations[10], including RSV. Numerous countries have reported a substantial reduction of the seasonal bronchiolitis outbreak following NPIs[11–13]. However, the overall benefit of such heterogeneous interventions on bronchiolitis may vary by country, raising the question of the optimal NPI strategy to reduce the bronchiolitis burden.

Despite their major impact on most respiratory infections, NPIs may not be sustainable for the long term due to the considerable economic and psychosocial cost for the general population[14]. Cousien et al. highlighted a drastic increase (+116% to +299%) in suicide attempts among children in late 2020 and early 2021 relative to the previous 10 years[15]. Thus, discriminating the respective effect of each NPI component on bronchiolitis outbreaks could help in reducing its global burden, while limiting the negative consequences for the population.

We aimed to assess the respective impact of the various NPIs on bronchiolitis cases in children < 1 year of age in 14 European countries.

Methods

Study design and population

We conducted a quasi-experimental interrupted time-series analysis based on a multicentre international study. The participating centres were included as part of the EPISODES international surveillance study[16] through the Research in Paediatric Emergency Medicine (REPEM) network. Twenty-seven paediatric emergency departments (PEDs) (Appendix 1) in 14 European countries (Austria, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Portugal, Spain, the Netherlands, Turkey, and the United Kingdom) participated in the study. All children < 1 year of age diagnosed with bronchiolitis presenting to the PED of one of the participating centres from January 1, 2018, to March 31, 2021, were included. The NPIs implemented in each country over time were extracted from the European Centre for Disease Prevention and Control (ECDC) database[17], with quality checking by national delegates and members of the research consortium.

Data collection

A clinical report form was constructed to record the monthly anonymized and aggregated data for each participating centre (Appendix 2). The clinical report form collected data on the sex, age, vital signs, triage in the PED, diagnostic and virology testing performed in the PED (blood sample, chest X-ray), type of oxygen therapy in the PED or during hospitalisation, outcome (admission to ward, paediatric intensive care unit (PICU), or death) and duration of the hospital stay. The identification of bronchiolitis cases was based on the ICD-10 classification coding[18] system and the diagnosis provided in the electronic health record by the physician. The data, collected retrospectively for each participating centre, were extracted from electronic health records and not reviewed manually. Data were entered into REDCap electronic data capture tools[19] hosted at Imperial College, London, between July and September 30, 2021.

A survey was sent to the 27 participating centres to collect information and compare the guidelines used for establishing the clinical diagnosis of bronchiolitis and management strategies of children with bronchiolitis between centres and over time. (Appendix 3)

Data on NPIs implemented in European countries over time were collected using open-data on country response measures to COVID-19 from the ECDC, edited weekly since the beginning of the pandemic[17]. For the two non-European participating countries (Israel and Turkey), data were obtained from governmental data by the country investigator of the study.

Based on the ECDC reports[17], 11 NPIs were included in this study:

- Social distancing
- Face masks in enclosed public spaces or everywhere (treated as separate NPIs)
- Limiting the size of public gatherings inside and outside
- Teleworking
- Closure of non-essential businesses
- Closure of pre-schools, primary schools, and secondary schools (treated as separate NPIs)
- Closure of universities
- Complete lockdown

The definition and implementation period of each NPI can be found in Appendix 4 and 5

Outcome measure

The main outcome was the overall monthly number of bronchiolitis cases among children < 1 year of age visiting PEDs over time before and during the implementation of NPIs, assessed by interrupted time-series analysis models at a multinational level. Secondary outcomes included sub-group analysis (i) at a national level, (ii) by age group (< or ≥ 3 months of age), (iii) by viral type (RSV positive or negative bronchiolitis, when information was available),

(iv) by severity (cases discharged to home, admitted to a hospital ward, or admitted to the PICU) globally and for each country, and (v) by time period (first, second and third waves). Data on the monthly number of new SARS-CoV-2 infections in each country and on the predominant variant strain over time were gathered from "Our World in Data" from John Hopkins University database on COVID-19[20] and ECDC's data on SARS-CoV-2 variants[21]."

Statistical analysis

The main analysis focused on the independent association between the implementation of each NPI and changes in bronchiolitis trend over time, assessed by interrupted time-series analysis models at a multinational level.

We first built interrupted time-series analysis models, overall and for each country, to determine the impact of NPIs on bronchiolitis cases over time and among subgroups (Appendix 6). We defined a pre-NPI period (from January 1, 2018, to March 30, 2020) and an NPI period (from April 1, 2020 to March 30, 2021). Outcomes were analysed by quasi-Poisson regression, accounting for seasonality, secular trend before and after NPI, and within and between overdispersion of data[22–24]. Seasonality was taken into account by including harmonic terms (sines and cosines), with 12-month periods to adjust for seasonal patterns.[24] A dummy variable accounted for the pre-NPI secular trend.[22,23] The chosen time unit was one month. For NPIs starting or ending during a month, a minimal duration of 10 days during the month was required to consider the NPI to have been implemented. The validity of the quasi-Poisson regression models was assessed by visual inspection of correlograms and residuals analysis[24] (Appendix 7). These models allowed us to estimate the fitted value of the number of observed bronchiolitis cases compared to the expected value based on the model parameters for each time point in each country.[24] Then, we assessed the independent association between each component of the NPI and bronchiolitis evolution. A final multivariate quasi-Poisson model was built; this included the fitted value of the number of bronchiolitis cases in each country for each time point as the response variable, the expected number of bronchiolitis cases without intervention for the corresponding time points as the offset, and the different NPIs implemented during the respective time points in each country as the explanatory variables. We used a backward stepwise approach to select the NPIs to be included in the final multivariate quasi-Poisson model, with a cut-off of $p<0.20$.

Sensitivity analysis were performed. First, we took into account the weight of each country in the model, based on the number of bronchiolitis cases reported in each country during the study period (Appendix 8). Second, we explored the potential contribution of three additional NPIs: private gathering restriction, closure of international borders and SARS-CoV-2 cases tracking by mobile app (Appendix 9). Detailed information on these additional NPIs were gathered from the European Commission Joint Research Centre's data base on NPIs[25] and are reported in appendix 4 (definition of each NPI) and appendix 5 (period of implementation of each NPI). These additional NPIs were not included in the main analysis because they were not retrieved from ECDC report[17]. Third, we took into account potential correlation between the different NPIs. Indeed, given the expected temporal overlap between NPIs, we explored the correlation between explanatory variables using the Spearman coefficient (> 0.7 considered substantial) and the multicollinearity with the variance inflation factor (VIF) (> 5 considered substantial)[26] (Appendix 10). We conducted sensitivity analyses by combining the variables that were substantially correlated (Appendix 11), based on the spearman coefficient and variance inflation factor analysis. Fourth, to explore the role of potential country-level confounder, we built a mixed quasi-Poisson model including a random effect for gross domestic product, age structure (classified as follow: < 1 year, 1 to < 5 year, 5 to < 18 years, 18 years or older) and sex ratio for each included country, and a fixed effect for all NPIs included in the main analysis (Appendix 12). Fifth, we added a dummy variable for each month of the year, along with the harmonic terms to take into account the seasonal pattern

(Appendix 13). Sixth, we tested for the interaction between the different NPIs, and built an additional model that included all significant interaction terms between NPIs (Appendix 14).

Finally, to explore a potential interaction between SARS-CoV-2 and other respiratory viruses that causes bronchiolitis, we analysed the correlation between the monthly number of bronchiolitis cases and the monthly number of new SARS-CoV-2 infections in each country over time, using the non-parametric Spearman correlation coefficient (Appendix 15). All analyses performed to describe and analyse the potential relation between SARS-CoV-2 evolution and bronchiolitis are detailed in appendix 15 to 17.

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. All analyses were performed using R statistical software, version 4.1.1 (http://www.R-project.org).

Results

General characteristics of the population and NPIs

In total, 42,916 patients < 1 years of age diagnosed with bronchiolitis in 14 European countries were included between January 1, 2018, and March 31, 2021, (38,988 from January 2018 to March 2020 and 3,928 in 2020-2021). The number and characteristics of the patients included in each participating country are presented in Table 1. Patients < 3 months accounted for 34.0% of all cases. Patients younger than 14 days represented 1.3% of the bronchiolitis cases during the pre-NPI period and 2.4% during the NPI period. PICU admission rates were 2.1% pre-NPI and 1.4% during the NPI period. No deceased patient was reported during the study period. (Table 1). Details on clinical diagnosis and management of bronchiolitis between centres and over time can be found in Appendix 3.

NPIs implemented varied quantitatively and qualitatively between European countries during the study period. All countries were under lockdown at some point during the NPI period, but the number of lockdowns and their duration varied from a few weeks to several months. Social distancing and limiting the size of gatherings were applied in all countries for most of the time period. The Netherlands was the only country in which wearing a face mask indoors or outdoors was never mandatory during the study period. The duration of school closures (pre-school, primary, secondary, and university) also varied substantially between countries. Details on the duration of the NPIs implemented in each country are available in Appendix 5.

Bronchiolitis evolution during the NPI period

Overall, there was a substantial decrease in bronchiolitis cases presenting to PEDs following the implementation of all NPIs, reaching a cumulative 78% reduction (95%CI [-100; -54], p<0.0001) by the end of the study (Figure 1). Correlograms and residuals analyses indicated satisfactory quality of the final model (Appendix 7). Similar results were obtained according to age (< and ≥ 3 months), outcomes (discharged home, admitted to ward or to PICU), and viruses isolated (RSV-positive or negative cases). A similar evolution was observed in the number of cases presenting with bronchiolitis over time in each severity sub-group, in each country (Appendix 6), as well as similar bronchiolitis reduction during the different SARS-CoV-2 waves (Appendix 6 and 17).

The magnitude of the decrease varied substantially between countries (Figure 2), ranging from -97% (95%CI [-100; -47], p<0.001) in Latvia to -36% (95%CI [-79; +07], p=0.105) in the Netherlands (Table 2).

Respective impact of the various NPIs on bronchiolitis cases

In multivariate quasi-Poisson regression models using data from all countries, full lockdown (IRR 0.21, 95%CI [0.14; 0.30], p<0.001) and secondary-school closure (IRR 0.33, 95%CI [0.20; 0.52], p<0.0001) were the strongest independent protective measures against bronchiolitis. Wearing a mask in closed public spaces (IRR 0.49, 95%CI [0.25; 0.94], p=0.034) and teleworking (IRR 0.55, 95%CI [0.31; 0.97], p=0.038) were also found to be independently associated with a reduced bronchiolitis caseload. The results are presented in Table 3. The main model found a substantial correlation between: (i) facial masking indoors and outdoors and (ii) between pre-school, primary-school, and secondary-school closure (details in Appendix 10). Sensitivity analysis combining these variables showed similar results (Appendix 11). All other sensitivity analyses provided similar results (Appendix 8 to 15), including analysis adjusted for the weight of each country (Appendix 8), analysis exploring the potential contribution of three additional NPIs (Appendix 9) and analysis including a random effect for country-level covariates (Appendix 12). No substantial correlation between SARS-CoV-2 and bronchiolitis evolution was found (Appendix 15).

Discussion

This multinational quasi-experimental interrupted time-series analysis assessed the respective impact of different NPIs on bronchiolitis cases. Following the implementation of NPIs, we observed an overall 78% reduction in the number of cases of bronchiolitis. This reduction varied substantially across countries, mirroring different NPI programs from country to country. Full lockdown and secondary-school closure were associated with the largest decrease in bronchiolitis cases presenting to PEDs, while face masking indoors and teleworking were also associated with a substantial reduction.

To our knowledge, no other study explored the impact of the different NPIs on bronchiolitis outbreak. However, other studies[27] assessed the effectiveness of different NPIs on SARS-CoV-2 circulation and suggested that school closing, teleworking and closing of businesses may be the most effective NPIs, in line with our results. As RSV and SARS-CoV-2 share a similar airborne transmission, these results may support our findings.

Numerous studies[11,12,28,29] reported a massive overall reduction in the 2020-2021 bronchiolitis outbreak in Europe and elsewhere. Although, bronchiolitis affects children < 1 year of age, we found NPIs targeting adults (teleworking) and older children (facial masking) to be strongly associated with the reduction in bronchiolitis cases. These results suggest that adults and older children may play a more important role in RSV circulation than previously expected. These finding echoes those of recent publications[30,31]. Skurnik et al.[30] highlighted the low impact of primary-school reopening on airborne virus transmission during the second COVID-19 wave in France, with the quasi-absence of bronchiolitis during the winter period, despite school opening. A similar finding was observed in Quebec, were Kindergarten (receiving children under five years of age) remained opened during the whole 2020-21 winter period while NPIs were maintained for adults, and despite this, no bronchiolitis outbreak was observed during this period[32]. Another similar unexpected observation was reported in 1995 in France during a public transport strike[33]. While schools remained opened, a substantial reduction of the bronchiolitis winter outbreak was observed. Overall, these findings suggest that older children and adults may represent an important component of RSV circulation during the winter period. However, our findings should be interpreted in the context of other NPIs also implemented. If confirmed by further studies, these population may be considered as potential targets for further public-health measures to reduce its transmission.

Currently, we have no knowledge of the consequences of the large reduction of bronchiolitis in 2020-2021 on further outbreaks. Cohen et al.[31] speculated that the absence of a strong RSV outbreak may increase the proportion of RSV-susceptible children, thus creating an “immune debt” that may expose the population to further stronger epidemics. Similarly, based on simulation models, Baker et al. predicted that the disruption of the seasonal transmission pattern of RSV could lead to larger outbreaks in future winters[34]. In Australia and New Zealand, unprecedented outbreaks occurred in the summer period following the quasi-absence of the usual winter bronchiolitis outbreak[35,36]. In Europe, where usual RSV outbreak is reversed compared to the southern hemisphere, several countries have also observed an earlier and stronger bronchiolitis outbreak since October, 2021[37], raising concerns about the long-term benefit of the quasi-absence of winter bronchiolitis outbreaks in this population. In this context, less stringent public health interventions, such as teleworking or facial masking during specific periods may be interesting strategies, as we may speculate that they could have a protective impact on bronchiolitis without creating a major immune debt. To explore these potential consequences, continuous surveillance of bronchiolitis at a multinational level will be critical.

Furthermore, several studies reported delayed motor and cognitive development[38], increase in suicide attempts or ideation[15] as well as other acute psychiatric disorders[39] in children since the start of the SARS-CoV-2 pandemic. It is still unclear whether the SARS-CoV-2 pandemic or NPIs introduced to reduce SARS-CoV-2 circulation led to these negative consequences. In this context, targeting a short period of intense RSV circulation (e.g., November-December in western countries) to implement facial masking or partial teleworking may reduce the risk of potential adverse psychosocial consequences in children. A careful continuous surveillance of the positive and negative impacts of these NPIs on short- and long-term outcomes, in the different age groups is required.

This study has several limitations. First, among the multiple NPIs implemented since the beginning of the SARS-CoV-2 pandemic, only 11 were analysed in this study. We decided to restrict our analysis to mandatory NPIs to reduce the risk of heterogeneous adhesion of the populations. Although, sensitivity analysis exploring three additional NPIs (private gathering restrictions, international border closure and SARS-CoV-2 cases tracking by mobile app) found unchanged results, we cannot fully exclude that, other interventions may have played a role in the bronchiolitis dynamics. Moreover, some heterogeneity in definition or adhesion of the population to NPIs may exist across countries and over time[40,41]. Indeed, some NPIs may have been officially recommended in a country, but not effectively applied by the population. This misclassification bias, would have led to underestimating the impact of these NPIs. Finally, we observed an important overlap between different NPIs. This may induce bias in effect estimates of the NPIs such as university closure. To better discriminate the respective impact of each NPI, we conducted a multinational analysis and sensitivity analyses, that combined correlated variables and included interaction terms between covariates. These yielded similar results. Further studies are required to explore the independent impact of these interventions or different combinations of interventions.

Second, the identification of bronchiolitis cases was based on ICD-10 classification coding[18] and cases were not reviewed manually to ensure the accuracy of the diagnoses or consistency in coding. However, a survey was sent to the participating centres to recall information on bronchiolitis diagnosis management in their PEDs over the study period. We found no change in bronchiolitis diagnosis and management after the implementation of NPIs, in line with a previous study which used the same multinational network[42]. Moreover, our surveillance system and data extraction methodology remained unchanged throughout the study period. Furthermore, RSV testing is not systematically performed and, in this study, only 8/27 sites could retrieve data on the results of RSV testing. Thus, our main analysis was based on the clinical diagnosis of bronchiolitis, regardless of the respiratory viruses that may have been involved. However, our subgroup analysis restricted to RSV-related bronchiolitis cases showed similar findings. Importantly, most children with bronchiolitis do not have any diagnostics performed, with testing only performed for those children admitted to hospital or those with more serious cases, resulting in a substantial underestimation of the burden of RSV in children. Hence, our study of clinical bronchiolitis provides a much more real world-like view than those presenting data of children testing positive for RSV or similar viruses.

Third, given the non-randomized design, causal relationship between NPIs and bronchiolitis cannot be drawn. A more causal association would not be possible to prove without an impractical clinical trial. Especially, we cannot exclude that, other factors not related to NPIs may also be involved in the decrease of bronchiolitis. Emergency departments visits for non-severe bronchiolitis may have been influenced by a reduced willingness of families to bring a symptomatic young child to the ED unless severely ill. However, we did not observe an increase in the percentage of severe cases (2.1% during the pre-NPI period and 1.4% during the NPI period) and our subgroup analysis depending on bronchiolitis severity (discharged bronchiolitis, admitted bronchiolitis, or bronchiolitis transferred to PICU) found similar trends according to the bronchiolitis severity, in line with the literature[43]. The circulation of SARS-CoV-2 may also have influenced RSV dynamics. However, we did not find a correlation between the monthly number of SARS-CoV-2 cases and bronchiolitis cases evolution over time in the different countries since the start of the pandemic. Moreover, we found no substantial differences in bronchiolitis trend depending on the SARS-CoV-2 waves or variant during the study period, overall and in each country, and we found similar reduction in RSV and non-RSV cases. Finally, the clinical experience from winter 2021/2022 showed that massive co-circulation of delta and omicron (BA.1/2) did not prevent the re-emergence of RSV and human metapneumovirus as main causes of bronchiolitis.

In conclusion, NPIs implemented to fight the worldwide COVID-19 pandemic led to a drastic decrease of the bronchiolitis cases in 2020-2021. However, this reduction varied widely between countries due to the different components of NPI implemented. Among them, full lockdown, school closure, teleworking and facial masking were associated with reducing the number of bronchiolitis cases. Some of these public health interventions may be considered to further reduce the global burden of bronchiolitis. Further studies are required to explore their long-term impact on bronchiolitis and other health outcomes.

Table 1. General characteristics of the population, N = 42,916.

Variables are reported as numbers (%). PICU: paediatric intensive care Unit, NPI: non-pharmaceutical intervention

*Triage classification:
- Very urgent: level 1-2 or Red-Orange
- Urgent: level 3 or Yellow
- Non-urgent: Level 4-5 or Green-Blue

Characteristics		Pre-NPI period January 1, 2018 to March 31, 2020	NPI period April 1, 2020 to March 31, 2021	Total period
Number of bronchiolitis cases	Austria	1,450 (3.7)	51 (1.3)	1,501 (3.5)
	France	11,714 (30.0)	2,477 (63.0)	14,191 (33.1)
	Germany	180 (0.5)	2 (0.1)	182 (0.4)
	Hungary	230 (0.6)	16 (0.4)	246 (0.6)
	Ireland	6,490 (16.6)	428 (10.9)	6,918 (16.2)
	Israel	925 (2.4)	24 (0.6)	949 (2.2)
	Italy	3,370 (8.6)	78 (2.0)	3,448 (8.0)
	Latvia	394 (1.0)	3 (0.1)	397 (0.9)
	Lithuania	253 (0.6)	11 (0.3)	264 (0.6)
	Netherland	223 (0.6)	55 (1.4)	278 (0.6)
	Portugal	2,416 (6.2)	128 (3.2)	2,544 (5.9)
	Spain	3,025 (7.8)	139 (3.5)	3,164 (7.4)
	Turkey	489 (1.3)	18 (0.5)	507 (1.2)
	UK	7,829 (20.1)	498 (12.7)	8,327 (19.4)
	All countries	38,988	3,928	42,916
Age	< 14 days	304/23,121 (1.3)	29/1,206 (2.4)	333/24,327 (1.4)
	14 days to 3 months	7,611/23,121 (32.9)	346/1,206 (28.7)	7,957/24,327 (32.7)
	3 months to 1 year	15,206/23,121 (65.8)	831/1,206 (68.9)	16,037/24,327 (65.9)
Triage*	Very urgent	10,011/23,925 (41.9)	522/1,235 (42.3)	10,533/25,160 (41.9)
	Urgent	8,950/23,925 (37.4)	455/1,235 (36.8)	9,405/25,160 (37.4)
	Non-urgent	4,964/23,925 (20.7)	258/1,235 (20.9)	5,222/25,160 (20.7)
Outcome	Home	16,918/30,333 (558)	1,072/2,276 (47.1)	17,990/32,609 (55.2)
	Short stay unit	2,412/30,333 (8.0)	43/2,276 (1.9)	2,455/32,609 (7.5)
	Admission to ward	10,356/30,333 (34.1)	1,129/2,276 (49.6)	11,485/32,609 (35.2)
	PICU	644 /30,333 (2.1)	31/2,276 (1.4)	675/32,609 (2.1)
	Death	0/30,333 (0)	0/2,276 (0)	0/32,609 (0)
	Left without being seen	3/30,333 (0.0)	1/2,276 (0.0)	4/32,609 (0.0)

Table 2. Impact of NPIs on bronchiolitis cases for each country, N = 42,916

NPI: non-pharmaceutical intervention

*Cumulative change: impact of the intervention from the start (April 1st 2020) to the end (March 31st 2021) of the intervention period.

Country	Cumulative change* by the end of the study	95%CI	P value
Austria	-88%	[-100; -54]	< 0.0001
France	-57%	[-100; -11]	0.020
Germany	-98%	[-100; +05]	0.067
Hungary	-83%	[-100; -36]	0.0014
Ireland	-83%	[-100; -49]	< 0.0001
Israel	-90%	[-100; -54]	< 0.0001
Italy	-93%	[-100; -63]	< 0.0001
Latvia	-97%	[-100; -47]	0.0005
Lithuania	-89%	[-100; -28]	0.006
Portugal	-87%	[-100; -63]	< 0.0001
Spain	-90%	[-100; -55]	< 0.0001
Netherland	-36%	[-79; +07]	0.105
Turkey	-90%	[-100; -49]	0.0001
United Kingdom	-88%	[-100; -64]	< 0.0001
All countries	-78%	[-100; -54]	< 0.0001

Table 3. Analysis of the independent association of each component of NPIs with changes in bronchiolitis cases (N = 42,916)

NPI: non-pharmaceutical intervention, IRR: incidence rate ratio

Intervention	Univariate analysis			Multivariate analysis		
	IRR	95%CI	P value	IRR	95%CI	P value
Full lockdown	0.39	[0.22; 0.55]	< 0.0001	0.21	[0.14; 0.30]	< 0.0001
Preschool closure	0.49	[0.24; 0.88]	0.029			
Primary-school closure	0.50	[0.28; 0.84]	0.014			
Secondary-school closure	0.49	[0.27; 0.82]	0.010	0.33	[0.20; 0.52]	< 0.0001
University closure	1.89	[1.19; 3.10]	0.010	4.72	[2.68; 8.48]	< 0.0001
Social distancing	0.45	[0.30; 0.67]	0.0002			
Facial mask inside	0.61	[0.39; 0.92]	0.022	0.49	[0.25; 0.94]	0.034
Facial mask outside	1.67	[1.12; 2.54]	0.015	0.60	[0.33; 1.11]	0.104
Limiting size gathering	2.90	[1.51; 6.41]	0.004			
Teleworking	1.55	[0.98; 2.55]	0.075	0.55	[0.31; 0.97]	0.038
Business closure	1.70	[1.12; 2.62]	0.015	1.61	[1.08; 2.37]	0.019

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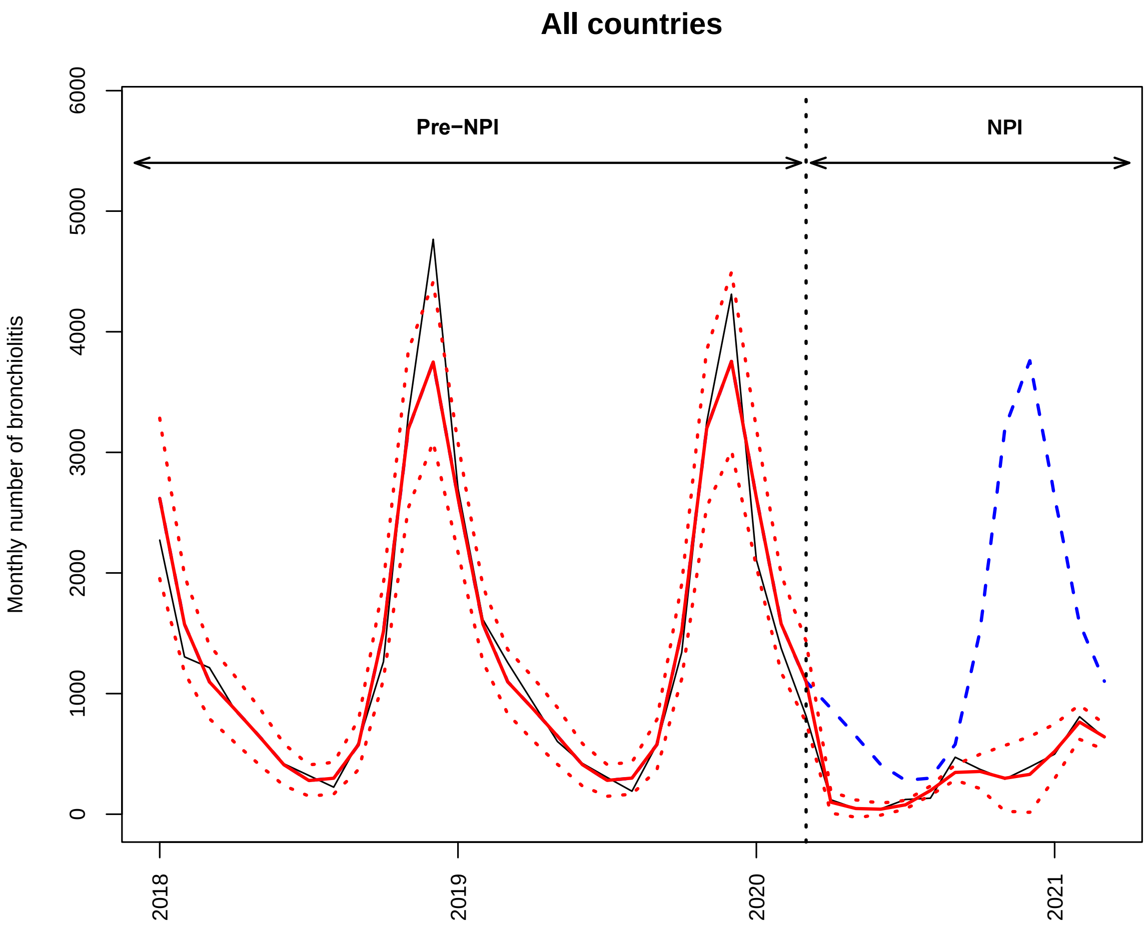
Figure 1. Overall impact of non-pharmaceutical interventions on bronchiolitis cases from January 1, 2018, to March 31, 2021 (N = 42,916)

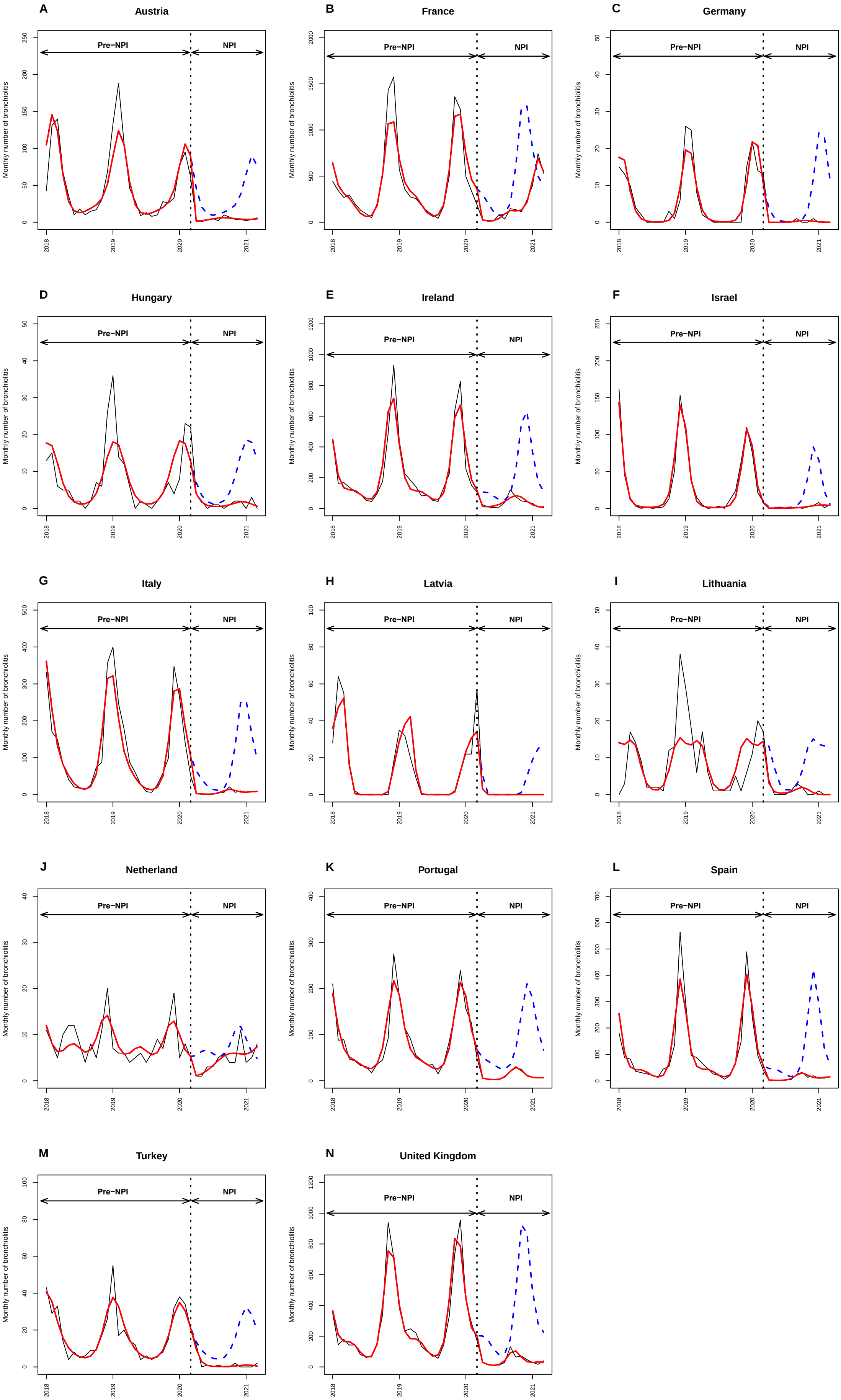


The black line shows the observed data. The solid red line shows the model estimates based on observed data (quasi-Poisson regression modelling). The dashed red lines show the 95%CI of the model estimates. The dashed blue line shows the expected values without NPIs in the post-intervention period (quasi-Poisson regression modelling). The implementation of NPIs is indicated by the vertical dashed dark line.

NPI: non-pharmaceutical intervention

Figure 2. Impact of non-pharmaceutical interventions on bronchiolitis cases by country from January 1, 2018 to March 31, 2021 (N = 42,916)

A: Austria, N = 1,501; B: France, N = 14,191; C: Germany, N = 182, D: Hungary, N = 246; E: Ireland, N = 6,918; F: Israel, N = 949; G: Italy, N = 3,448; H: Latvia, N = 397; I: Lithuania, N = 264; J: Netherlands, N = 278; K: Portugal, N = 2,544; L: Spain, N = 3,164; M: Turkey, N = 507; N: United Kingdom, N = 8,327


A
Austria
B
France
C
Germany
D
Hungary
E
Ireland
F
Israel
G
Italy
H
Latvia
I
Lithuania
J
Netherland
K
Portugal
L
Spain
M
Turkey
N
United Kingdom
Pre−NPI
NPI
Monthly number of bronchiolitis
2018
2019
2020
2021

The black line shows the observed data. The bold red line shows the model estimates based on observed data (quasi-Poisson regression modelling). The dashed blue line shows the expected values without NPIs in the post-intervention period (quasi-Poisson regression modelling). The implementation of NPIs is indicated by the vertical dashed dark line.

NPI: non-pharmaceutical intervention

Declaration of interests: Naim Ouldali reports travel grants from Pfizer, GSK, and Sanofi. No other authors have conflicts of interest to disclose.

Appendix – Table of contents

Appendix 1. List and map of participating sites (N = 27)

AUS001	Clinical Division of Paediatric Pulmonology, Allergology and Endocrinology, Department of Paediatrics and Adolescent Medicine, Comprehensive Centre for Paediatrics, Medical University of Vienna, Vienna, Austria
AUS003	Department of Paediatric and Adolescent Surgery, Paracelsus Medical University, Salzburg, Austria
AUS004	Medical University of Graz, Department of General Paediatrics, Graz, Austria
FR001	Assistance Publique-Hôpitaux de Paris, Paediatric Emergency Department, Hopital Universitaire Robert-Debre, Paris, France
FR002	Assistance Publique-Hôpitaux de Paris, Paediatric Emergency Department, Louis Mourier Hospital, Colombes, France
FR003	Assistance Publique-Hôpitaux de Paris, Paediatric Emergency Department, Armand Trousseau Hospital, Paris, France
FR004	Assistance Publique-Hôpitaux de Paris, Paediatric Emergency Department, Jean Verdier Hospital, Bondy, France
GER001	Paediatric Intensive Care Unit and Emergency Department, Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
HUN001	Paediatric Emergency Department, Heim Pal National Paediatric Institute, Budapest, Hungary
IRE001	Paediatric Emergency Department, Children's Health Ireland at Crumlin, Dublin, Ireland
IRE002	Paediatric Emergency Department, Children's Health Ireland at Temple Street, Dublin, Ireland
IRE003	Paediatric Emergency Department, Children's Health Ireland at Tallaght, Dublin, Ireland
ISR001	Paediatric Emergency Department, Schneider Children’s Medical Center of Israel and Sackler Faculty of Medicine
IT001	Division of Paediatric Emergency Medicine, Department of Women’s and Children’s Health – University Hospital of Padova, Italy
IT002	Department of Woman’s and Children’s Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
IT005	Emergency Department, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
LAT001	Paediatric Emergency Department, Children's Clinical University Hospital, Riga Stradins University, Riga, Latvia
LIT001	Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Lithuania
NL001	Department General Paediatrics, ErasmusMC – Sophia, Rotterdam, The Netherlands
POR004	Departamento da Criança e do Jovem- Urgencia Pediatrica, Hospital Prof. Doutor Fernando da Fonseca, Amadora, Portugal
SP001	Paediatric Emergency Department, Cruces University Hospital, Barakaldo, Spain
SP002	Paediatric Emergency Unit, Hospital Universitario Río Hortega, Valladolid, Spain
TUR001	Paediatric Emergency Department, Ondokuz Mayıs University, Samsun, Turkey

TUR002	Division of Paediatric Emergency Medicine, Department of Paediatrics, Hacettepe University School of Medicine, Ankara, Turkey
UK001	Paediatric Emergency Medicine Leicester Academic (PEMLA) Group, Leicester Hospitals, Leicester, UK
UK002	Paediatric Emergency Department, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
UK005	Department of Paediatric Emergency Medicine, Division of Medicine, St. Mary's Hospital; Imperial College NHS Healthcare Trust, London, UK

Appendix 2. Clinical Report Form to record the monthly anonymized and aggregated data of each participating centre

This form describes the data of children presenting to the emergency department of

Hospital code:
*based on data availability for the centre: certain categories will NOT appear if data are not available at all in a setting.

For the month of:
Period of data describes a period starting on every first day of the month until the last day of the month.

Beginning [enter date, DD/MM/YYYY]
Ending [enter date, DD/MM/YYYY]

Study ID	[automatically generated]	
Local Study ID	[optional: local team to link the study ID with the month or week of entry]	

Acute Bronchiolitis – ICD codes

J21.0, J21.1, J21.8 and J21.9

Skirrow H, Wincott T, Cecil E, Bottle A, Costelloe C, Saxena S. Preschool respiratory hospital admissions following infant bronchiolitis: a birth cohort study. Arch Dis Child. 2019 Jul;104(7):658-663. doi: 10.1136/archdischild-2018-316317. Epub 2019 Mar 6. PMID: 30842095.

Total number of visits (< 1 year-old)[1]	[1]number of visits for bronchiolitis seen by physician/ANP or eq. in the PED Include only unplanned urgent and emergency care; no planned/scheduled medical care.	
Gender	Male	(n)
	Female	(n)
	Number of not available data.	*(n)*
Age	0 - < 14 days	(n)

	14 days - < 3 months	(n)
	3 months - < 1 year	(n)
	Number of not available data.	*(n)*
Triage urgency	Level 1-2 Emergency – very urgent: RED - ORANGE	(n)
	Level 3 Urgent: YELLOW	(n)
	Level 4-5 Non urgent – standard: GREEN - BLUE	(n)
	Number of not available data.	(n)
Vital signs	Tachycardia APLS definition	(n)
	Tachypnoea APLS definition	(n)
	Reduced level of consciousness GCS < 14	(n)
	O_2 saturation < 94%	(n)
	Temperature > 37.9	(n)
	Number of not available data.	(n)
Diagnostics performed *(not mandatory if manually retrieved)*	Blood tests If child had ANY performed, including blood gases	(n)
	Imaging: Chest XR	(n)
	RSV test performed (bedside or virology panel)	(n)
	Positive RSV test (bedside or virology panel)	(n)
	Number of not available data.	*(n)*
Treatment in the PED *(not mandatory if manually retrieved)*	Non-invasive ventilation (high flow, CPAP, BiPap, or CNEP)	(n)
	Oxygen therapy (nasal cannula, O_2 mask, non-rebreathing mask)	(n)
	Number of not available data.	*(n)*
Treatment during hospitalisation *(not mandatory if manually retrieved)*	Non-invasive ventilation (high flow, CPAP, BiPap, or CNEP)	(n)
	Oxygen therapy (nasal cannula, O_2 mask, non-rebreathing mask)	(n)

	Number of not available data.	*(n)*
Outcome	Admission to short stay unit	(n)
	Admission to hospital ward	(n)
	Admission to PICU	(n)
	Duration of hospital stay - < 24 h - 24-48 h - 48-72 h - > 72 h	(n)
	Death (in PED)	(n)
	Number of not available data.	*(n)*

Appendix 3. Local site survey on bronchiolitis management

1) Do you have local guidance for bronchiolitis?
   - Yes, American guidelines (AAP) 2/27 participating centers
   - Yes, national guidelines 10/27 participating centers
   - Yes, local guidelines 15/27 participating centers

2) What are the admission criteria for bronchiolitis under 1 year old in your hospital?
   - Need for IV fluids, 25/27 participating centers
   - need for NG feeds, 24/27 participating centers
   - cyanose or need for O2 to achieve O2 saturation > 92%, 27/27 participating centers
   - apneas, 26/27 participating centers
   - any infant < 3 months, 4/27 participating centers
   - any infant < 6 weeks, 10/27 participating centers
   - GA<32 weeks and now corrected GA <6 months, 8/27 participating centers
   - Comorbidities, 15/27 participating centers
   - Other [specify] Socio-economic reasons 3/27 participating centers
Tachypnea 1/27 participating centers

3) Did your admission criteria change after the beginning of the COVID-19 pandemic?
   - No 27/27 participating centers
   - Yes, during the first wave 0/27 participating centers
   - Yes, during the second wave 0/27 participating centers

Appendix 4. Definition of the studied NPIs implemented in the 14 participating countries.

Non-Pharmaceutical Intervention	Definition
Social distancing*	Recommendation to avoid physical contact and keep a physical distance of 1-2 meter on private gatherings
Face mask indoors only*	Protective mask use in closed public spaces/transport enforced by law
Face mask outdoors*	Protective mask use in all public spaces enforced by law
Limiting size of gatherings*	Interventions in place to limit outdoor and indoor mass/public gatherings
Teleworking*	Teleworking recommendations
Closure of non-essential businesses*	Closure of non-essential shops
Pre-school closure*	Closure of day-car or nursery – outside of usual vacation period
Primary-school closure*	Closure of primary schools – outside of usual vacation period
Secondary-school closure*	Closure of secondary school – outside of usual vacation period
University closure*	Closure of universities – outside of usual vacation period
Complete lockdown*	Stay-at-home orders for the general population
Private gathering restrictions**	Any measure or legislation which prohibits the gathering in a private or public space, between 2 and 30 people. Any measure referring to households, private dwellings, or private events (i.e. wedding ceremonies, funerals, etc.) with or without specifying a maximum number of people, also fall under this category.
International border closure**	Total international border closure
SARS-CoV-2 cases tracking by mobile app**	The use mobile apps to support contact tracing around COVID-19 confirmed cases.

*NPIs included in the main analysis and selected from the ECDC's "Data on country's response to COVID-19".
**3 additional NPIs included in sensitivity analysis and selected from the European Commission Joint Research Centre's data on "EU Measures against SARS-CoV-2".

Appendix 5. NPIs implemented in each participating country during the study period, N = 14 countries.

MAIN ANALYSIS NPI – AUSTRIA	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	0	0	0	0	0	0	1	0	0	0	0
Face mask indoors only	1	1	1	1	1	1	0	0	0	0	0	0
Face mask outdoors	0	0	0	0	0	0	1	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	0	0	1	1	1	1	1	1
Teleworking	1	1	1	1	1	1	1	1	1	1	1	1
Closure of non-essential businesses	1	0	0	0	0	0	0	1	1	1	0	0
Pre-school closure	1	0	0	0	0	0	0	1	1	0	0	0
Primary-school closure	1	0	0	0	0	0	0	1	1	1	0	0
Secondary-school closure	1	0	0	0	0	0	0	1	1	1	0	0
University closure	1	1	1	0	0	1	0	1	1	1	1	1
Full lockdown	1	0	0	0	0	0	0	1	1	1	0	0

SENSITIVITY ANALYSIS NPI – AUSTRIA	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	1	0	0	0	0	0	0	1	0	0	0	0
International border closure	1	1	1	1	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	1	1	1	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – FRANCE	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	0	0	0	1	0	0	0	0	0
Face mask indoors only	0	1	1	1	1	1	1	0	0	0	0	0
Face mask outdoors	0	0	0	0	0	0	0	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	1	1	1	1	1	1	1	1
Teleworking	1	1	0	0	0	0	0	1	1	1	1	1
Closure of non-essential businesses	1	1	0	0	0	0	0	1	1	1	1	1
Pre-school closure	1	1	0	0	0	0	0	0	0	0	0	0
Primary-school closure	1	1	0	0	0	0	0	0	0	0	0	0
Secondary-school closure	1	1	0	0	0	0	0	0	0	0	0	0
University closure	1	1	1	0	0	0	0	1	1	1	1	1
Full lockdown	1	1	0	0	0	0	0	1	1	0	0	0

SENSITIVITY ANALYSIS NPI – FRANCE	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	1	1	1	0	0	0	0	1	1	1	1	1
International border closure	1	1	1	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	0	0	0	0	0	1	1	1	1	1

MAIN ANALYSIS NPI – GERMANY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	0	0	0	0	0	0	0	1	1	1	1	1
Face mask indoors only	0	1	1	1	1	1	1	1	1	1	1	1
Face mask outdoors	0	0	0	0	0	0	0	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	1	1	1	1	1	1	1	1
Teleworking	0	0	0	0	0	0	0	0	1	1	1	1
Closure of non-essential businesses	1	0	0	0	0	0	0	0	1	1	1	1
Pre-school closure	1	1	1	0	0	0	0	0	1	1	1	1
Primary-school closure	1	1	1	0	0	0	0	0	1	1	1	1
Secondary-school closure	1	1	1	0	0	0	0	0	1	1	1	1
University closure	1	1	1	0	0	0	0	0	1	1	1	1
Full lockdown	1	1	1	0	0	0	0	0	1	1	1	1

SENSITIVITY ANALYSIS NPI – GERMANY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	0	0	0	0	0	0	1	1	1	1	1
International border closure	1	1	1	0	0	0	0	0	0	1	1	0
SARS-CoV-2 cases tracking by mobile app	0	0	1	1	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – HUNGARY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	0	0	0	0	1	1	1	1	1
Face mask indoors only	1	1	1	1	1	1	1	1	0	0	0	0
Face mask outdoors	0	0	0	0	0	0	0	1	1	1	1	1
Limiting size of gatherings	1	1	1	0	0	0	0	1	1	1	1	1
Teleworking	1	1	1	1	1	1	1	1	1	1	1	1
Closure of non-essential businesses	1	1	0	0	0	0	0	0	0	0	0	1
Pre-school closure	1	1	0	0	0	0	0	0	0	0	0	1
Primary-school closure	1	1	1	0	0	0	0	0	0	0	0	1
Secondary-school closure	1	1	1	0	0	0	1	1	1	1	1	1
University closure	1	1	1	0	0	0	0	1	1	1	1	1
Full lockdown	1	1	0	0	0	0	0	0	0	0	0	0

SENSITIVITY ANALYSIS NPI – HUNGARY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	0	0	0	0	0	0	1	1	1	1	1
International border closure	1	1	1	1	0	1	1	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	1	1	1	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – IRELAND	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	0	0	0	1	1	1	1	1	1
Face mask indoors only	0	0	0	1	1	1	1	1	1	1	1	1
Face mask outdoors	0	0	0	0	0	0	0	0	0	0	0	0
Limiting size of gatherings	1	1	1	1	1	1	1	1	0	1	1	1
Teleworking	1	1	1	1	1	1	1	1	1	1	1	1
Closure of non-essential businesses	1	1	1	0	0	0	1	1	0	1	1	1
Pre-school closure	1	1	1	0	0	0	0	0	0	0	0	0
Primary-school closure	1	1	1	0	0	0	0	0	0	1	1	0
Secondary-school closure	1	1	1	0	0	0	0	0	0	1	1	0
University closure	1	1	1	0	0	1	1	1	1	1	1	1
Full lockdown	1	1	0	0	0	0	1	1	0	1	1	1

SENSITIVITY ANALYSIS NPI – IRELAND	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	1	1	1	0	0	0	1	1	0	1	1	1
International border closure	1	1	1	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	0	1	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – ISRAEL	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	1	1	1	1	1	1	1	1	1
Face mask indoors only	1	1	1	1	1	1	1	1	1	1	1	1
Face mask outdoors	1	1	1	1	1	1	1	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	0	0	0	0	0	1	1	1
Teleworking	1	1	0	0	1	1	1	0	0	1	1	0
Closure of non-essential businesses	1	1	0	0	0	1	1	0	0	1	1	0
Pre-school closure	1	0	0	0	0	1	1	0	0	1	1	0
Primary-school closure	1	0	0	0	0	1	1	0	0	1	1	0
Secondary-school closure	1	0	0	0	0	1	1	0	0	1	1	0
University closure	1	0	0	0	0	1	1	0	0	1	1	0
Full lockdown	1	0	0	0	0	0	1	0	0	1	1	0

SENSITIVITY ANALYSIS NPI – ISRAEL	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
International border closure	1	1	0	0	0	0	0	0	1	1	1	0
SARS-CoV-2 cases tracking by mobile app	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

MAIN ANALYSIS NPI – ITALY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	0	0	0	1	1	1	1	1	1
Face mask indoors only	1	0	0	1	1	1	1	0	0	0	0	0
Face mask outdoors	0	1	1	0	0	0	1	1	1	1	1	1
Limiting size of gatherings	1	1	1	0	0	0	1	1	1	1	1	1
Teleworking	1	1	1	1	1	1	1	1	1	1	1	1
Closure of non-essential businesses	1	1	0	0	0	0	0	0	0	1	0	0
Pre-school closure	1	1	1	0	0	1	1	1	1	1	1	1
Primary-school closure	1	1	1	0	0	1	1	1	1	1	1	1
Secondary-school closure	1	1	1	0	0	1	1	1	1	1	1	1
University closure	1	1	1	0	0	1	1	1	1	1	1	1
Full lockdown	1	0	0	0	0	0	0	0	0	0	0	0

SENSITIVITY ANALYSIS NPI – ITALY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	0	0	0	0	0	0	0	0	0	1	1
International border closure	1	1	1	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	1	1	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – LATVIA	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	0	0	0	0	0	0	1	1	1	1	1	1
Face mask indoors only	0	1	1	0	0	0	1	1	1	1	1	1
Face mask outdoors	1	1	1	0	0	0	0	0	0	0	0	0
Limiting size of gatherings	1	1	1	1	1	1	1	1	1	1	1	1
Teleworking	1	1	1	1	1	1	1	1	1	1	1	1
Closure of non-essential businesses	0	0	0	0	0	0	0	1	1	1	1	1
Pre-school closure	1	1	1	0	0	0	0	0	0	0	0	1
Primary-school closure	1	1	1	0	0	0	0	1	1	1	1	1
Secondary-school closure	1	0	1	0	0	0	0	1	1	1	1	1
University closure	1	1	1	0	0	0	0	1	1	1	1	1
Full lockdown	0	0	0	0	0	0	0	0	0	1	0	0

SENSITIVITY ANALYSIS NPI – LATVIA	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	0	0	0	0	0	1	1	1	1	1	1
International border closure	1	1	1	0	0	0	0	0	0	0	1	0
SARS-CoV-2 cases tracking by mobile app	0	0	1	1	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – LITHUANIA	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	1	1	1	1	1	1	0	0	0
Face mask indoors only	0	0	0	0	0	0	0	0	0	0	0	0
Face mask outdoors	1	1	1	0	1	1	1	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	1	0	0	1	1	1	1	1
Teleworking	1	1	1	0	0	0	0	0	0	0	0	0
Closure of non-essential businesses	1	1	1	1	1	1	1	1	1	1	1	1
Pre-school closure	1	1	0	0	0	0	0	0	0	0	0	0
Primary-school closure	1	1	1	0	0	0	0	0	1	1	1	1
Secondary-school closure	1	1	1	0	0	1	1	1	1	1	1	1
University closure	1	1	1	0	0	1	1	1	1	1	1	1
Full lockdown	0	0	0	0	0	0	0	0	1	1	1	1

SENSITIVITY ANALYSIS NPI – LITHUANIA	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	0	0	0	0	0	0	1	1	0	0	0
International border closure	1	1	0	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	0	0	0	0	0	0	0	0	0	0

MAIN ANALYSIS NPI – PORTUGAL	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	0	1	1	1	1	1	1	1	1	1	1	1
Face mask indoors	0	1	1	1	1	1	1	0	0	0	0	0
Face mask outdoors	0	0	0	0	0	0	0	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	1	1	1	1	1	1	1	1
Teleworking	1	1	1	1	1	1	1	0	0	1	1	1
Closure of non-essential businesses	1	1	1	1	1	1	1	1	0	1	1	1
Pre-school closure	1	1	0	0	0	0	0	0	0	0	1	1
Primary-school closure	1	1	1	0	0	1	0	0	0	0	1	1
Secondary-school closure	1	1	1	0	0	1	0	0	0	0	1	1
University closure	1	1	1	0	0	0	0	0	0	0	1	1
Full lockdown	0	0	0	0	0	0	0	0	0	1	1	1

SENSITIVITY ANALYSIS NPI – PORTUGAL	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	1	1	1	1	1	1	1	1	1	1	1
International border closure	1	1	1	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	0	0	0	0	0	0	0	0	0	0

MAIN ANALYSIS NPI – SPAIN	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	1	1	1	1	1	1	1	1	1
Face mask indoors only	0	1	0	0	0	0	0	0	0	0	0	0
Face mask outdoors	0	0	1	1	1	1	1	1	1	1	1	1
Limiting size of gatherings	1	1	1	0	0	0	0	0	0	1	1	1
Teleworking	1	0	0	0	0	0	0	0	0	0	0	0
Closure of non-essential businesses	0	0	0	0	0	0	0	0	0	0	0	0
Pre-school closure	1	1	1	1	1	0	0	0	0	0	0	0
Primary-school closure	1	1	1	0	0	0	0	0	0	0	0	0
Secondary-school closure	1	1	1	0	0	0	0	0	0	0	0	0
University closure	1	1	1	0	0	0	0	0	0	0	0	0
Full lockdown	1	0	0	0	0	0	0	0	0	0	0	0

SENSITIVITY ANALYSIS NPI – SPAIN	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	0	0	0	0	0	0	0	0	0	0	0	0
International border closure	1	1	1	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	0	0	1	1	1	1	1	1	1	1

MAIN ANALYSIS NPI – THE NETHERLANDS	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	0	1	1	1	1	1	1	1	1
Face mask indoors only	0	0	0	0	0	0	0	0	0	0	0	0
Face mask outdoors	0	0	0	0	0	0	0	0	0	0	0	0
Limiting size of gatherings	1	1	1	1	1	1	1	1	1	1	1	1
Teleworking	1	1	1	1	1	1	1	1	1	1	1	1
Closure of non-essential businesses	0	0	0	0	0	0	0	0	1	1	1	1
Pre-school closure	1	1	0	0	0	0	0	0	1	1	0	0
Primary-school closure	1	1	0	0	0	0	0	0	1	1	0	0
Secondary-school closure	1	1	1	0	0	0	0	0	1	1	1	0
University closure	1	1	1	0	0	0	0	0	1	1	1	1
Full lockdown	0	0	0	0	0	0	0	0	1	1	0	0

SENSITIVITY ANALYSIS NPI – THE NETHERLANDS	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions 1 1 1 0 1	1	1	1 1	1	1	1						
International border closure	1	1	1	0	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	0	0	0	0	0	0	1	1	1	1	1	1

MAIN ANALYSIS NPI – TURKEY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	0	0	0	0	0	0	0	0	0	1	1	1
Face mask indoors only	0	0	0	0	0	1	1	1	1	1	1	1
Face mask outdoors	0	0	1	1	1	1	1	1	1	1	1	1
Limiting size of gatherings	1	1	1	1	1	1	1	1	1	1	1	1
Teleworking	1	1	0	0	0	0	0	0	0	0	0	0
Closure of non-essential businesses	1	1	0	0	0	0	0	0	0	0	0	0
Pre-school closure	1	1	1	1	1	1	0	0	0	0	0	0
Primary-school closure	1	1	1	0	0	1	0	0	0	0	0	0
Secondary-school closure	1	1	1	0	0	1	1	1	1	1	1	0
University closure	1	1	1	0	0	1	1	1	1	1	1	0
Full lockdown	1	0	0	0	0	0	0	0	0	0	0	0

SENSITIVITY ANALYSIS NPI – TURKEY	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
International border closure	1	1	1	1	0	0	0	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

MAIN ANALYSIS NPI – UNITED KINGDOM	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Social distancing	1	1	1	0	0	1	1	1	0	0	0	0
Face mask indoors only	0	0	0	0	1	1	1	1	1	1	1	1
Face mask outdoors	0	0	0	0	0	0	0	0	0	0	0	0
Limiting size of gatherings	0	1	1	1	1	1	1	1	0	0	0	0
Teleworking	1	0	0	0	0	0	0	0	0	0	0	0
Closure of non-essential businesses	1	1	1	0	0	0	0	1	0	0	0	0
Pre-school closure	1	1	1	1	1	0	0	0	0	0	0	0
Primary-school closure	1	1	1	0	0	0	0	0	0	0	0	0
Secondary-school closure	1	1	1	0	0	0	0	0	0	0	0	0
University closure	1	1	1	0	0	0	0	0	0	0	0	0
Full lockdown	1	1	1	0	0	0	0	1	0	0	0	0

SENSITIVITY ANALYSIS NPI – UNITED KINGDOM	04/20	05/20	06/20	07/20	08/20	09/20	10/20	11/20	12/20	01/21	02/21	03/21
Private gathering restrictions	1	1	1	0	0	1	1	1	0	0	0	0
International border closure	1	1	1	1	1	1	1	0	0	0	0	0
SARS-CoV-2 cases tracking by mobile app	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Appendix 6. Impact of NPIs on bronchiolitis cases among subgroups.

Subgroup	Cumulative change by the end of the study	95% CI	P value
Age			
< 3 months, N=8,290	-89%	[-100; -63]	<0.0001
≥ 3 months, N=16,037	-86%	[-100; -62]	<0.0001
RSV positive bronchiolitis, N=774	-96%	[-100; -42]	0.001
RSV negative bronchiolitis, N=677	-79%	[-100; -27]	0.006
Outcome			
ALL COUNTRIES - Discharged home, N=17,990	-86%	[-100; -60]	<0.0001
First & second wave of SARS-CoV-2	-83%	[-100; -58]	
Third (Alpha) wave of SARS-CoV-2	-92%	[-100; -64]	
ALL COUNTRIES - Admission to ward, N=11,453	-73%	[-100; -48]	<0.0001
First & second wave of SARS-CoV-2	-82%	[-100; -54]	
Third (Alpha) wave of SARS-CoV-2	-58%	[-77; -38]	
ALL COUNTRIES - Admission to PICU, N=675	-87%	[-100; -48]	0.0001
First & second wave of SARS-CoV-2	-83%	[-100; -46]	
Third (Alpha) wave of SARS-CoV-2	-93%	[-100; -51]	
AUSTRIA - Discharged home, N= 397	-93%	[-100; -57]	<0.0001
First & second wave of SARS-CoV-2	-89%	[-100; -54]	
Third (Alpha) wave of SARS-CoV-2	-98%	[-100; -60]	
AUSTRIA - Admission to ward, N=760	-85%	[-100; -45]	0.0002
First & second wave of SARS-CoV-2	-73%	[-100; -39]	
Third (Alpha) wave of SARS-CoV-2	-93%	[-100; -49]	
AUSTRIA - Admission to PICU, N=18	-70%	[-100; +75]	0.343
First & second wave of SARS-CoV-2	-17%	[-100; +128]	
Third (Alpha) wave of SARS-CoV-2	-99%	[-100; +62]	
IRELAND - Discharged home, N=4,657	-83%	[-100; -50]	<0.0001
First & second wave of SARS-CoV-2	-80%	[-100; -48]	
Third (Alpha) wave of SARS-CoV-2	-91%	[-100; -54]	
IRELAND - Admission to ward, N=1,409	-84%	[-100; -41]	0.0004

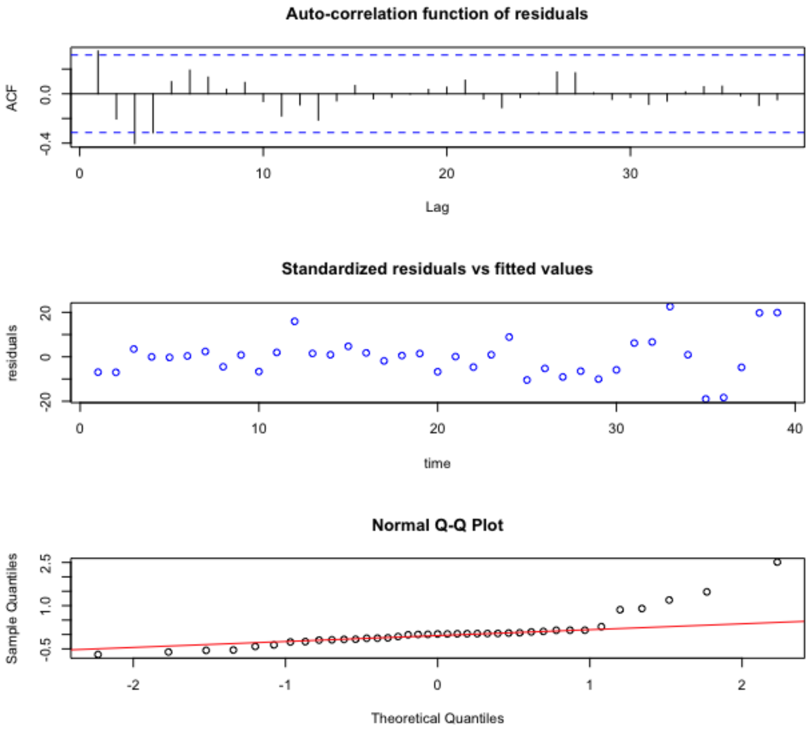
First & second wave of SARS-CoV-2	-80%	[-100; -40]	
Third (Alpha) wave of SARS-CoV-2	-94%	[-100; -46]	
IRELAND - Admission to PICU, N=57	-92%	[-100; -36]	0.002
First & second wave of SARS-CoV-2	-93%	[-100; -36]	
Third (Alpha) wave of SARS-CoV-2	-91%	[-100; -35]	
ISRAEL - Discharged home, N=417	-86%	[-100; -43]	0.0003
First & second wave of SARS-CoV-2	-90%	[-100; -45]	
Third (Alpha) wave of SARS-CoV-2	-80%	[-100; -40]	
ISRAEL - Admission to ward, N=300	-94%	[-100; -62]	<0.0001
First & second wave of SARS-CoV-2	-96%	[-100; -64]	
Third (Alpha) wave of SARS-CoV-2	-92%	[-100; -61]	
ISRAEL - Admission to PICU, N=13	-90%	[-100; +14]	0.094
First & second wave of SARS-CoV-2	-100%	[-100; +16]	
Third (Alpha) wave of SARS-CoV-2	-81%	[-100; +13]	
ITALY - Discharged home, N=1,506	-93%	[-100; -62]	<0.0001
First & second wave of SARS-CoV-2	-91%	[-100; -60]	
Third (Alpha) wave of SARS-CoV-2	-96%	[-100; -64]	
ITALY - Admission to ward, N=1,031	-92%	[-100; -57]	<0.0001
First & second wave of SARS-CoV-2	-91%	[-100; -56]	
Third (Alpha) wave of SARS-CoV-2	-94%	[-100; -58]	
ITALY - Admission to PICU, N=195	-93%	[-100; -3]	0.047
First & second wave of SARS-CoV-2	-85%	[-100; -3]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; -4]	
LITHUANIA - Discharged home, N=96	-91%	[-100; -10]	0.031
First & second wave of SARS-CoV-2	-89%	[-100; -10]	
Third (Alpha) wave of SARS-CoV-2	-94%	[-100; -11]	
LITHUANIA - Admission to ward, N=138	-88%	[-100; -22]	0.011
First & second wave of SARS-CoV-2	-80%	[-100; -20]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; -25]	
LITHUANIA - Admission to PICU, N=0	NA	NA	
First & second wave of SARS-CoV-2	NA	NA	
Third (Alpha) wave of SARS-CoV-2	NA	NA	

PORTUGAL - Discharged home, N=1,484	-87%	[-100; -49]	<0.0001
First & second wave of SARS-CoV-2	-83%	[-100; -47]	
Third (Alpha) wave of SARS-CoV-2	-93%	[-100; -53]	
PORTUGAL - Admission to ward, N=84	-100%	[-100; +140]	0.99
First & second wave of SARS-CoV-2	-100%	[-100; +140]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; +140]	
PORTUGAL - Admission to PICU, N=25	-67%	[-100; +50]	0.261
First & second wave of SARS-CoV-2	-76%	[-100; +33]	
Third (Alpha) wave of SARS-CoV-2	-45%	[-100; -57]	
SPAIN - Discharged home, N=2,136	-90%	[-100; -55]	<0.0001
First & second wave of SARS-CoV-2	-89%	[-100; -55]	
Third (Alpha) wave of SARS-CoV-2	-93%	[-100; -57]	
SPAIN - Admission to ward, N=448	-93%	[-100; -45]	0.0004
First & second wave of SARS-CoV-2	-92%	[-100; -45]	
Third (Alpha) wave of SARS-CoV-2	-95%	[-100; -46]	
SPAIN - Admission to PICU, N=19	-67%	[-100; +19]	0.127
First & second wave of SARS-CoV-2	-83%	[-100; +11]	
Third (Alpha) wave of SARS-CoV-2	-40%	[-100; +23]	
TURKEY - Discharged home, N=136	-100%	[-100; +145]	0.99
First & second wave of SARS-CoV-2	-100%	[-100; +145]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; +145]	
TURKEY - Admission to ward, N=99	-93%	[-100; -45]	0.013
First & second wave of SARS-CoV-2	-92%	[-100; -45]	
Third (Alpha) wave of SARS-CoV-2	-95%	[-100; -46]	
TURKEY - Admission to PICU, N=52	-93%	[-100; -41]	0.001
First & second wave of SARS-CoV-2	-84%	[-100; -37]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; -44]	
UNITED KINGDOM - Discharged home, N=4,867	-85%	[-100; -58]	<0.0001
First & second wave of SARS-CoV-2	-84%	[-100; -57]	
Third (Alpha) wave of SARS-CoV-2	-90%	[-100; -62]	
UNITED KINGDOM - Admission to ward, N=1,131	-90%	[-100; -68]	<0.0001
First & second wave of SARS-CoV-2	-91%	[-100; -69]	

Third (Alpha) wave of SARS-CoV-2	-90%	[-100; -67]	
UNITED KINGDOM - Admission to PICU, N=142	-89%	[-100; -28]	0.007
First & second wave of SARS-CoV-2	-86%	[-100; -27]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; -31]	

Abbreviations: NPI: non-pharmaceutical intervention. PICU: paediatric intensive care unit
Data not available or insufficient to conduct interrupted time series analysis for France, Germany, Hungary. Latvia and Netherland.

Appendix 7. Correlograms and residuals analysis of the quasi-Poisson regression model analysing the overall impact of NPIs on bronchiolitis cases in all countries, N = 42,916



Abbreviations: NPI: non-pharmaceutical intervention. ACF: auto-correlation function

To assess the quality of the Quasi-Poisson model, we used correlograms and residuals analysis.
The inspection of the correlograms relies on identifying remaining autocorrelation or seasonal pattern of the residuals. The significance of any remaining autocorrelation or seasonality is defined by a correlation higher than +1.96 standard error or lower than – 1.96 standard error for each lag of the time series. We checked whether the residuals of the models were normally distributed and had a constant variance over time. The correlograms were satisfactory (no remaining autocorrelation nor seasonal pattern of the residuals).
Between-countries overdispersion test using a Poisson regression: $p<0.0001$.
The following R packages were used to conduct the main analysis: timeDate; zoo; forecast; nlme; astsa; tseries; fUnitRoots; TSA; lmtest; Epi.

Appendix 9. Analysis of the independent association of each component of NPIs with bronchiolitis epidemics change, N = 42,916.
Analysis with 3 additional NPIs: private gathering restrictions, closure of international borders and SARS-CoV-2 case tracking by mobile app.

Intervention	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Full lockdown	0.39	[0.22; 0.55]	<0.0001	0.21	[0.14; 0.30]	<0.0001
Preschool closure	0.49	[0.24; 0.88]	0.029			
Primary school closure	0.50	[0.28; 0.84]	0.014			
Secondary school closure	0.49	[0.27; 0.82]	0.010	0.33	[0.20; 0.52]	<0.0001
University closure	1.89	[1.19; 3.10]	0.010	4.72	[2.68; 8.48]	<0.0001
Social distancing	0.45	[0.30; 0.67]	0.0002			
Facial mask inside	0.61	[0.39; 0.92]	0.022	0.49	[0.25; 0.94]	0.034
Facial mask outside	1.67	[1.12; 2.54]	0.015	0.60	[0.33; 1.11]	0.104
Limiting size gathering	2.90	[1.51; 6.41]	0.004			
Teleworking	1.55	[0.98; 2.55]	0.075	0.55	[0.31; 0.97]	0.038
Business closure	1.70	[1.12; 2.62]	0.015	1.61	[1.08; 2.37]	0.019
Border closure	0.66	[0.32; 1.19]	0.204			
Private gathering	1.79	[1.10; 3.02]	0.024			
Contact tracing	1.43	[0.83; 2.67]	0.223			

Appendix 10. Analysis of correlations between explanatory variables

A) Variance Inflation Factor (VIF)

Explanatory variable	VIF	Increased Standard error
Low Correlation		
Full lockdown	1.19	1.09
Limiting size of gatherings	1.39	1.18
Business closure	2.18	1.48
Social distancing	2.46	1.57
University closure	3.35	1.83
Teleworking	3.44	1.86
Preschool closure	3.93	1.98
Substantial Correlation		
Facial mask outdoors	5.71	2.39
Facial mask indoors	6.27	2.50
Secondary-school closure	11.97	3.46
Primary-school closure	12.35	3.51

B) Spearman correlation matrix

Explanatory variable	Social distancing	Facial mask indoors	Facial mask outdoors	Limiting size of gatherings	Teleworking	Business closure	Preschool closure	Primary school closure	Secondary school closure	University closure	Full lockdown
Social distancing											
Facial mask indoors	-0.13										
Facial mask outdoors	0.17*	0.34****									
Limiting size of gatherings	0.17*	0.15	0.04								
Teleworking	0.11	0.22**	0.00	0.05							
Business closure	0.17*	0.16*	0.03	0.27***	0.29***						
Preschool closure	0.22**	0.18*	0.06	0.17*	0.24**	0.36****					
Primary-school closure	0.15	0.11	0.02	0.25**	0.18*	0.42****	0.75****				
Secondary-school closure	0.28***	-0.15	0.14	0.28***	0.05	0.38****	0.62****	0.78****			
University closure	0.07	0.13	0.05	0.33****	0.26***	0.39****	0.52****	0.62****	0.70****		
Full lockdown	0.03	0.08	0.06	0.14	0.11	0.65****	0.35****	0.41****	0.35****	0.31****	

****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05

Appendix 11. Independent association of each NPI component with changes in bronchiolitis cases: Sensitivity analysis combining substantially correlated variables, N = 42,916

A) Pre-school, primary school, and secondary school closure combined

Intervention	Multivariate analysis		
	IRR	**95% CI**	**P value**
Full lockdown	0.21	[0.14; 0.30]	< 0.0001
School closure	0.33	[0.20; 0.52]	< 0.0001
University closure	4.75	[2.70; 8.53]	< 0.0001
Facial mask indoors	0.49	[0.25; 0.94]	0.034
Facial mask outdoors	0.60	[0.33; 1.10]	0.100
Teleworking	0.55	[0.31; 0.97]	0.039
Business closure	1.60	[1.07; 2.36]	0.020

Abbreviations: NPI: non-pharmaceutical intervention, IRR: incidence rate ratio

B) Facial mask indoors and outdoors combined

Intervention	Multivariate analysis		
	IRR	**95% CI**	**P value**
Full lockdown	0.24	[0.17; 0.34]	< 0.0001
Secondary-school closure	0.26	[0.16; 0.40]	< 0.0001
University closure	5.90	[3.53; 10.21]	< 0.0001
Facial mask	0.48	[0.25; 1.02]	0.042
Teleworking	0.65	[0.39; 1.07]	0.096

Abbreviations: NPI: non-pharmaceutical intervention, IRR: incidence rate ratio

Appendix 12. Independent association of each NPI component with changes in bronchiolitis epidemics: Sensitivity analysis with a mixed quasi-Poisson model including a random effect for gross domestic product, age structure (classified as follow: < 1 year, 1 to < 5 year, 5 to < 18 years, 18 years or older) and sex ratio for each included countries.

Intervention	**Multivariate analysis**		
	IRR	**95% CI**	**P value**
Full lockdown	0.23	[0.16; 0.32]	< 0.0001
Secondary-school closure	0.36	[0.20; 0.63]	0.0005
University closure	3.85	[2.04; 7.41]	< 0.0001
Facial mask indoors	0.43	[0.23; 0.82]	0.009
Facial mask outdoors	0.40	[0.21; 0.77]	0.005
Teleworking	0.79	[0.41; 1.52]	0.49
Business closure	1.61	[1.03; 2.47]	0.034

Abbreviations: NPI: non-pharmaceutical intervention, IRR: incidence rate ratio

Appendix 13. Independent association of each NPI component with changes in bronchiolitis epidemics: sensitivity analysis with a quasi-Poisson model including a dummy variable for each month of the year along with the harmonic terms to take into account the seasonal pattern.

Intervention	**Multivariate analysis**		
	IRR	**95% CI**	**P value**
Full lockdown	0.23	[0.16; 0.33]	< 0.0001
Secondary-school closure	0.26	[0.15; 0.41]	< 0.0001
University closure	6.19	[3.70; 10.8]	< 0.0001
Facial mask indoors	0.37	[0.19; 0.73]	0.005
Facial mask outdoors	0.58	[0.29; 1.20]	0.145
Teleworking	0.48	[0.27; 0.82]	0.009

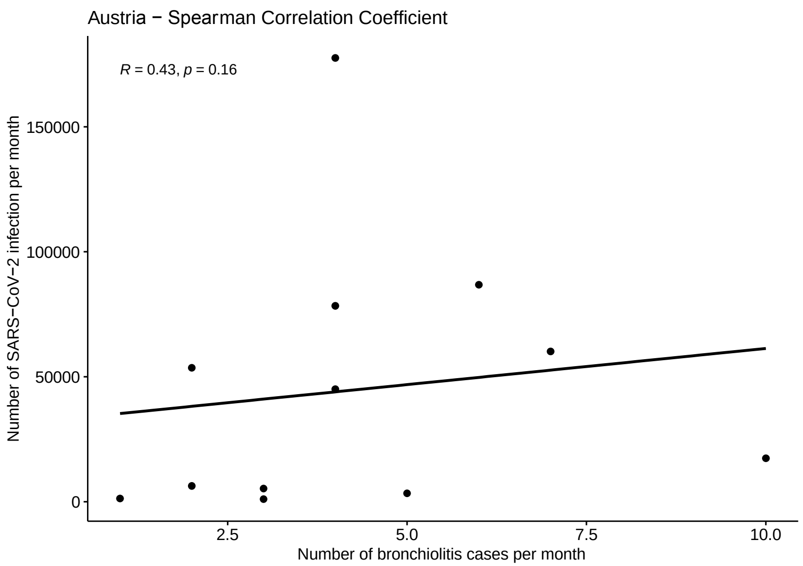
Abbreviations: NPI: non-pharmaceutical intervention, IRR: incidence rate ratio

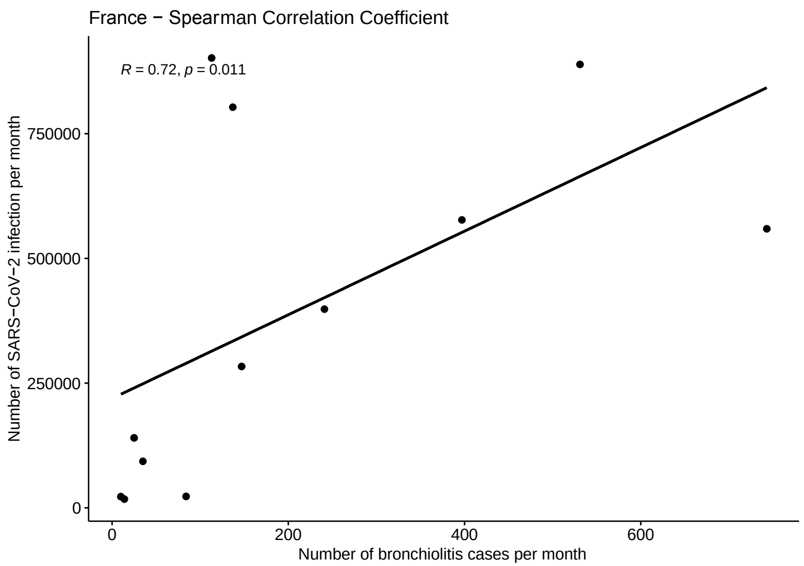
Appendix 14. Independent association of each NPI component with changes in bronchiolitis epidemics: Sensitivity analysis with a quasi-Poisson model including significant interaction terms between NPIs.

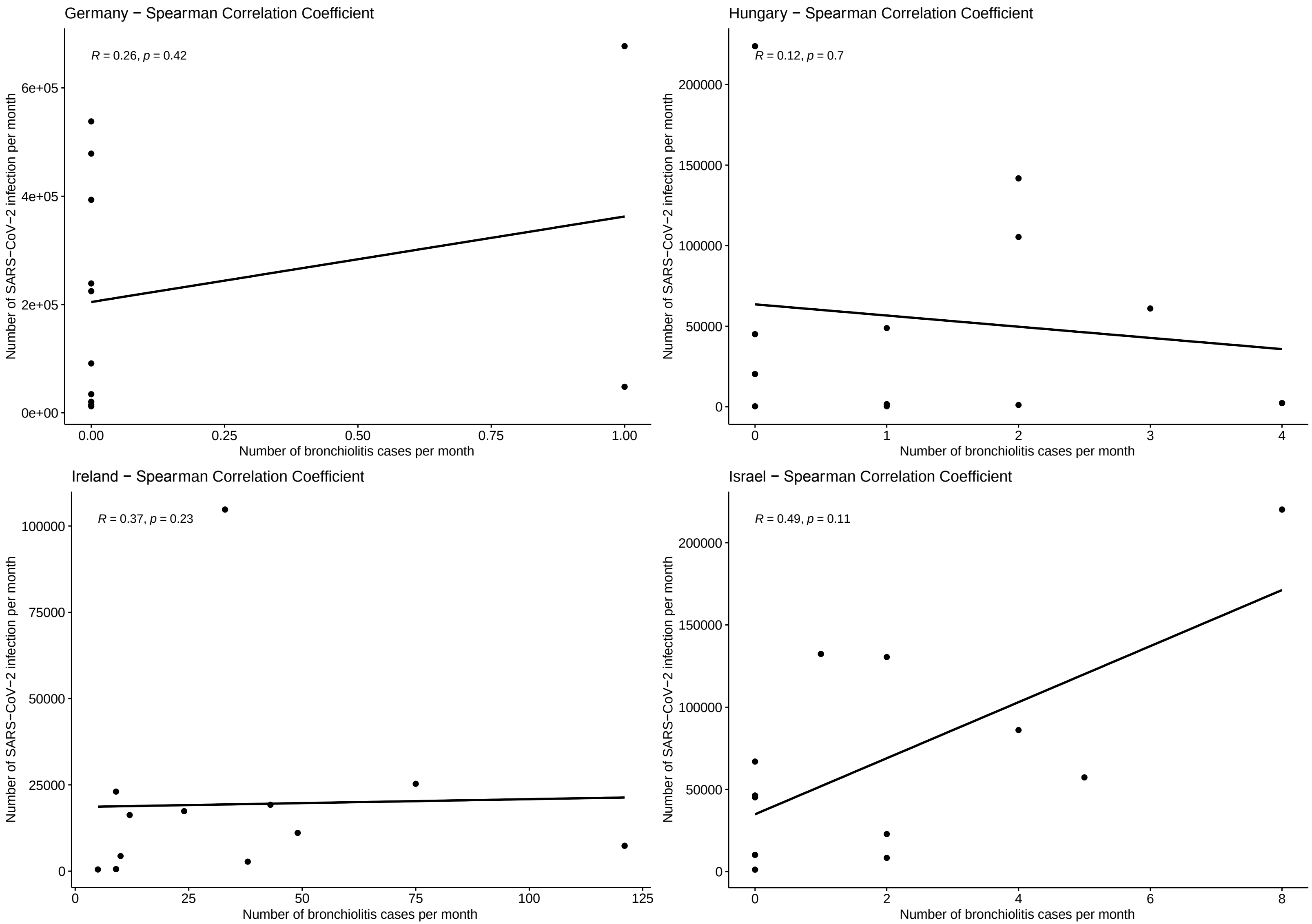
Intervention	Multivariate analysis		
	IRR	95% CI	P value
Full lockdown	0.17	[0.11; 0.24]	< 0.0001
Secondary-school closure	0.35	[0.17; 0.66]	0.003
University closure	1.73	[0.89; 3.35]	0.105
Facial mask indoors	0.23	[0.09; 0.72]	0.008
Facial mask outdoors	0.30	[0.16; 0.55]	0.006
Teleworking	0.62	[0.34; 1.14]	0.124
Business closure	0.33	[0.06; 1.75]	0.188

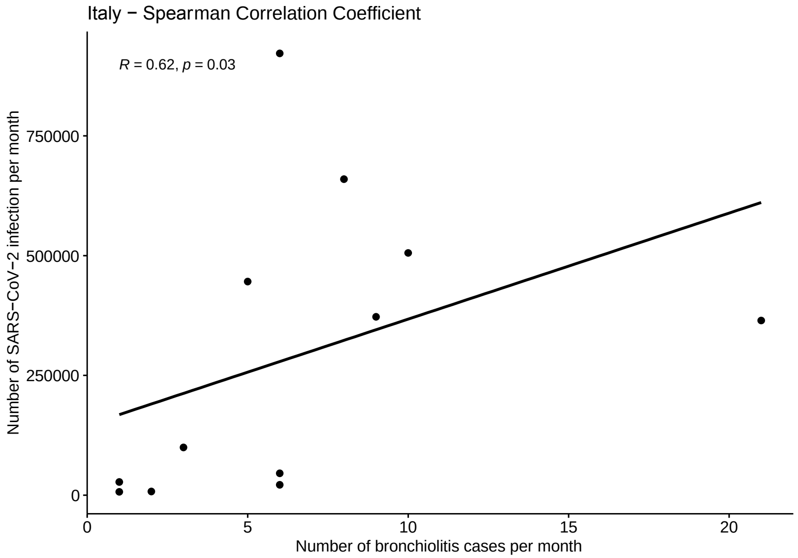
Added interaction terms: full lockdown*facial mask indoors, Secondary-school closure*facial mask indoors, university closure*business closure, facial mask indoors*business closure, facial mask outdoors*business closure, teleworking*business closure. All significant interactions between variables were in the same direction.
Abbreviations: NPI: non-pharmaceutical intervention, IRR: incidence rate ratio

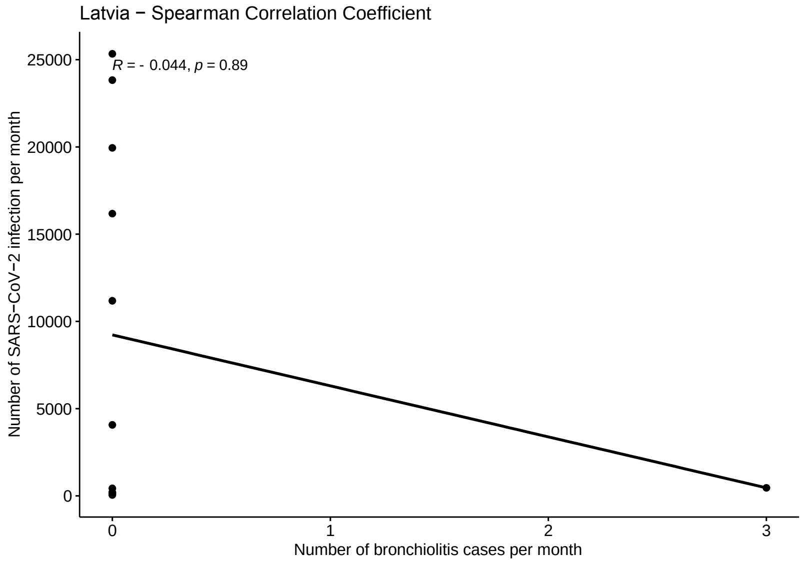
Appendix 15. Spearman correlation coefficient between the monthly number of SARS-CoV-2 and bronchiolitis cases for each country

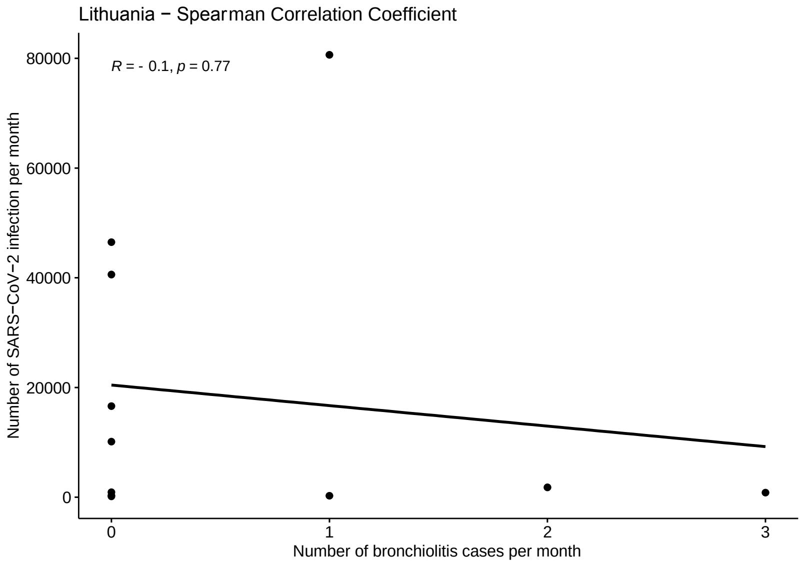


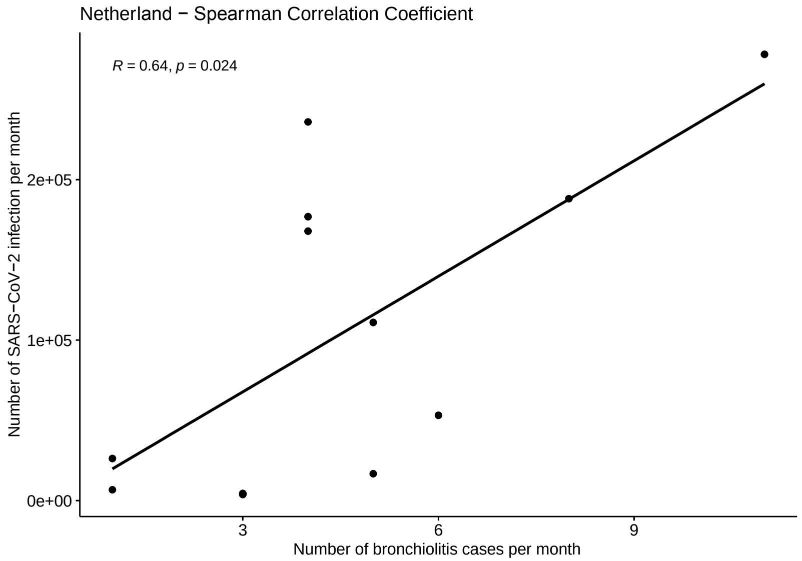


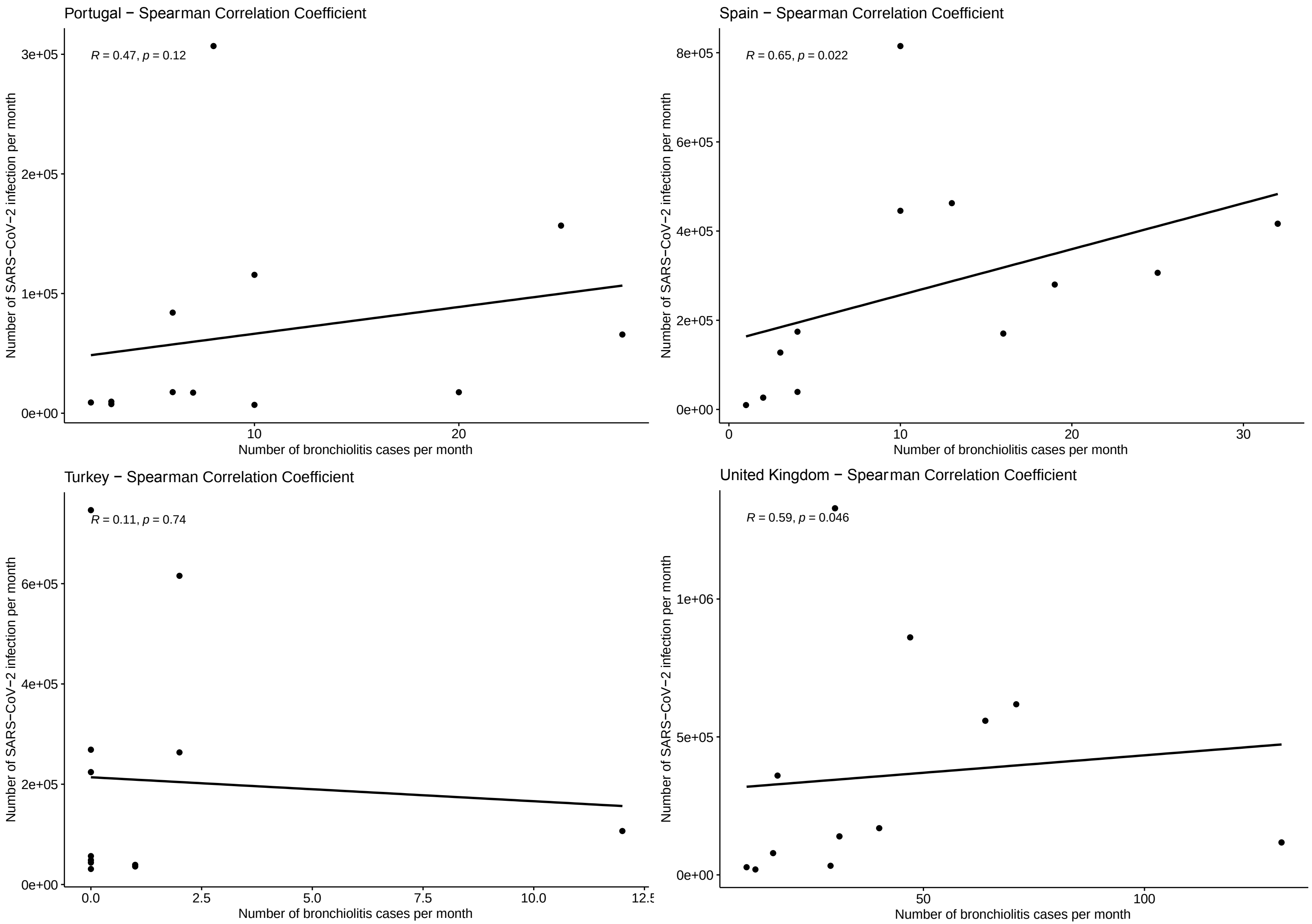

Germany − Spearman Correlation Coefficient
R = 0.26, p = 0.42
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month
Hungary − Spearman Correlation Coefficient
R = 0.12, p = 0.7
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month
Ireland − Spearman Correlation Coefficient
R = 0.37, p = 0.23
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month
Israel − Spearman Correlation Coefficient
R = 0.49, p = 0.11
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month


Italy − Spearman Correlation Coefficient
R = 0.62, p = 0.03
Number of SARS−CoV−2 infection per month
750000
500000
250000
0
0
5
10
15
20
Number of bronchiolitis cases per month


Latvia − Spearman Correlation Coefficient
R = - 0.044, p = 0.89
Number of SARS−CoV−2 infection per month
25000
20000
15000
10000
5000
0
0
1
2
3
Number of bronchiolitis cases per month


Lithuania − Spearman Correlation Coefficient
R = - 0.1, p = 0.77
Number of SARS−CoV−2 infection per month
80000
60000
40000
20000
0
0
1
2
3
Number of bronchiolitis cases per month


Netherland − Spearman Correlation Coefficient
R = 0.64, p = 0.024
Number of SARS−CoV−2 infection per month
2e+05
1e+05
0e+00
3
6
9
Number of bronchiolitis cases per month



Portugal − Spearman Correlation Coefficient
R = 0.47, p = 0.12
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month
Spain − Spearman Correlation Coefficient
R = 0.65, p = 0.022
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month
Turkey − Spearman Correlation Coefficient
R = 0.11, p = 0.74
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month
United Kingdom − Spearman Correlation Coefficient
R = 0.59, p = 0.046
Number of SARS−CoV−2 infection per month
Number of bronchiolitis cases per month

Appendix 16. Analyses assessing the relationship between SARS-CoV-2 and bronchiolitis evolution over time**.**

To explore the potential relationship between SARS-CoV-2 evolution and bronchiolitis over time, several analyses were performed:

- Subgroup analysis assessing the evolution of bronchiolitis cases for each SARS-CoV-2 wave, in each country.
- Subgroup analysis in each severity subgroup (bronchiolitis discharged home, admitted to ward, admitted to PICU), in each country and globally, for each SARS-CoV-2 wave
- Correlation analysis between the monthly number of bronchiolitis cases and the monthly number of new SARS-CoV-2 infections in each country over time, using the non-parametric Spearman correlation coefficient.

Data regarding the monthly number of new SARS-CoV-2 infections in each country (Dong et al. An interactive web-based dashboard to track COVID-19 in real time, Lancet Inf Dis 2020) allowed us to define the timing of the different waves in each country and ECDC's data on SARS-CoV-2 variants allowed us to define the predominant SARS-CoV-2 variant over the study period. Two strains of SARS-CoV-2 were circulating during the study period: the savage strain during the first and second waves and the alpha variant during the third wave.

Appendix 17. Impact of NPIs on bronchiolitis epidemics across countries, depending on SARS-CoV-2 wave/variant, N = 42,916**.**

Country	Cumulative change by the end of the study	95% CI	P value
All countries, N = 42,916	-78%	[-100; -54]	<0.0001
First & second wave of SARS-CoV-2	-73%	[-95; -51]	
Third (Alpha) wave of SARS-CoV-2	-78%	[-100; -54]	
Austria, N = 1,501	-88%	[-100; -54]	<0.0001
First & second wave of SARS-CoV-2	-80%	[-100; -49]	
Third (Alpha) wave of SARS-CoV-2	-95%	[-100; -58]	
France, N = 14,191	-57%	[-100; -11]	0.020
First & second wave of SARS-CoV-2	-81%	[-100; -49]	
Third (Alpha) wave of SARS-CoV-2	-0%	[-46; +47]	
Germany, N = 182	-98%	[-100; +05]	0.067
First & second wave of SARS-CoV-2	-92%	[-100; +05]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; +04]	
Hungary, N = 246	-83%	[-100; -36]	0.0014
First & second wave of SARS-CoV-2	-72%	[-100; -31]	
Third (Alpha) wave of SARS-CoV-2	-93%	[-100; -40]	
Ireland, N = 6,918	-83%	[-100; -49]	<0.0001
First & second wave of SARS-CoV-2	-80%	[-100; -47]	
Third (Alpha) wave of SARS-CoV-2	-93%	[-100; -55]	
Israel, N = 949	-90%	[-100; -54]	<0.0001
First & second wave of SARS-CoV-2	-93%	[-100; -55]	
Third (Alpha) wave of SARS-CoV-2	-86%	[-100; -51]	
Italy, N = 3,448	-93%	[-100; -63]	<0.0001
First & second wave of SARS-CoV-2	-91%	[-100; -61]	
Third (Alpha) wave of SARS-CoV-2	-96%	[-100; -65]	
Latvia, N = 397	-97%	[-100; -47]	0.0005
First & second wave of SARS-CoV-2	-86%	[-100; -41]	
Third (Alpha) wave of SARS-CoV-2	-100%	[-100; -48]	
Lithuania, N = 264	-89%	[-100; -28]	0.006
First & second wave of SARS-CoV-2	-82%	[-100; -26]	

Third (Alpha) wave of SARS-CoV-2	-99%	[-100; -31]	
Portugal, N = 2,544	-87%	[-100; -63]	<0.0001
First & second wave of SARS-CoV-2	-83%	[-100; -60]	
Third (Alpha) wave of SARS-CoV-2	-94%	[-100; -68]	
Spain, N = 3,164	-90%	[-100; -55]	<0.0001
First & second wave of SARS-CoV-2	-89%	[-100; -55]	
Third (Alpha) wave of SARS-CoV-2	-92%	[-100; -56]	
Netherland, N = 278	-36%	[-79; +07]	0.105
First & second wave of SARS-CoV-2	-46%	[-99; +09]	
Third (Alpha) wave of SARS-CoV-2	-03%	[-46; +40]	
Turkey N = 507	-90%	[-100; -49]	0.0001
First & second wave of SARS-CoV-2	-83%	[-100; -45]	
Third (Alpha) wave of SARS-CoV-2	-97%	[-100; -52]	
United Kingdom, N = 8,327	-88%	[-100; -64]	<0.0001
First & second wave of SARS-CoV-2	-87%	[-100; -64]	
Third (Alpha) wave of SARS-CoV-2	-90%	[-100; -66]	

Abbreviations: NPI: Non-Pharmaceutical Intervention.