

101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP1 – RSV epidemiology and impact of COVID-19

D1.7 Report on impact of COVID-19 and COVID-19 NPIs on RSV healthcare burden

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Definitions

- **Participants** of the PROMISE Consortium are referred to herein according to the following codes:
 1. **UEDIN**. The University of Edinburgh (United Kingdom)
 2. **UMCU**. Universitair Medisch Centrum Utrecht (Netherlands)
 3. **UA**. Universiteit Antwerpen (Belgium)
 4. **Imperial**. Imperial College of Science, Technology and Medicine (United Kingdom)
 5. **UOXF**. The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom)
 6. **THL**. Terveystieteiden tutkimuskeskus (Finland)
 7. **RIVM**. Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
 8. **NIVEL**. Stichting Nederlands Instituut voor Onderzoek van de Gezondheidszorg (Netherlands)
 9. **TUCH**. Varsinais-Suomen Sairaanhoidopiirin Kuntayhtymä (Finland)
 10. **TEAMIT**. TEAM IT Research, S.L. (Spain)
 11. **ReSViNET**. Stichting Resvinet (Netherlands)
 12. **SSI**. Statens Serum Institut (Denmark)
 13. **SERGAS**. Servizo Galego de Saúde (Spain)
 14. **PENTA**. Fondazione PENTA - For the treatment and care of children with HIV and related diseases - ONLUS (Italy)
 15. **FISABIO**. Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (Spain)
 16. **MLU**. Martin-Luther-Universitaet Halle-Wittenberg (Germany)
 17. **SP**. Sanofi Pasteur, S.A. (France)
 18. **GSK**. GlaxoSmithKline Biologicals, S.A. (Belgium)
 19. **JANSSEN**. Janssen Pharmaceutica, N.V (Belgium)
 20. **Novavax**. Novavax, Inc. (United States)
 21. **Pfizer**. Pfizer Limited (United Kingdom)
 22. **AZ**. AstraZeneca AB (Sweden)

- **Grant Agreement**. (Including its annexes and any amendments) The agreement signed between the beneficiaries of the action and the IMI2 JU for the undertaking of the PROMISE project (Grant Agreement No. 101034339).

- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The PROMISE Consortium, comprising the above-mentioned participants.
- **Consortium Agreement.** The agreement concluded amongst PROMISE participants for the implementation of the Grant Agreement. The agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

Acronym / Abbreviation	Meaning
COVID-19	Coronavirus Disease 2019
ECDC-JRC RMD	European Centre for Disease Prevention and Control and the Joint Research Centre of the European Commission Response Measures Database
IgA	Immunoglobulin A
IgG	Immunoglobulin G
LMIC	Low- and middle-income countries
LRTI	Lower Respiratory Tract Infection
NPI	Non-Pharmaceutical Intervention
OxCGRT	Oxford COVID-19 Government Response Tracker
PHM	Public Health Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SI	Stringency Index
WHO	World Health Organisation

Abstract

Background

Since the start of the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), two main public health control and mitigation measures: non-pharmaceutical interventions (NPIs) and coronavirus disease 2019 (COVID-19) vaccination were introduced to curtail the spread of the virus and protect against severe forms of COVID-19. The introduction of the NPIs leading to changes in community mixing and interaction, local and global connectivity, changes in personal hygiene, and adherence to preventive measures have had consequences on the transmission of other respiratory viruses, notably respiratory syncytial virus (RSV) and influenza. In addition to the implemented NPIs, the social and health-services-related effects of SARS-CoV-2 transmission and the massive introduction of COVID-19 vaccines impacted the circulation and activities of other respiratory viruses, and it is suggested that RSV and other respiratory viruses may be directly or indirectly suppressed, whilst others co-circulate with SARS-CoV-2, notably influenza virus in the winter months. Additionally, the widespread public health vaccination campaigns during the pandemic may have essentially modified behaviour and attitudes toward vaccination not only for COVID-19 but also for other vaccines. During the COVID-19 pandemic, we observed drastic reductions in RSV and other respiratory viruses as evidenced by low positivity rates and frequencies, no viral epidemics, and instances of delayed epidemics. The suppressive effects of SARS-CoV-2 on RSV and other respiratory viruses may have possibly led to a temporary change in the healthcare burden of RSV and other viruses.

Recent evidence suggests a co-circulation of SARS-CoV-2 and other respiratory viruses at a phase that is characterised by a change in clinical presentation such as reporting more severe RSV cases. RSV activities may begin to increase and as already seen in some cases RSV circulation already shows some signals of increase as we transition to the era of a post-COVID-19 pandemic. Depending on the stringency, durations, and timing of COVID-19 NPIs, RSV significantly continued to remain low; however, the dynamics in the post-COVID-19 pandemic period could define the RSV epidemiology and healthcare burden. In the post-COVID-19 pandemic era, a re-emergence of RSV, modified disease presentation as a result of RSV-naïve children, and low maternal immunoglobulin levels may likely influence the RSV healthcare burden. This may be determined by the amount of external seeding of RSV as well as the stringency, duration, and timing of the lifting and/or relaxation of restriction-based NPIs. A shift in seasonal epidemic occurred especially for the first or

second late summer and early autumn after the lifting of NPIs, after which it is expected that RSV epidemics would come back to the observed season as before the start of the COVID-19 pandemic.

Aim

To explore how SARS-CoV-2/COVID-19 and COVID-19 control measures interact with RSV and/or RSV healthcare burden

Research questions

- What are the effects of SARS-CoV-2 transmission on other respiratory viral activities such as RSV in terms of biological, ecological, and social effects?
- How do COVID-19 non-pharmaceutical interventions (NPIs) affect other respiratory viral activities, especially RSV, regarding changes related to community mixing, local and global connectivity, personal hygiene, and COVID-19 preventive measures?
- Is there an effect of COVID-19 vaccination on other respiratory viruses, especially RSV?
- How did/does SARS-CoV-2/COVID-19 affect the healthcare burden of RSV and other respiratory infections?

Approach

We conducted a review of the literature to build a conceptual framework to understand the interactions between SARS-CoV-2 and COVID-19, NPIs, and biological interventions (like vaccinations), and RSV transmission and healthcare burden. This was supplemented by an analysis of national administrative health data to estimate the burden of RSV disease in infants and adults before and during the COVID-19 pandemic using a time series modelling approach. Preliminary results from four countries and one region are included in this report.

Insights

It is suggested that the culmination of the effects of the SARS-CoV-2 transmissions and the public health control and mitigation measures would present a post-COVID-19 RSV healthcare burden that is different from the pre-COVID-19 pandemic burden with possible high rates of severe illnesses and modified long-term effects of RSV.

The attribution analyses in the time series modelling help define the real hospital disease burden of RSV. The analyses show that the incidence in older adults (≥ 65 years) is largely comparable across

countries, and increases strongly with age. These findings and quantitative estimates are of considerable public health relevance and are crucial in subsequent cost-effectiveness analyses.

1. Introduction

Respiratory syncytial virus (RSV) is a common virus that causes a significant global health burden, particularly in infants, young children, and the elderly (Munro *et al.*, 2023). In 2019, there were approximately 33 million RSV-associated acute lower respiratory tract infections (LRTIs), 3.6 million RSV-associated acute LRTI hospital admissions, and 101,400 RSV-attributable deaths in children aged 0-5 years old (Li *et al.*, 2022a). Furthermore, RSV caused approximately 336,000 adult hospitalisations and an estimated 14,000 in-hospital deaths in 2015 (Shi *et al.*, 2019). RSV is an enveloped, single-stranded, negative-sense RNA virus belonging to the family Paramyxoviridae (Crowe & Williams, 2014). RSV primarily targets the respiratory epithelium, with transmission occurring through respiratory secretions or contact with contaminated surfaces (Kaler *et al.*, 2023). RSV can cause a spectrum of clinical manifestations ranging from mild flu-like symptoms to a more severe LRTI. Prior to 2023, there were no vaccines for RSV; disease prevention relied on utilising passive immunisation therapeutics such as palivizumab. Palivizumab is a monoclonal antibody which binds to the F glycoprotein on RSV's surface to inhibit virus-cell membrane fusion (Meijas & Ramilo, 2008). Palivizumab is administered as an intramuscular dose at monthly intervals over the course of the RSV season (NHS, 2021). However, as RSV confers no long-lasting immunity, this form of prevention can only provide short-term protection (NHS Scotland, 2020). To combat this, in 2022/2023, nirsevimab (a monoclonal antibody to prevent RSV in infants) and newly developed RSV vaccines have been approved that target at-risk groups – older adults (Ruckwardt, 2023). However, these vaccines are yet to be fully rolled out globally.

1.1. The COVID-19 pandemic

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had profound impacts on the global health landscape. To contain the transmission of SARS-CoV-2, non-pharmaceutical interventions (NPIs) such as societal closures, stay-at-home orders, personal protectives such as face masks, and social distancing were introduced in most communities. Since the emergence of the COVID-19 pandemic, efforts have been made to understand SARS-CoV-2, ultimately leading to rapid advancements in the development of targeted diagnostics and therapeutics. However, what remains underexplored are the indirect effects of the outbreak on broader respiratory pathogens, especially those which share transmission dynamics with SARS-CoV-2.

1.2. COVID-19 and RSV intersection

Until 2020, RSV exhibited predictable seasonality, with infections primarily occurring during the winter months in the northern hemisphere (Staadegaard et al., 2021). This is largely attributed to RSV's restricted host range, alongside colder temperatures stabilising the virus's lipid envelope which enables more successful transmission in this season (Morley *et al.*, 2018). Viral transmission is largely dependent on seasonal changes that are linked to demographics and human behavioural factors (Morley *et al.*, 2018). Therefore, given the similar transmission dynamics of RSV and SARS-CoV-2 (Liu et al., 2020; Meyerowitz et al., 2021; van Doremalen et al., 2020; Pastorino et al., 2020), the NPIs that were introduced to curb SARS-CoV-2 transmission had a noticeable effect on RSV circulation and epidemiology. However, the exact drivers behind these changes remain underexplored in the literature.

This systematic review and time series analysis aimed to explore the interaction between SARS-CoV-2, NPIs and RSV and evaluate the impact of the COVID-19 pandemic and its associated control measures on RSV epidemiology.

2. Methods

This report contains three different sections which together aim to understand the interaction between SARS-CoV-2/COVID-19 and RSV. The first part of the report is a systematic literature review which aims to synthesise evidence on the interactions between SARS-CoV-2/COVID-19 and RSV. It focuses on reporting RSV testing, hospital admissions, and severity during the COVID-19 pandemic. The second aspect of the report involves times series modelling using national hospital admissions data to estimate the burden of RSV during the pandemic in four European countries and the Valencia Region, Spain. The third part of the report is a conceptual framework on the possible interactions between SARS-CoV-2/COVID-19 and RSV based on the understanding of the burden of RSV during the pandemic synthesised from the literature and supported by the time series modelling. These three distinct parts of the report aim to provide a comprehensive understanding of the interaction and impact of SARS-CoV-2/COVID-19 on the epidemiology of RSV during the pandemic.

2.1. Systematic literature review

This review adheres to procedures detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, ensuring replicability and methodological rigour (Page *et al.*, 2021).

RSV classification

For this review, RSV cases were defined in accordance with established clinical and virological criteria as documented in the studies included in this review. RSV-associated bronchiolitis, a common manifestation of RSV in infants and children under 5 years was included in the scope of this review. Bronchiolitis was considered to be RSV-associated when RSV was confirmed or when explicitly stated. The inclusion of RSV-associated bronchiolitis aims to comprehensively allow for analysis of RSV epidemiology throughout all phases of the COVID-19 pandemic.

Pandemic period classification

Given the variability in COVID-19 persistence periods across different countries and regions, the classification of pandemic periods was reliant upon criteria outlined by each respective author. Where clear classifications of pandemic periods were excluded from papers, data reported from before December 2019 was classed as 'pre-pandemic', data between 11 March 2020 and late 2021

were classed as 'during the pandemic', and data reported in 2022 onwards was classed as 'post-pandemic'. Data reported between 01 January and 11 March 2020 in countries in Europe were classified as pre-pandemic where data from China within this period was considered pandemic.

Eligibility criteria

To undertake this review, the PICO framework was utilised to aid in framing research questions. PICO refers to population(s), intervention(s), comparison(s), and outcome(s) of the studies to be included in the review. For this review, the PICO criteria were defined as the following:

Population: Individuals susceptible to RSV infection

Intervention(s): COVID-19 pandemic and associated control measures

Comparison(s): RSV epidemiology before vs during/after the COVID-19 pandemic

Outcome(s): Changes in RSV epidemiology

Search strategy

Three databases (MEDLINE, Embase, and Global Health) were searched between 02 January 2024 and 02 February 2024. As shown in Annex I Table 1, search strategies were mostly similar, with changes in keywords where necessary. Publication date restrictions were applied to only include papers published during or after 2019. No language restrictions were applied at this stage but all articles retrieved were in English.

Search Methodology

Studies identified from selected databases were imported into the Covidence app (version 2024) – a systematic review platform. To enhance objectivity and minimise bias, two reviewers independently screened the titles and abstracts of the studies. Eligible studies which met inclusion criteria (Annex II, Table 1), were moved to a full-text eligibility assessment in which two reviewers independently reviewed the selected articles. Conflicts resulting from title and abstract screening and full-text review were resolved through discussion and consensus. The relevant data were extracted from the eligible studies and included in this review. Due to a high degree of data heterogeneity within included studies, no meta-analysis was conducted. Instead, a descriptive analysis of the data was conducted.

2.2. Time series modelling methods

Data collection

We used national hospital registries containing individual-level patient data on all hospital admissions for The Netherlands, Denmark, Finland, and England and prospective hospital-based surveillance data for Spain-Valencia. From these data sources, described in detail in the D1.6 Report, we aggregated age-specific weekly numbers of hospital admissions with the outcome of interest, i.e., all respiratory infections. The outcome of interest was defined using ICD-10 codes. The ICD-10 codes were selected to cover all acute respiratory tract infections (RTIs) (ICD-10: J00, J02-06, J09-18, J20-22, J40, U07.1, U07.2, U08-10) and RSV-coded hospitalisations were identified when any RSV code was related to the admission (RSV codes ICD-10: J12.1, J20.5, J21.0, B97.4). Hospital admissions were defined as any hospitalisation lasting more than 12 hours. Scheduled or routine admissions were excluded. Hospitalisations were divided into analytic groups based on age at admission: 0-2 months, 3-5 months, 6-11 months, 1-2 years, 3-4 years, 5-17 years, 18-64 years, 65-74 years, 75-84 years, and 85+ years. Using the country-specific sources of virological data, aggregated non-age-specific weekly numbers of positive tests of Influenza A, B, RSV and SARS-CoV-2 were generated.

Time series analysis

Attribution of RTI hospital admissions that were due to RSV was performed using Poisson regression. In these analyses, the number of RTIs in each country and age group is explained by the background rate at which RTIs are observed, and by the main respiratory pathogens influenza A and B, RSV, and SARS-CoV-2 overall circulation. Specifically, the background rate was modelled using penalised splines, and covariates included the number of positives for the respiratory pathogens in the virological surveillance data of each country (in England, the positivity rates were used as covariates). In addition, we allowed lags or leaps of the time series of the respiratory pathogen positives relative to the RTI case data to account for the fact that epidemics in different age groups may be shifted relative to each other and relative to the virological data ([Johannesen et al. 2022](#)).

Specifically, if we denote the set of pathogens being considered as covariates by $P = \{RSV, influenza A, influenza B, SARS-CoV-2\}$, the expected number of cases in age group a at time t , $E(Y_{a,t})$, is given by

$$E(Y_{a,t}) = \exp \left(s_a(t) + \sum_{i \in P} \beta_{i,a} N_{i,t-t_i} \right), \quad (1)$$

where $s_a(t)$ represents the penalised spline function in age group a , $t_i \in \{-3, -2, \dots, 2, 3\}$ denotes the shift in weeks for pathogen i , and $\beta_{i,a}$ are the pathogen- and age-specific regression coefficients. As the observed cases, $y_{a,t}$, are assumed to be Poisson distributed, we have

$$y_{a,t} \sim \text{Poisson} \left(E(Y_{a,t}) \right). \quad (2)$$

Throughout, we employed second-order spline penalisation, and the number of knots was allowed to vary between 10 and 50. Fitting of the regression models was performed using restricted maximum likelihood (REML), and for each country and age group selection of the optimal shifts was based on the Akaike Information Criterion (AIC). Notice that if all pathogens were included this implies a comparison of $7^4 = 2,401$ models. Not all countries could include all pathogens, however, and for analysis restricted to the pre-pandemic period SARS-CoV-2 was not included as SARS-CoV-2 was not circulating, yielding a maximum of $7^3 = 343$ models. R-code using the package ‘mgcv’ ([Wood 2017](#)) to construct the regression equations was shared between countries. For each country, age group, and period (pandemic versus pre-pandemic), attribution of RTI cases to RSV was based on the best fitting model. Specifically, attribution was based on the difference between the expected number of RTI cases in the full best fitting model with the best fitting model when the number of virological positives was set to zero.

Country-specific details

The Netherlands: Weekly age-stratified hospital admissions with RTI and coded RSV were obtained from the Dutch Hospital Data (DHD). These data cover over 99% of hospital admissions in the Netherlands. The Dutch Hospital Data (DHD) registration collects, manages and processes hospital data and manages standards for its registration. Demographic data were obtained from Statistics Netherlands (CBS). Linking individual-level data from DHD with demographics data was performed in the microdata services of CBS, and properly aggregated and anonymised data were

subsequently exported for analysis. Weekly age-aggregated virological data from 20 hospitals and peripheral diagnostic laboratories spread throughout the Netherlands were obtained for RSV, influenza A and B, and SARS-CoV-2 from the Dutch Working Group for Clinical Virology (NWKV).

Denmark: Weekly RTI infections were aggregated from individual contacts in the Danish National Patient Registry (NPR). Infections that lasted longer than one week were counted only for the first week of hospitalisation. Weekly positive tests of RSV, SARS-CoV-2, and Influenza (A/B) were aggregated from the national microbiological database (MiBa).

Finland: The Finnish weekly RTI hospitalisations were based on the Finnish Care Register for Health Care (HILMO). HILMO covers individual-level clinical and administrative data from inpatient care, specialised outpatient care, and day surgeries. The weekly pathogen data was obtained through the National Infectious Diseases Register (NIDR). The NIDR captures records of selected microbiological findings and related diagnoses that all laboratories and physicians are obliged to report under the Communicable Disease Act. All positive test results for RSV, Influenza A, Influenza B, and SARS-CoV-2 are included in the register. General demographic records and dates of death for the study population were obtained from the Population Information System which is maintained by Statistics Finland.

England: Weekly hospital admissions with RTI were provided by the Hospital Episode Statistics (HES) database that monitors >98% of England's population (Hospital Episode Statistics, 2023). Weekly positivity rates for RSV, SARS-CoV-2, and influenza, as well as the number of cases for influenza A and influenza B were provided by the United Kingdom Health Security Agency, based on the DataMart surveillance system and outcomes publicly published in the weekly reports ([Weekly National Flu Reports, 2024](#)). The Respiratory DataMart sentinel system was initially set up in 2009 to automate the collection of all influenza A(H1N1) pdm09 laboratory testing information in England. It is now an important sentinel laboratory surveillance tool, monitoring all major respiratory viruses in England, with 17 laboratories contributing data at present through weekly automatic electronic outputs. Participating laboratories test swabs for respiratory viruses using real-time reverse transcription polymerase chain reaction (RT-PCR), although not all laboratories test for or report all viruses. The positivity rate for influenza A and influenza B was computed from these raw sources. The population comes from the various United Kingdom censuses from the National Office for Statistics; for 2021/2022 the population described in the Census 2021 was used, and for previous seasons' populations the mid-year census of the respective year (i.e., week 27 of the surveillance

year) (Office for National Statistics, 2021; Office for National Statistics, 2024) was used. For 2022/2023 as the census was not yet publicly available, we assumed the same population for mid-2022 as the one in mid-2021.

Spain (Valencia): In Valencia, all hospital admissions via an emergency room that met preliminary inclusion criteria (catchment area residents, not institutionalised patients and not hospitalised in the previous 30 days) and gave their written consent were interviewed. Patients ≥ 5 years old were included if, upon admission, they met symptoms compatible with influenza-like-illness (ILI), defined as the presence of at least one respiratory symptom (cough, sore throat or shortness of breath) with an onset of symptoms within 7 days before admission. In patients under 5 years, no specific symptom was required but respiratory symptoms had to have appeared no more than 7 days before hospitalisation. All included patients were systematically tested for RSV and Influenza A and B via a multiplex RT-PCR. The data was collected as part of the Study of Influenza and other Respiratory Viruses (VAHNSI), an active prospective hospital-based surveillance network (~1 million catchment population, 21% of the total Valencia population) coordinated by the Vaccine Research Department of FISABIO-Public Health.

As the active surveillance was not conducted throughout the whole year, to perform the time series modelling we imputed data for weeks where no surveillance was performed (58 weeks in total). Data was imputed for the variables N_RSV, N_INFA, N_INFB, and for each age group using the seasonally decomposed missing value imputation from the *imputTS* R package (Moritz & Bartz-Beielstein, 2017). Once the imputed values were obtained, they were adjusted by rounding the values to the nearest integer and making sure they were positive, and replacing them with 0 in case the values were negative. Annex III Table 1 describes the available and imputed weeks in Spain-Valencia.

2.3. Conceptual framework of the interaction between COVID-19 NPIs and RSV

From the evidence gathered in the literature and the preliminary time series modelling, we illustrated a potential interaction between SARS-CoV-2, COVID-19 NPIs, and RSV to demonstrate how this interaction impacted RSV epidemiology during the COVID-19 pandemic.

3. Results

3.1. Systematic review

Search Outcomes

The search yielded 6146 studies with 4263 progressing into title and abstract screening after duplicates were identified and subsequently removed. Only 277 studies then progressed into full-text eligibility screening. Following these screening stages, 20 studies were included in the final systematic review. The search strategy steps taken to gather studies for utilisation in the main review are depicted in Figure 1, highlighting the key reasons for exclusion during screening stages.

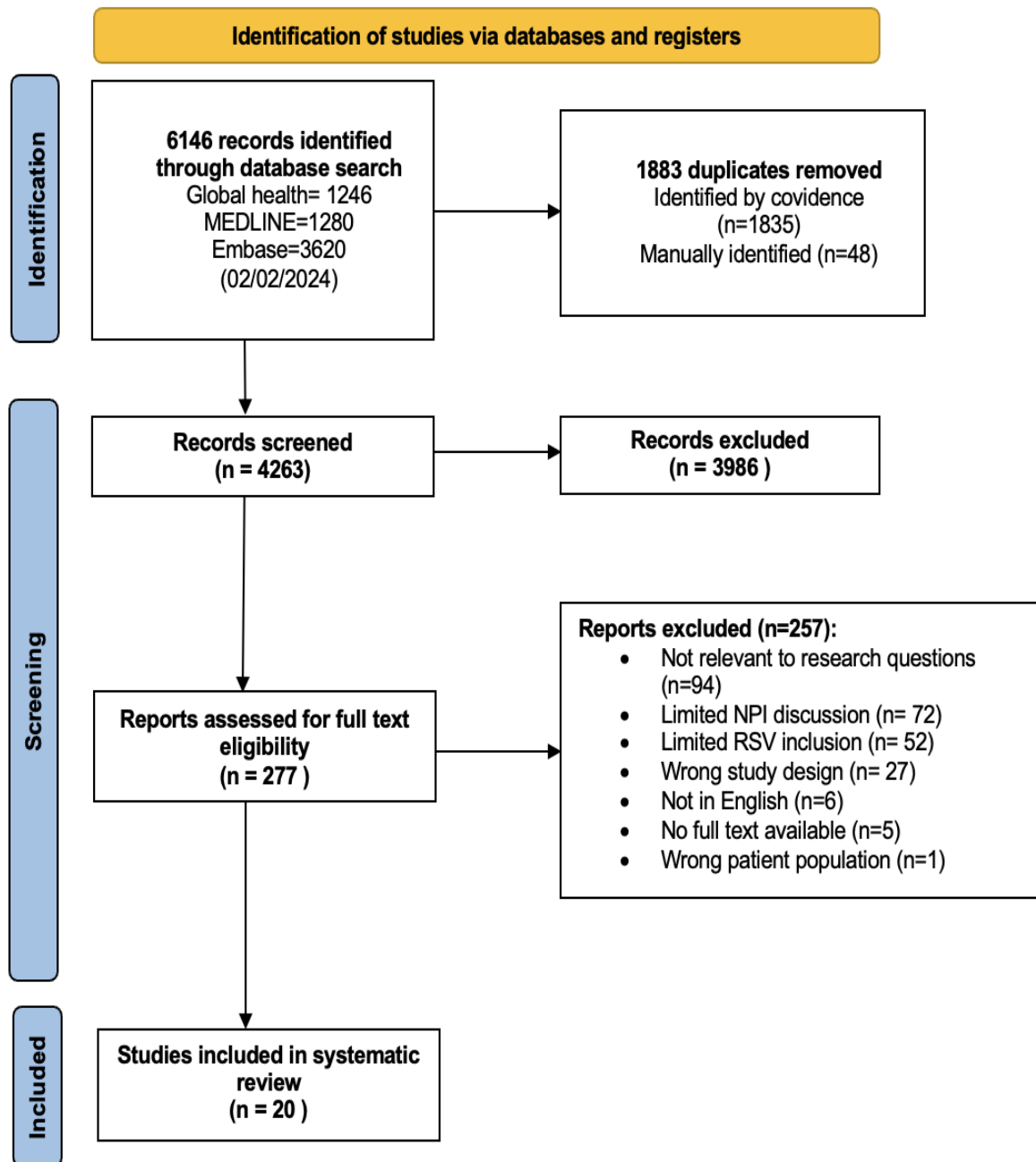


Figure 1: PRISMA flow diagram. 1) Identification phase: Three database were searched with 6146 resultant studies. Covidence identified 1835 duplicates that were subsequently removed. 2) Screening phase: titles and abstracts of 4263 studies were screened against inclusion criteria, excluding 3986 studies at this stage. 3) Eligibility phase: 277 studies underwent full-text screening, removing those which did not fulfil the inclusion criteria and research questions. Resultantly, 20 studies were included in the final systematic review. PRISMA framework taken and adapted from

Page *et al* (2021).

Study characteristics

Twenty studies were included in this review. A detailed summary of each study describing their characteristics and main findings is presented in Table 1 of Appendix 1. The main results of these papers are described in the following sections, presented in accordance with key epidemiological parameters.

Impact of COVID-19 control measures on RSV epidemiology.

I. RSV incidence rate

Nine studies evaluated changes in RSV incidence rate during the COVID-19 pandemic, highlighting substantial declines in RSV cases across eight reported countries (Germany, England, Saudi Arabia, China, Qatar, Australia, Spain and Turkey). A 37.5% decrease in seasonal peak of RSV (RT-PCR) positivity from 6.4% in 2017/2018 (week 41 of 2017 to week 22 of 2018) to 4.0% in 2019/2020 (week 45 of 2019 to week 14 of 2020) was reported in Germany (Hönemann *et al.*, 2023). Similarly, an 89.4% decrease in RSV test positivity from 47% in 2018/2019 to 5% in 2019/2020 was reported in England (Bardsley *et al.*, 2023). Decreasing trends were also observed in Saudi Arabia and China, with decreases from 2019-2020 ranging from 6.5%-38% (Jiang *et al.*, 2022; AlBahrani *et al.*, 2024;). A 97% decrease in RSV detections from 21.2% in December 2019 to 0.7% in December 2020 was observed in Qatar with Australia detecting RSV cases that were 98% lower in 2020 compared to pre-pandemic years (Yeoh *et al.*, 2020; Pérez-López *et al.*, 2022). The average number of RSV cases in 2020 decreased by 85% compared to the previous 6 monitored epidemiological years (2014-2019) in China (Wagatsuma *et al.*, 2021). Studies from Spain and Turkey reported declines in 2020, with Turkey reporting 0 cases in the 2020/2021 period, declining from 102 cases in 2018/2019 (Reyes-Dominguez *et al.*, 2021; Çağlar *et al.*, 2023). Cong *et al.*, (2024) observed significant declines in RSV incidence rates in their multi-country analysis, noting that the hospitalisation burden of RSV-associated acute LRTI in children younger than five years was significantly reduced during the first year of the pandemic (Cong *et al.*, 2024).

II. RSV seasonality

Nine studies evaluated RSV seasonality during the COVID-19 pandemic. A noticeable shift in RSV seasonality was reported in Germany with case detections from June-February in 2021/2022, opposing an October-May RSV season in 2017-2019 (Hönemann *et al.*, 2023). In the 2021/2022

season, the cases were observed between week 27 of 2021 (June) and week 9 of 2022 (February). In the season of 2019/2020, the cases were mainly observed between week 45 of 2019 (November) and week 14 of 2020 (April) (Hönemann *et al.*, 2023).

In Australia, pre-pandemic RSV peaks were in June/July and RSV activity declined and remained very low relative to previous seasons during the pandemic, even following the sequential relaxation of local COVID-19 restrictions (Yeoh *et al.*, 2020). Additionally, in Australia, RSV peaks were reported to have occurred in early summer (December) in 2020, compared to normal winter peaks (June/July) in 2015-2019 (Saravanos *et al.*, 2022). In 2020, a study from China noted, typical seasonality in RSV cases, with numbers gradually declining from December 2020 to March 2020. However, in December 2020, there was a sudden increase in RSV cases, indicating an atypical presentation (Jiang *et al.*, 2023). Hu *et al.*, 2024 reported that throughout 2019 in Hangzhou, China, the RSV-positive rate decreased to a very low level since mid-spring (April) and started to rise in late autumn (November) with a peak occurring in winter (December). The trend of RSV-positive rates in 2020 was similar to that in 2019, and the rates were slightly higher in 2020 than those 2019 from October to December (Hu *et al.*, 2024). However, in 2021, the RSV-positive rate went up dramatically in July with a peak presenting in October; while in 2022, it increased swiftly from July with a highest rate in December. In 2023, there was an out-of-season outbreak of RSV in spring, and we observed a peak in May that was significantly higher than that in previous years (Hu *et al.*, 2024).

This trend of unusual seasonality was further reported by Billard *et al* (2022) which found that across ten countries, the average delay in onset of the first RSV epidemic was around 39 weeks. Studies from both France and England reported limited RSV cases during 2020/2021 periods, highlighting a disappearance of RSV seasonality during the pandemic (Fourgeaud *et al.*, 2021; Bardsley *et al.*, 2023). In contrast, a study from Turkey reported the same January RSV peak in 2019/2020 as in pre-pandemic years due to the fact that the first case of COVID-19 in Turkey was reported in March 2020 (Çağlar *et al.*, 2023).

Role of specific NPIs in modifying RSV patterns

Many previously published studies that evaluated the impact of the COVID-19 pandemic on RSV epidemiology focused on NPIs as a collective, challenging the ability to decipher the individual roles of each NPI in RSV activity. To unravel this, the following section delves into the examination of specific NPIs and their influence on RSV epidemiology.

I. School closures

Two studies explored the role of school closures on observed changes to RSV epidemiology. Billard *et al* (2022) reported a significant negative correlation between school closures and the difference between observed and expected RSV positivity rates ($r=-1.31$, $p=0.04$) across a range of countries, with reopening schools reported as associated with an absolute increase in RSV activity (Billard *et al.*, 2022). Similar findings were reported in Qatar with observed fluctuations in RSV cases corresponding to the timings of openings and closures of schools and nurseries (Pérez-López *et al.*, 2022).

II. Travel restrictions

Four studies evaluated the impact of travel restrictions on RSV epidemiology. Billard *et al* (2022) identified negative correlations between observed RSV positivity rates and various travel restrictions, including restrictions on internal movements ($r=-2.27$) and public transport closures ($r=-1.73$), however, these findings were not significant. Furthermore, for every unit increase in the restriction of internal movements there was a corresponding decrease of approximately 1.33 units in the difference between observed and expected RSV positivity rates (Billard *et al.*, 2022). Wagatsuma *et al* (2022) reported that increases in international and domestic airline passenger arrivals in China correlated with a subsequent increase in monthly RSV activity. Similarly, strong positive correlations ($r=0.84$, $p=0.001$) between international visitors and RSV infections, with a notable decline in RSV cases following decreased international travel were reported in Qatar (Pérez-López *et al.*, 2022). The closure of borders in Australia was reported to coincide with decreases in RSV cases (Yeoh *et al.*, 2020).

III. Mask mandates

One study assessed the relationship between mask mandates and RSV epidemiology. Billard *et al* (2022) reported that mask mandates were not significantly associated with reductions in RSV activity in any of the eleven investigated countries (South Africa, South Korea, France, Israel, US, the Netherlands, Japan, Canada, Brazil, Taiwan, and China).

NPI stringency index and RSV dynamics

Three studies utilised the Oxford COVID-19 Government Response Tracker (OxCGRT) to evaluate correlations between NPI stringency and RSV dynamics. Stringency index (SI) collects publicly available information on NPIs implemented by governments worldwide (Hale *et al.*, 2021). The

OxCGRT assigns an SI score (0-100) to each country based on the intensity of implemented NPIs, allowing for exploration of their correlation with observed RSV trends (University of Oxford, 2023). Significant negative correlations between SI and the difference in RSV activity were reported by two studies, emphasising that lower SI levels were associated with higher RSV positivity rates (Billard *et al.*, 2022; Pérez-López *et al.*, 2022). In Qatar, a significant negative correlation between SI and the monthly number of RSV infections in children was reported ($r=-0.66$, $p=0.0007$) (Pérez-López *et al.*, 2022). Similarly, Billard *et al.* (2022) reported that across eleven countries, a 10-point decrease in SI was significantly associated with an absolute increase in the difference between observed and expected RSV positivity rates ($p=0.04$). These findings were supported by a study in Spain which observed a significant correlation between the implementation of public health measures (PHMs), and reductions in admissions for RSV acute bronchiolitis in the paediatric population (Reyes-Dominguez *et al.*, 2021).

Post-pandemic epidemiological trends

I. Resurgence of RSV cases

Ten studies evaluated the resurgence of RSV cases. In Germany, overall seasonal peak of RSV RT-PCR positivity increased from 4.0% in 2019/2020 to 11.5% in 2021/2022 (Hönemann *et al.*, 2023). Similarly, a study from France reported an 11% RSV positivity percentage rate increase from 2021 compared to rates from 2020 and 2019, with a study from China reporting a similar 15% increase in peak cases in 2021 compared to 2020 (Delestrain *et al.*, 2021; Jiang *et al.*, 2022). In the UK, a summer surge of RSV activity occurred in 2021 with a 527.3% higher test positivity (Bardsley *et al.*, 2023). In October-December 2021 in Qatar, a 4075% increase in RSV test positivity was reported compared to the same period in 2020 (Pérez-López *et al.*, 2022). Similar trends of increased percentage positivity of RSV were reported across multiple Australian territories by Eden *et al.* (2022) between April 2020 and January 2021, with a study from Saudi Arabia reporting a resurgence of RSV infections in October 2022 following declines in RSV cases from 2019-2021 (Eden *et al.*, 2022; AlBahrani *et al.*, 2024). A study from Turkey reported an increase of RSV cases from 0 in 2020/2021 to 56 in 2021/2022, with a study from Taiwan reporting no RSV cases in 2021 before increasing to 58 cases in October 2022 (Çağlar *et al.*, 2023; Lee *et al.*, 2023). Similar trends of increased case rates from 2020 to 2021 were observed in England and the US (Bardsley *et al.*, 2023; Wang *et al.*, 2023). Interestingly, the US reported peak RSV incidence rates in 2022 that were significantly higher than expected, representing an increase in cases between 96.4%-131.6%, indicating a more severe RSV resurgence pattern compared to pre-pandemic years (Wang *et al.*, 2023).

II. New seasonality

Five studies evaluated RSV seasonality following the pandemic, reporting differing trends across four reported countries. Studies from Turkey and the US reported returns to typical pre-pandemic seasonality, with Çağlar *et al* (2023) reporting that following an early RSV peak in November in 2021/2022, the 2022/2023 season saw a peak in January representing a shift towards typical pre-pandemic trends. Similarly, Wang *et al* (2023) reported that in 0-5-year-olds, the seasonal pattern of RSV returned to observing winter peaks in 2022/2023, following on from an early resurgence in 2021. In contrast, studies from China reported a lack of return to typical seasonality with Jiang *et al* (2022) reporting a low RSV epidemic from October 2021 following a consistent RSV presence of 10% from June-September. Furthermore, Hu *et al* (2023) reported RSV positivity rates increasing from July 2021 and peaking in October. Furthermore, in 2022 peaks fell in December with out of season spring outbreaks peaking in May 2023, representing a lack of return of typical seasonality (Hu *et al.*, 2023). Similarly, a study from England observed an atypical summer seasonality in 2021, with a 1258.3% increase in cases reported from expected values (Bardsley *et al.*, 2023). Furthermore, no RSV cases were reported in 2021/2022, representing a 26.9% change from pre-pandemic expected values (Bardsley *et al.*, 2023).

III. Age demographics

Six studies evaluated age demographics of those presenting with RSV infection after the emergence of COVID-19. In Saudi Arabia, there was an observed increase in the mean age of patients with RSV from 0.50 to 1.08 years old (AlBahrani *et al.*, 2024). In France, compared to patients admitted between 2018-2020, patients presenting with RSV in the 2020/2021 interseasonal epidemic were 97% more frequently aged 6-11 months old (Fourgeaud *et al.*, 2021). A study from China reported that from January 2020-December 2022, reported cases were mainly in children under 12 months old, however, after December 2022, there was an atypical summer presentation in which most cases were observed in children aged 1-3 years old (Hu *et al.*, 2023). Similarly, a study from Australia reported that the median age of children with RSV hospitalisations was higher in 2020 than what was observed in previous years (Saravanos *et al.*, 2022). In contrast, studies from both Turkey and Taiwan reported no significant age differences for children during any phase of the pandemic (Çağlar *et al.*, 2023; Lee *et al.*, 2023).

IV. RSV-specific antibody levels

Three studies assessed RSV antibody levels during and following the COVID-19 pandemic.

Grobben *et al* (2022) reported significantly reduced RSV immunoglobulin-G (IgG) but not immunoglobulin-A (IgA) in human milk by a factor of 1.7 following the pandemic. In contrast, maternal serum antibodies increased during the pandemic by a factor of 1.7 ($p < 0.01$) (Grobben *et al.*, 2022). Hartog *et al* (2023) reported significant decreases in post fusion F IgG antibody concentrations during the pandemic. Neither Grobben or Hartog *et al* reported data on antibody functions, however, Reicherz *et al* (2022) determined both RSV IgG and neutralisation titres. Prefusion RSV F IgG levels were significantly reduced in women of childbearing age and infants in 2021 compared to the same individuals in 2020. Respiratory virus neutralisation titres in women in 2021 were 12-fold lower compared to that of 2020, and 3.4-fold lower in infants (Reicherz *et al.*, 2022).

3.2. Time series modelling preliminary results for the Netherlands, Denmark, Finland, England, and Spain (Valencia Region)

RSV-coded hospital admissions

The yearly average number of RSV-coded hospital admissions was not directly comparable between countries, but followed a similar trend, with the highest average number of admissions in the youngest children (0-2 months of age), and the lowest number in the oldest children (3-4 years and 5-17 years). We observed a rise in numbers with age occurring in all countries but with relatively lower numbers in Denmark and Spain (Tables 1-5). In Valencia, the RSV-coded admissions were substituted for RSV laboratory-confirmed admissions as testing was systematic and performed in all included patients. For all contributing countries, the pre-pandemic season patterns are clear in the younger age groups, up until 3-4 years. A delayed peak is also found in these age groups, after a period of low incidence in 2020. In Finland, the RSV-coded hospital admission in adults 65-74, 75-84, and 85+ years of age also shows a seasonal pattern, with seasons alternating in size every other year. In 2021 and 2023 two substantial peaks of RSV-coded hospital admissions were found in the same Finish age groups.

RTI-coded hospital admissions

The numbers of RTI-coded hospital admissions differ between both age groups and countries, as shown by the grey dots in Figures 2-6. Clear patterns of seasonal variation were observed in the age-specific RTI-coded hospital admissions, with yearly peaks. With the increase in age, the

number of out-of-season RTI-coded hospitalisations rise in all participating countries. The predicted numbers of RTI-coded hospital admissions closely follow the observed numbers in the youngest age groups (0-2 months, 3-5 months, 6-11 months) and the elderly age groups (65-74 years, 75-84 years, and 85+ years), an indication that the seasonal patterns are clearest in these age groups in Denmark, Finland, and the Netherlands (Figures 2-4 (grey lines)). In Valencia, RTI-coded hospital admissions belong to influenza-like illness (ILI) hospital admissions which could explain the lower numbers observed compared to other countries, especially among adults.

RSV-attributed RTI admissions - numbers and %

Through the age group- and country-specific time series analysis, we can provide estimates on the number of RTI admissions that can be attributed to RSV. The average yearly number of RSV-attributed RTI admissions for Denmark ranged from 36 hospitalisations (3-4 years) to 960.7 admissions (75-84 years), with more than 800 yearly attributable cases in all age groups between 18 and 84 years (Table 2). The ratio of attributed RSV admissions to RSV-coded admissions informs the relation between actual clinical practice with diagnostic codes and the modelled number of admissions attributed to RSV in this study. We found that the ratio was around 1-2 attributed cases per coded case in Danish children under 4 years, with an increasing ratio with age (0.88-2.29, 0-2 months - 3-4 years). In Denmark, the average yearly number of RSV admissions among adults is low (30 per year in the age group 18-64 years, 15 per year in the age group 85+ years). The ratio of attributed RSV admissions for adults in Denmark ranged from 28.72 RSV admissions attributed per RSV-coded admission (18-64 years) to 48.64 in 85+ years. This ratio is the highest ratio seen in any country or age group.

In Denmark, the weekly number of attributed RSV admissions followed the RTI cases quite closely in young children and had a high degree of concurrence between peaks of RSV-attributed admissions and peaks of RTI-coded admissions among patients older than 5 years (Figure 3). In England, the average yearly number of RSV-attributed RTI admissions ranged from 3,677.1 hospitalisations (5-17 years) to 19,308.1 admissions (18-64 years), with approximately 15,000 yearly attributable cases in all age groups 75-84 years and 85+ years (Table 4). When looking at the ratio of attributed RSV admissions in England, we found the ratio in age groups younger than 5 years to be between 3.09 and 4.75 RSV admissions attributed per RSV-coded admission (Table 4). The ratio of attributed RSV admissions for adults in England ranged from 12.85 RSV admissions attributed per RSV-coded admission (65-74 years) to 20.39 in the 18-64-year age group. The average yearly number of RSV-attributed RTI admissions in Finland was highest in the age

group 85+ years with 711.2 admissions. In age groups 3-4 years, 5-17 years, and 18-64 years attribution to RSV admissions was not possible. The attributed number of hospitalisations was set to 0 (Table 3). The ratio of attributed RSV admissions in age groups younger than 3 years in Finland ranged between 0.43 (6-11 months) and 0.98 (1-2 years) RSV admissions attributed per RSV-coded admission (Table 3). The ratio of attributed RSV admissions for adults in Finland ranged from 1.92 RSV admissions attributed per RSV-coded admission (65-74 years) to 2.88 in the 85+ years age group. These are among the lowest ratios for adults. At the same time, the Finnish numbers of average yearly RSV-coded admissions are some of the highest in this study proportional to population size.

In the Netherlands, the average yearly number of RSV-attributed RTI admissions ranged from 155.3 hospitalisations (5-17 years) to 2122.1 admissions (75-84 years), with more than 1400 yearly attributable cases in all age groups between 18 and 84 years (Table 1). When looking at the ratio of attributed RSV admissions in the Netherlands in age groups younger than 5 years, we found ratios between 0.93 and 7.00 RSV admissions attributed per RSV-coded admission, trending from lowest to highest with increasing age (Table 1). The ratio of attributed RSV admissions for adults in the Netherlands ranged from 5.08 RSV admissions attributed per RSV-coded admission (18-64 years) to 10.39 in the 85+ years age group.

In Valencia, the average yearly number of RSV-attributed ILI admissions ranged from 11.2 (6-11 months) to 91.1 (75-84 years). In age groups 3-4 years and 5-17 years, calculations of attributions were not possible. In Valencia, the RSV-coded admissions were substituted for RSV laboratory-confirmed admissions as testing was systematic and performed in all included patients. The ratio of attributed RSV admissions to RSV laboratory-confirmed admissions in Valencia ranged from 0.41 (3-5 months of age) to 4.79 (18-64 years) (Table 5).

RSV-attributed RTI admissions - incidences

To align different country sizes, the incidence of RSV-attributable hospitalisations per 100,000 person-years in the age group was calculated. In all countries, the incidence rates follow a clear trend. The highest incidences are found in the youngest age groups (e.g., 0-2 months: 2279.5 in the Netherlands, 2200.2 in Valencia, 3852.6 in England). In age groups 3-4 years and 5-17 years, the incidences fall to under 50 per 100,000 in all countries able to estimate the RSV-attributed admissions (England age group 3-4 years being the exception with incidence 304.1). In older adults the attributed yearly incidence per 100,000 was relatively constant across countries, with England

having the highest incidences and Valencia having the lowest, ranging from approximately 100 in adults 65-74 years (Denmark: 110; England: 140; the Netherlands: 87; Finland: 53; Spain: 38.1), approximately 200 in persons 75-84 years (Denmark: 210; England: 430; the Netherlands: 220; Finland: 160; Spain: 140), and approximately 500 in persons 85+ years (Denmark: 590; England: 1100; Finland: 490; the Netherlands: 480; Spain: 270) (Tables 1-5).

RSV-attributed hospitalisations during the pandemic

In all the participating countries, except Valencia, where the data analysis was ended at the beginning of the pandemic, the RSV-attributable admissions to hospitals were close to 0 in the first pandemic year, from March 2020 to March 2021 (Figures 2-6). In the second pandemic year, RTI hospital admissions were again attributed to RSV from the middle of 2021 in all countries, but not in all age groups. In the Netherlands, there were no recurrences of RSV-attributable cases in age groups 3-4 years, 5-17 years, and 18-64 years (Figure 2). The pre-pandemic pattern of epidemic peaks followed by periods of few to no admissions was re-established after 2021 in Denmark, Finland, and to some extent in the Netherlands and England. In the Netherlands, RSV attributions show a twin-peaked season in 2021-2022 for age groups 0-2 months, 3-5 months, 6-11 months, 1-2 years, 64-74 years, 75-84 years, and 85+ years. In England the RSV-attributable admissions took on another form after the pandemic, with one broad epidemic curve in 2021, followed by a double-peaked curve in 2022 (Figure 5).

The Netherlands

Table 1: RSV-coded admissions, attributed RSV admissions, proportion of attributed per coded RSV and RTI, and attributed RSV incidence per 100,000 population age group per year in the Netherlands

Age group	Coded RSV (number/ yr)	Attributed RSV (number/ yr)	Attributed per coded RSV	Attributed per coded RTI	Attributed RSV incidence (100,000/yr)
0-2m	1055.0	978.4	0.93	27%	2279.5
3-5m	415.1	496.1	1.20	26%	1155.8
6-11m	322.3	633.0	1.97	22%	737.4

1-2y	259.1	906.3	3.50	16%	258.2
3-4y	49.6	347.1	7.00	15%	3.3
5-17y	30.6	155.3	5.07	6.1%	43.1
18-64y	290.3	1474.6	5.08	6.2%	58.3
65-74y	256.7	1545.3	6.02	7.5%	87.3
75-84y	280.0	2122.1	7.58	8.8%	222.0
85+y	156.0	1702.0	10.91	12%	483.0

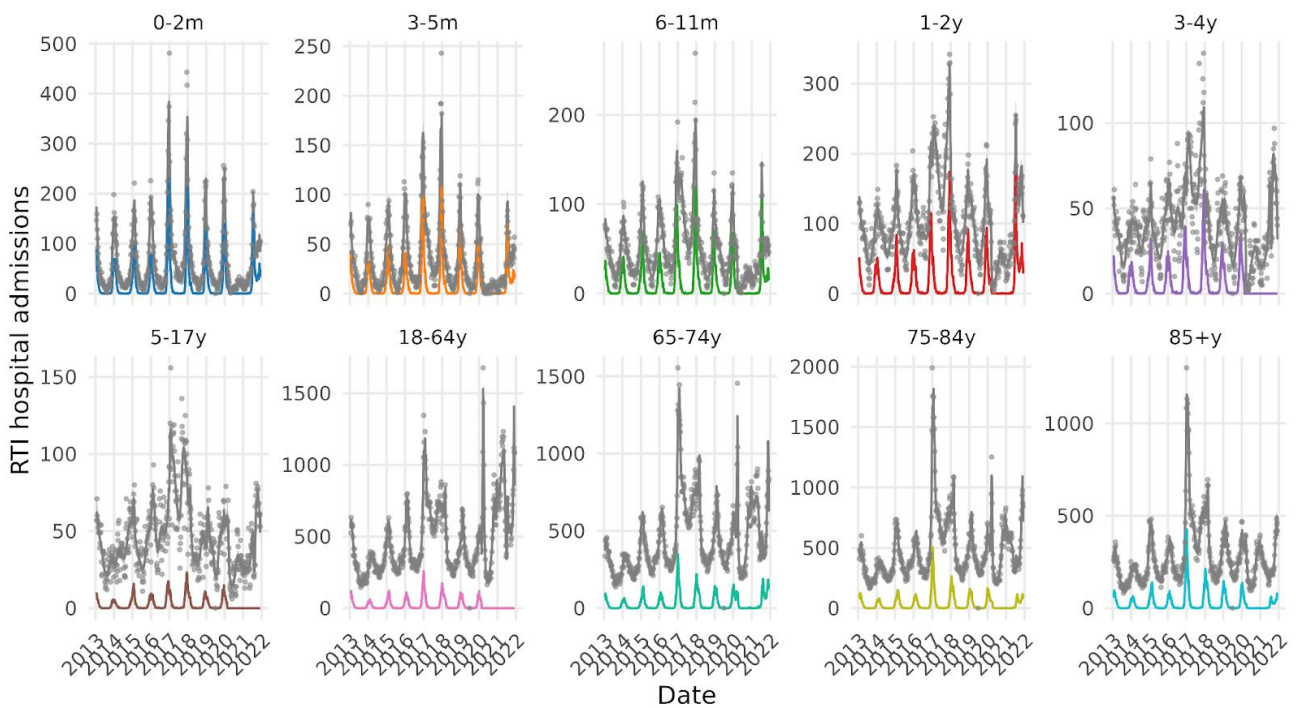


Figure 2: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in The Netherlands (2013-2021, 9 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

Denmark

Table 2: RSV-coded admissions, attributed RSV admissions, proportion of attributed per coded RSV and RTI, and attributed RSV incidence per 100,000 population age group per year

in Denmark

Age group	Coded RSV (Number/ yr)	Attributed RSV (number/ yr)	Attributed per coded RSV	Attributed per coded RTI	Attributed incidence (100,000 /yr)
0-2m	301	266	0.882	37%	1714.6
3-5m	276	298	1.08	33%	1926.7
6-11m	132	230	1.74	19%	741.8
1-2y	180	380	2.11	12%	310.0
3-4y	16	37	2.28	4%	30.3
5-17y	4	104	26.05	9%	12.2
18-64y	30	862	28.72	9%	24.6
65-74y	21	806	38.39	9%	125.6
75-84y	29	961	33.12	8%	252.9
85+y	15	730	48.64	8%	588.1

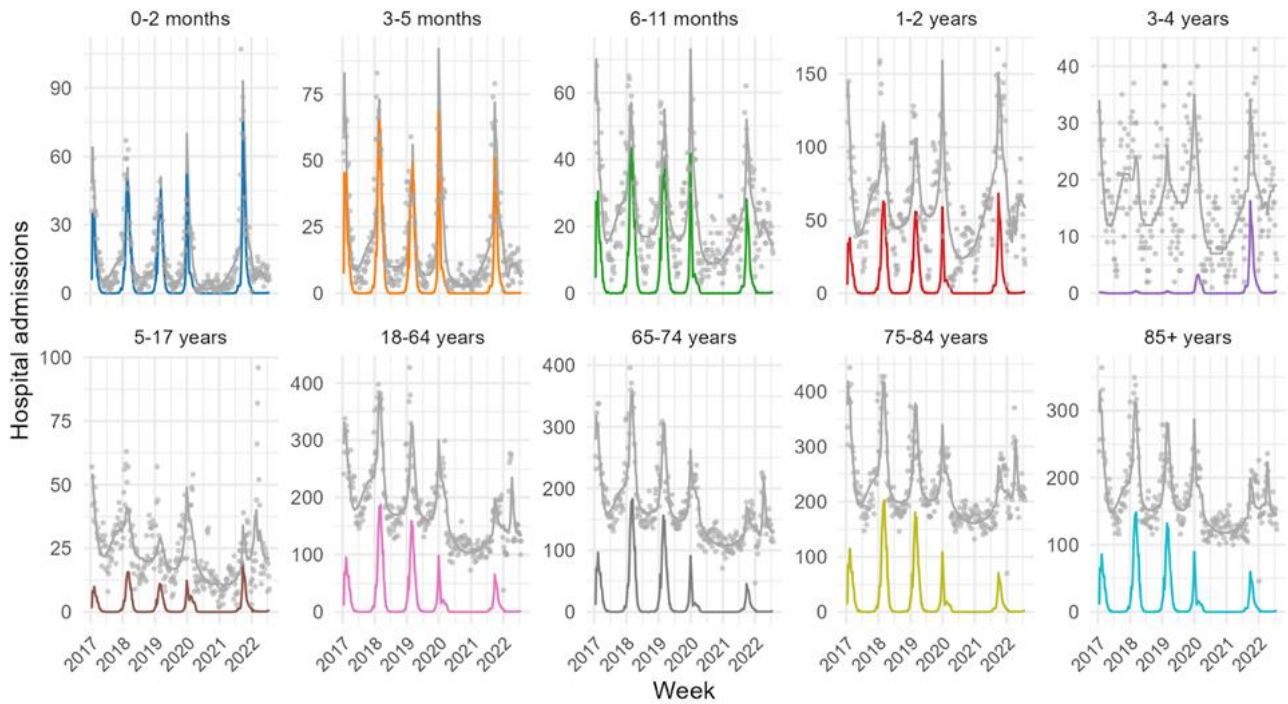


Figure 3: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV laboratory-confirmed in Denmark (201-2022, 6 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

Finland

Table 3: RSV-coded admissions, attributed RSV admissions, proportion of attributed per coded RSV and RTI, and attributed RSV incidence per 100,000 population per age group per year in Finland

Age group	Coded RSV (Number/ yr)	Attributed RSV (number/ yr)	Attributed per coded RSV	Attributed per coded RTI	Attributed incidence (100,000 /yr)
0-2m	588	268	0.53	22%	2124
3-5m	271	146	0.63	26%	1154
6-11m	176	76	0.51	10%	302

1-2y	259	255	1.14	10%	234
3-4y	71	0	NA	NA	0
5-17y	33	0	NA	NA	0
18-64y	171	0	NA	NA	0
65-74y	186	357	2.24	4%	53
75-84y	242	581	2.79	4%	162
85+y	247	711	3.37	6%	489

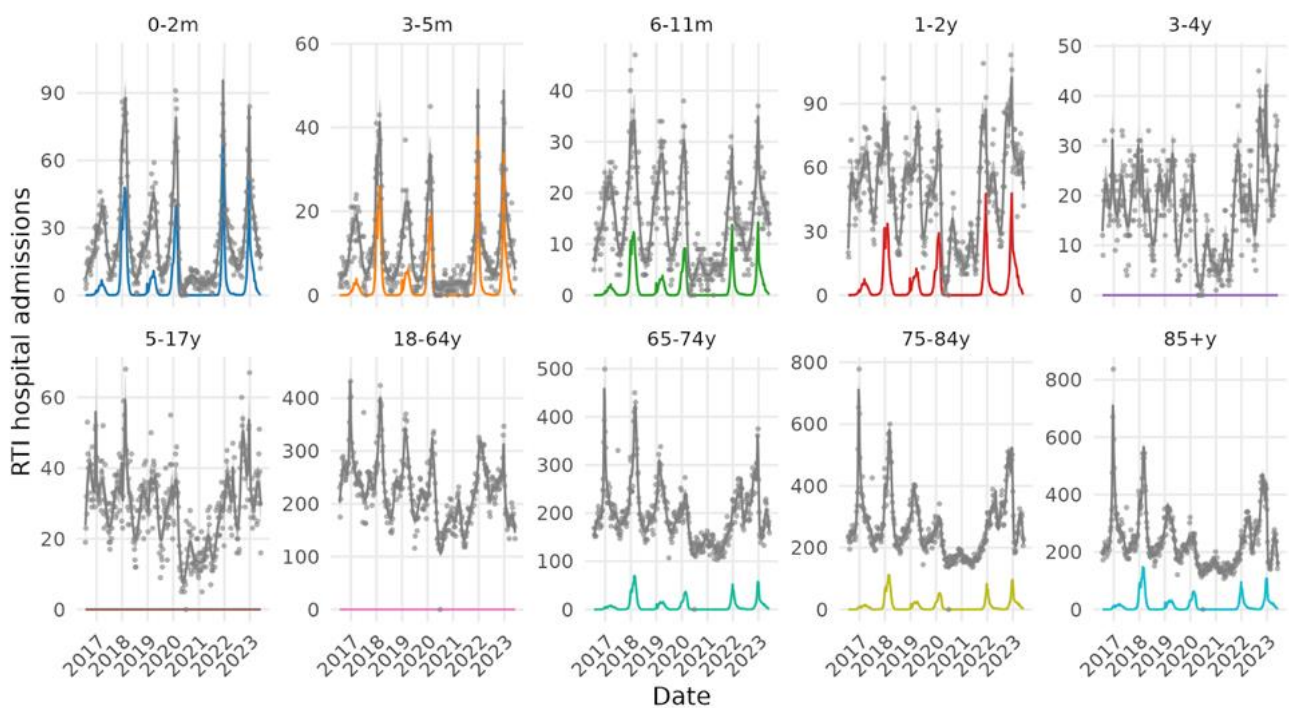


Figure 4: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in Finland (2017-2023, 7 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

England

Table 4: RSV-coded admissions, attributed RSV admissions, proportion of attributed per coded RSV and RTI, and attributed RSV incidence per 100,000 population per age group per year in England

Age group	Coded RSV (Number/ yr)	Attributed RSV (number/ yr)	Attributed per coded RSV	Attributed per coded RTI	Attributed incidence (100,000 /yr)
0-2m	1907.1	5 891.3	3.09	26%	3852.6
3-5m	962.6	3 779.2	3.93	24%	2471.4
6-11m	1158.0	5 195.9	4.49	18%	1698.9
1-2y	2178.4	10 355.4	4.75	17%	804.2
3-4y	553.4	4 068.9	7.35	16%	304.1
5-17y	334.8	3 677.1	10.98	10%	42.4
18-64y	947.0	19 308.1	20.39	8%	56.8
65-74y	617.8	7 940.6	12.85	6%	142.9
75-84y	857.2	14 463.7	16.87	8%	429.2
85+y	828.6	15 145.9	18.29	9%	1100.0

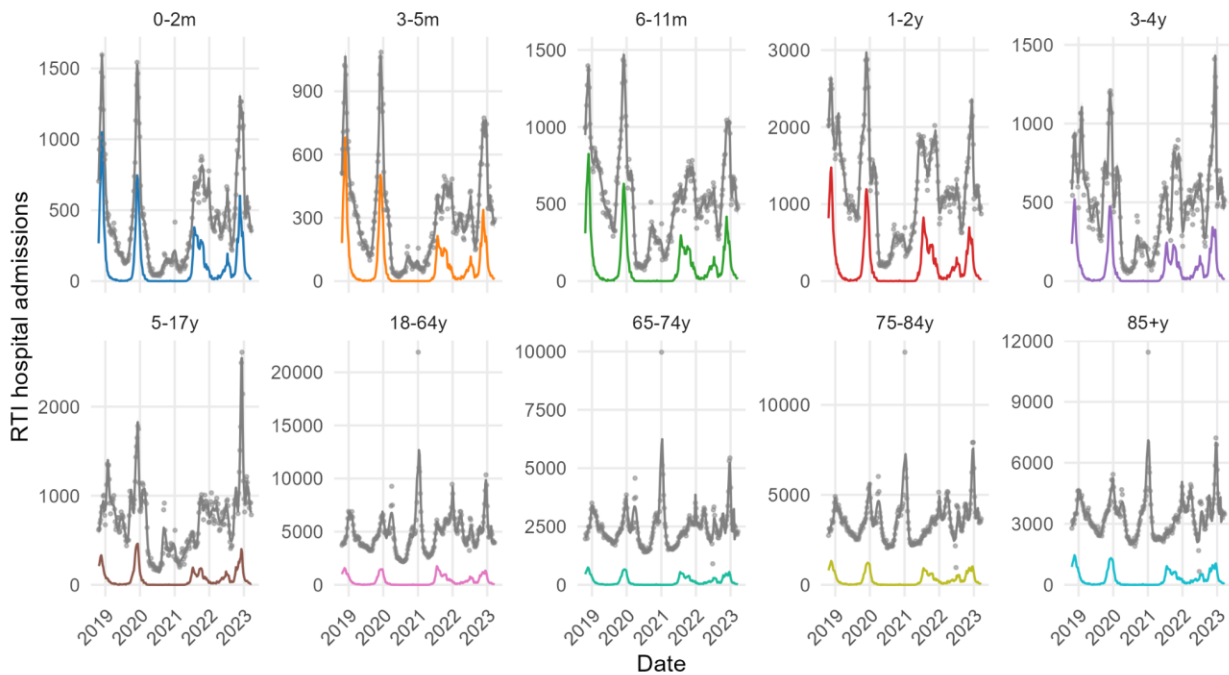


Figure 5: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in England (2017-2023, 7 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

Table 5: RSV lab-confirmed admissions, RSV-attributed ILI admissions, the proportion of attributed RSV admissions to RSV lab-confirmed admissions, the proportion of attributed RSV admissions to ILI admissions, and attributed RSV incidence per 100,000 population per age group per year in Spain-Valencia

Age group	RSV lab-confirmed (Number/yr)	Attributed RSV (Number/yr)	Attributed per RSV lab-confirmed admissions	Attributed per ILI admissions	Attributed incidence (100,000 /yr)
0-2m	74.5	49.6	66.6%	25.6%	2200.2
3-5m	40.8	28.1	68.8%	28.3%	1244.1

6-11m	27.2	11.2	41.2%	13.5%	248.8
1-2y	37.8	35.1	92.9%	16.9%	179.8
3-4y	6.2	NA	NA	NA	NA
5-17y	0.2	NA	NA	NA	NA
18-64y	15.2	73.1	479.2%	10.7%	10.5
65-74y	19	39.8	209.5%	7.1%	38.1
75-84y	34.5	91.1	264.1%	11.0%	135.3
85+y	29	79	272.5%	11.9%	268.3

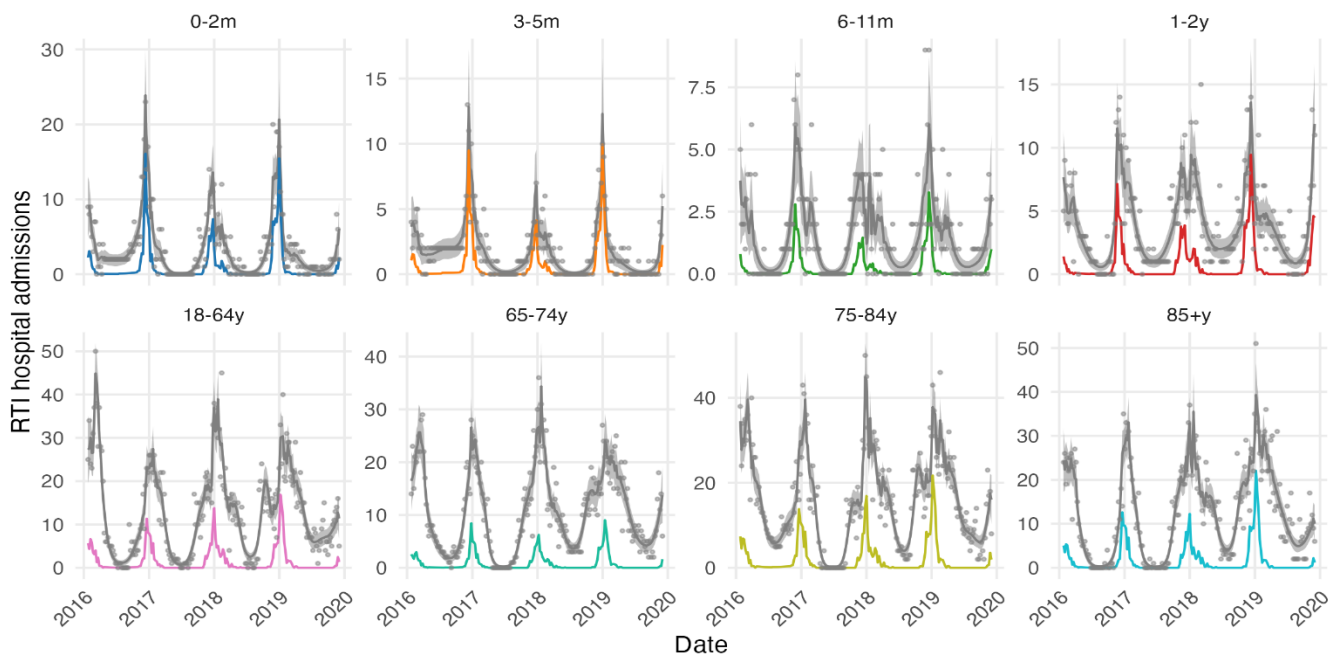


Figure 6: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in Spain (2016-2019, 4 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

3.3. Conceptual Framework

The transmission mechanisms of respiratory viruses are either via direct and/or indirect contact as illustrated in Figure 7. RSV and influenza spread through direct person-to-person contact and indirectly via contaminated intermediates (fomites) (Kutter et al., 2018). Under certain conditions, influenza could additionally spread through small aerosols. SARS-CoV-2 is primarily transmitted through close direct person-to-person contact and exposure to small respiratory particles at a short range; under favourable conditions transmission can occur over a longer distance. SARS-CoV-2 can be seeded into the environment by both infected symptomatic and asymptomatic individuals through sneezing, sweating, skin contact, etc. (Liu et al., 2020; Meyerowitz et al., 2021; van Doremalen et al., 2020). Fomite transmission of SARS-CoV-2 is a viable route for the spread of the virus and recent evidence suggests that the virus can remain on plastic and stainless steel for about 6 hours (Meyerowitz et al., 2021; Pastorino et al., 2020; van Doremalen et al., 2020) and can be isolated from various common surfaces including glass, paper, both polymer and paper banknotes, etc. about 72 hours after infection (Meyerowitz et al., 2021; van Doremalen et al., 2020). At 20°C, SARS-CoV-2 can still be isolated from these surfaces up to 28 days after infection (Riddell et al., 2020). These pieces of evidence support a possible fomite route of transmission of SARS-CoV-2 similar to RSV and influenza.

The effects of the transmission of SARS-CoV-2 can be classified into biological (viral interactions), ecological niches (environmental and geographical effects and adaptability of circulating variants of SARS-CoV-2), social (targeting reduction in social mixing), and health services-related effects (orange shape pathway of Figure 7). With the emergence of SARS-CoV-2, two main public health control and mitigation measures: NPIs (blue shape pathway of Figure 7) and COVID-19 vaccination (grey shape pathway of Figure 7) were introduced to curtail the spread of the virus and protect against severe forms of COVID-19. The introduction of NPIs leading to changes in community mixing and interaction, local and global connectivity, changes in personal hygiene, and adherence to preventive measures have had consequences on the transmission of other respiratory viruses, notably RSV and influenza (Williams et al., 2021) (green shape pathway of Figure 7). In addition to the implemented NPIs (Liu et al., 2021), the social and health services-related effects of SARS-CoV-2 transmission and the mass introduction of COVID-19 vaccines impacted the circulation and activities of other respiratory viruses, and it is suggested that RSV and other respiratory viruses may be directly or indirectly suppressed (Hsieh et al., 2020; Liu et al., 2021), whilst others co-circulate with SARS-CoV-2 (NIVEL, 2022), notably influenza virus in the winter months. Additionally, the

widespread public health vaccination campaigns during the pandemic may have essentially modified behaviour and attitudes toward vaccination not only for COVID-19 but also for other diseases. During the COVID-19 pandemic, we observed drastic reductions in RSV and other respiratory viruses as evidenced by low positivity rates and frequencies, no viral epidemics, and instances of delayed epidemics (Williams et al., 2021). The suppressive effects of SARS-CoV-2 on RSV and other respiratory viruses may have possibly led to a temporary change in the healthcare burden of RSV and other viruses.

Recent evidence suggested co-circulation of SARS-CoV-2 and other respiratory viruses. It is possible that RSV activity may begin (currently has begun in several countries) to increase as we transition to a post-COVID-19 pandemic era. Depending on the stringency, durations, and timing of COVID-19 NPIs, RSV significantly continued to remain low (Fourgeaud et al., 2021; Opek et al., 2021; Zheng et al., 2021); however, the dynamics in the post-COVID-19 pandemic period are potentially defining the RSV epidemiology and healthcare burden (seen in the green shape pathway of Figure 7). In the post-COVID-19 pandemic era, a re-emergence of RSV, modified disease presentation as a result of RSV-naïve children, and low maternal immunoglobulin levels likely influenced the RSV healthcare burden. This may have been determined by the amount of external seeding of RSV (Yeoh et al., 2021; Zheng et al., 2021) as well as the stringency, duration, and timing of the lifting and/or relaxation of restriction-based NPIs.

It was hypothesised that the culmination of the effects of SARS-CoV-2 transmission and public health control and mitigation measures would present a post-COVID-19 RSV healthcare burden that is different from the pre-COVID-19 pandemic burden with possible high rates of severe illnesses and modified long-term effects of RSV (Zheng et al., 2021).

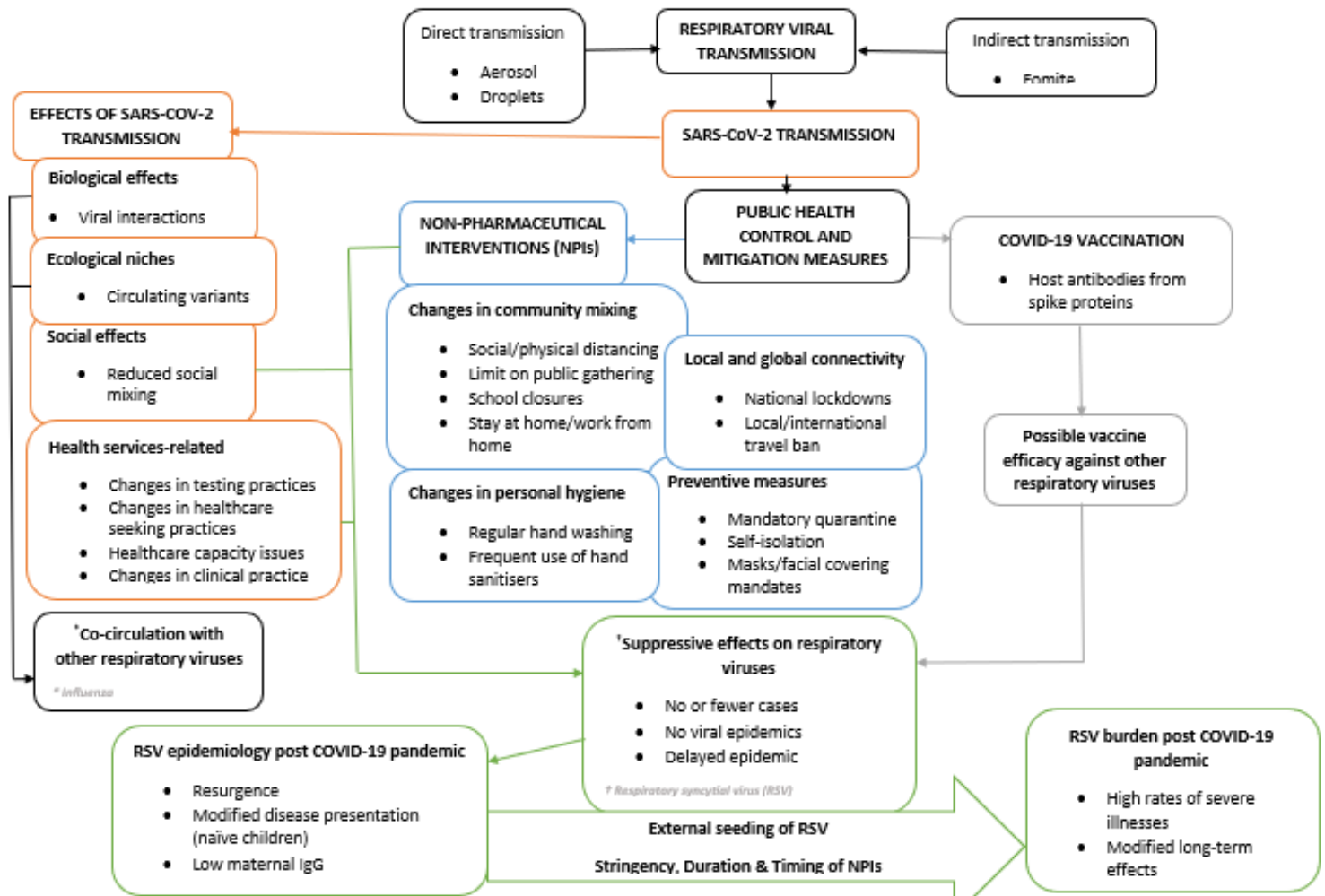


Figure 7: Conceptual framework of interaction between SARS-CoV-2 & RSV

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4. Discussion

The aim of the report was to evaluate the impact of SARS-CoV-2/COVID-19 and its associated control measures on RSV epidemiology. Firstly, a systematic review of the literature demonstrates that the role of NPIs in RSV epidemiological changes is complex and influenced by a range of factors. Cong *et al* (2024) observed significant declines in RSV incidence rates in their multi-country analysis, noting that the hospitalisation burden of RSV-associated acute LRTI in children younger than five years was significantly reduced during the first year of the pandemic (Cong *et al.*, 2024). During periods of NPI restrictions, shifts in health-seeking behaviour and reduced attention towards non-COVID-19 pathogens may have led to an underrepresentation of RSV cases, with fewer tests being administered and subsequently documented (Jun *et al.*, 2021). To contest this, Stamm *et al* reported a 5-fold increase in the number of tests performed for RSV between 2018/2019 and 2019/2020 and 2020/2021 (Stamm *et al.*, 2021). Considering the similar transmission dynamics of RSV and SARS-CoV-2 and the nature of NPIs enforcing reduced social contact, the implementation of COVID-19 control measures was likely directly correlated with the observed declines in RSV cases during the pandemic (Chuang *et al.*, 2023).

Notable absences of RSV seasonality throughout 2020 were found in this review, suggesting significant disruptions to RSV circulation during periods of NPI implementation. However, the included studies from China and Turkey reported opposing trends, observing limited changes to RSV seasonality in early-mid 2020, but this trend was reportedly impacted by the epidemic in Turkey. Upon closer analysis, the Chinese study conducted by Hu *et al* (2022) identified similar RSV surges in 2020 to that of 2019, reporting from a single tertiary centre in Hangzhou. However, previous studies that encompassed broader geographic regions in China opposed Hu *et al*'s findings, with Jiang *et al* (2023) reporting interruptions to typical RSV activity in 2020 (Jiang *et al.*, 2023). Hence, the limited population cohort of Hu *et al*'s study may reveal its inability to represent overall RSV trends across China, restricting its power in demonstrating limited RSV seasonal changes in 2020. Considering that China displayed one of the most aggressive control responses in early stages of the pandemic, it becomes clear that Hu *et al*'s study may not have captured the true extent of RSV activity outside of their tertiary centre (Cheng *et al.*, 2023).

Consistent with this review's findings, modelling studies suggest that the reopening of schools can substantially increase the risk of RSV rebound (Li *et al.*, 2022b). School-age children play an important role in RSV spread as they represent a core-group for RSV transmission, particularly as

they can transmit RSV to younger siblings (Munywoki *et al.*, 2014). Therefore, in circumstances where schools are closed, a main RSV transmission route is blocked, likely contributing to reductions in RSV activity.

Masks act as a vital barrier between infected respiratory droplets and susceptible individuals (Rahman *et al.*, 2022). However, the World Health Organisation (WHO) did not recommend masking in children under the age of 6 years old during the pandemic. In accordance with these guidelines no European country enforced this mandate in that age group (Høeg *et al.*, 2023). Considering that young children represent the main transmitters of RSV, the lack of mask-mandate policies may have prevented an association between this PHM and decreases in RSV activity.

PHMs that focused on travel restrictions during the pandemic restricted RSV spread across the population, resulting in observed decreases in RSV activity. However, RSV is primarily transmitted through direct close contact within communities rather than long-distance travel (Kaler *et al.*, 2023). Therefore, local transmission dynamics may have had a more integral role in RSV suppression, revealing a potential lack of clear causation between international travel restrictions and RSV activity.

This report revealed negative correlations between SI and RSV positivity rates during the pandemic, indicating that regions which implemented stricter NPIs observed lower RSV activity. While the SI provides comprehensive measures of pandemic restrictions, its accuracy may be influenced by discrepancies in NPI reporting. Heemskerk *et al.* (2024) compared different NPI databases, evaluating that both the OxCGRT as well as the European Centre for Disease Prevention and Control and the Joint Research Centre of the European Commission Response Measures Database (ECDC-JRC RMD) displayed a range of discrepancies, revealing inaccuracies and potential biases in their NPI reporting (Heemskerk *et al.*, 2024).

The lifting of NPIs allowed for the resumption of RSV transmission chains, enabling RSV to resurface as a prominent pathogen within the population. Interestingly, this review reported that the US saw significantly higher RSV rates in 2022 than expected in comparison to pre-pandemic years, suggesting a more active RSV activity following the pandemic. This was consistent with findings from Germany which reported significantly higher proportions of RSV cases during the 2022/2023 season compared with pre-pandemic RSV seasons (Cai *et al.*, 2024).

During 2020, when there were reduced RSV cases compared to pre-pandemic years, there was a build-up of susceptible individuals, particularly in infants who had not been previously exposed to RSV (Baraldi *et al.*, 2022). Consequently, when NPIs began to be lifted, such individuals may have displayed a heightened vulnerability to infection, contributing to greater severe case presentation post-pandemic.

Passively acquired maternal antibodies can enter the foetal bloodstream, acting as a protective shield against pathogens upon birth (Niewiesk, 2014). The near-zero incidence of RSV during the pandemic resulted in limited immune stimulation of the population to RSV, limiting the levels of antibodies that could be passed *in utero*, resulting in a deficit of passively transferred RSV-specific antibodies in infants in 2021. This deficit could be linked to the concept of 'immunity debt' which refers to circumstances in which there is reduced exposure of the population to pathogens, contributing to an expanded 'naïve' population (Cohen *et al.*, 2023). This decline in passively acquired RSV antibodies, coupled with reductions in RSV exposure during periods of NPI implementation, could be contributing to older children, who had not been previously exposed to RSV during infancy, presenting with more severe RSV illness once NPIs were lifted. Cohen *et al.* (2023) supported this, reporting that the lack of pathogen exposure during the pandemic could decrease children's adaptative immunity, resulting in increased RSV severity following NPI relaxation (Cohen *et al.*, 2023).

Conversely, some experts have argued that the increased RSV severity post-pandemic may be attributed to the increased use of RT-PCR as a reference diagnostic method instead of previous viral culture methods, which are less sensitive (Onwuchekwa *et al.*, 2023). Recent studies have reported an increase in RT-PCR tests for respiratory virus detections during the COVID-19 pandemic in comparison to pre-pandemic years noting an increase of around 220 tests within their single-centre analysis (Nairz *et al.*, 2023; (Petros *et al.*, 2024)). Therefore, changes in diagnostic methods may have increased RSV detection, contesting the notion that more people became infected post-pandemic.

Returns to pre-pandemic seasonality were observed in a number of countries in 2022. However, China exhibited a differing trend post-pandemic, with an atypical spring surge in 2023. Despite the initial success of aggressive control measure implementation, China remained one of the last countries to lift all of their COVID-19 control measures, only having downgraded its travel restrictions at the start of January 2023 (British Council, 2023). This suggests an opening of

opportunities for reintroduction of RSV into the local population, contributing to an atypical surge particularly if these strains were genetically distinct from locally circulating strains.

Moving forward, public health authorities should focus on enhancing the interpretability of existing surveillance systems for various respiratory viruses. By consolidating data streams from various surveillance networks, a unified platform for monitoring multi-virus dynamics can be created. This integrated approach could facilitate a more comprehensive analysis of respiratory virus trends, enabling early detection of activity changes. However, restrictions to this recommendation are clear, particularly in low- and middle-income countries (LMICs), which have a considerable burden of RSV-attributed deaths (Torres-Fernandez & Bassat, 2024). Optimising surveillance systems requires significant investments in infrastructure and technology, proving difficult in resource-constrained settings or during periods of economic uncertainty. Therefore, fostering global cooperation will be imperative to overcome these resource constraints by providing financial resources and backing. The foundations of these investments should be set as soon as possible to strengthen responses ahead of future global health threats.

In 2022, nirsevimab, a monoclonal antibody, became available for the prevention of RSV in infants in Europe and as of autumn 2023, RSV vaccines became available, representing a revolutionary development in RSV therapeutics (Martín-Torres *et al.*, 2023b). Spain was among the first European countries to introduce nirsevimab into its national immunisation programs with early reports suggesting declines in RSV-related admissions since their rollout (Martín-Torres *et al.*, 2023a; López-Lacort *et al.*, 2024). To maximise public health impact, efforts are needed to streamline the regulatory processes around these vaccines for use worldwide. On a more local level, comprehensive education should be given to paediatricians and healthcare providers about the importance of RSV vaccination and how it could be key to closing the observed ‘immune gap’ that emerged during the pandemic (Cohen *et al.*, 2022).

Our time series analyses have provided data on the age-specific rates of RSV-coded hospital admissions in five European countries, spanning the full North-South axis and including both the pandemic and pre-pandemic periods. The analyses have also yielded quantitative estimates of the rates of age-specific RSV-attributed RTI hospital admissions in these five countries. Rates of RSV hospital admissions were invariably much higher in infants and young children than in other age groups. However, RSV hospital admissions were also observed in other age groups and increased with increasing age in older age groups. This was true for the RSV-coded hospital admissions as

well as for the RSV-attributed RTI admissions and was observed in all countries included in the analyses. In these older age groups, we observed considerable differences between the number of RSV-coded infections and RSV-attributed infections, with the latter consistently being multiple times higher than the former. This is of considerable interest given the current discussion on vaccination in older adults and calls for a closer investigation into the causes of RTI hospital admissions in older adults to uncover the true burden of disease caused by RSV. These findings align with the evidence from the literature where patients presenting with RSV disease during and immediately after the COVID-19 pandemic were generally in the younger populations. Though the lowest attribution was seen in the adult population compared to the infant population, in the older adult populations, we found the highest RSV attribution in adults aged 85+ years in all countries when looking at incidences.

There are limitations in the time series analysis which need to be highlighted. As RTIs can be caused by a broad variety of pathogens, we assumed a smoothly varying background rate at which RTIs are generated by pathogens not included in the virological data, modelled with penalised splines. In this manner, sudden peaks in RTI admissions that co-occur with peaks in virological positives could be ascribed to the pathogens included as covariates. This could have caused both over- or under-attribution of RTI admissions to RSV. A main cause for over-attribution could be the widespread circulation of pathogens not included as covariates in the analyses, and that peaked at the same time in the year when the RSV epidemic peaked. These pathogens include human metapneumovirus (hMPV), parainfluenza virus, and rhinovirus, and some RSV cases could have been captured by the background rates. Other potential issues include regression coefficients time independence (reporting of cases and pathogen evolution) and viral interference between respiratory pathogens. In Spain-Valencia, the study was restricted to ILI cases, which underestimated the real number of cases; however, RSV cases can be reliably estimated because of the availability and use of RT-PCR results and not RSV codes for the analysis. Not all weeks were available throughout the whole year, and some of the data is imputed (we imputed data from 58 weeks from a total of 208 weeks, ~28% of the weeks). As the number of RSV and influenza cases outside the active surveillance period is negligible, the imputation is most likely not affecting the laboratory estimates. However, for the number of ILI hospitalisations, errors in the estimations are possible in the missing weeks. It is striking that in Valencia, the attributed RSV hospitalisations in children are lower compared to the RSV-confirmed hospitalisations. This shows that the time series model has some important limitations in the attributed hospitalisations in young children as described above. Sensitivity analyses are planned to be incorporated in the final analyses by each

partner country to address the potential limitations.

5. Conclusion and next steps

The systematic review has provided valuable insights into the impact of the COVID-19 pandemic on RSV epidemiology. NPIs evidently play integral roles in curbing transmission rates, highlighting them to be essential PHMs during global health emergencies. However, their individual role in observed RSV epidemiological changes during the COVID-19 pandemic is complex. The findings of this report have demonstrated that the timing and intensity of NPIs have a large impact on RSV, impacting both RSV seasonality and population susceptibility. Moving forward, Immunological studies are required to uncover the exact mechanisms behind 'immunity debt' concepts and to unravel their significance within observed RSV activity, ultimately aiding in the prediction of RSV epidemiological trends that extend beyond 2024. With various RSV immunisation approaches now available, it will be essential to gain approval for their use in a wider range of countries to counteract epidemiological changes provided by the pandemic. Until then, it will be integral to continue monitoring RSV activity to ensure early detection, inform public health strategies, and optimise resource allocations, ultimately acting to safeguard vulnerable populations and reduce RSV-associated morbidity and mortality worldwide.

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ANNEXES

ANNEX I

Table 1: Search strategies for selected databases.

This table illustrates the search terms applied to each database and the number of studies that were retrieved from each database.


Databases	Search Strategy	Results
MEDLINE	<ol style="list-style-type: none"> 1. *Respiratory Syncytial Viruses/ or *Respiratory Syncytial Virus Infections/ or respiratory syncytial.mp or *Respiratory Syncytial Virus, Human/ 2. Coronavirus.mp. or SARS-CoV-2/or COVID-19/or exp Coronavirus / 3. 1 and 2 4. Disease burden.mp. 5. Healthcare burden.mp. 6. 4 or 5 7. Spread.mp 8. Infection.mp. or exp Infections/or exp co-infection/ 9. Interaction.mp 10. Transmission.mp 11. 7 or 8 or 9 or 10 12. (Non-pharmaceutical or NPI).mp. 13. Prevent*/ or control/or exp measures/ 14. Vaccinations.mp or exp Vaccines/or exp Vaccine/or exp pharmaceutical/ 15. 12 or 13 or 14 16. Immunological.mp 17. Immunity.mp 18. 16 or 17 19. ep.fs. 	1280 studies

	20. 6 or 11 or 15 or 18 21. 3 and 20 22. Limit 21 to humans	
Embase	1. Respiratory syncytial virus.mp. or exp Human respiratory syncytial virus/ or exp Respiratory syncytial pneumovirus/ 2. Coronavirus.mp. or SARS-CoV-2/or COVID-19/or exp Coronavirus/ 3. 1 and 2 4. Disease burden.mp. 5. Healthcare burden.mp. 6. 4 or 5 7. transmission.mp 8. spread.mp 9. Infection.mp. or exp Infections/or exp co-infection/ 10. Interaction.mp 11. 7 or 8 or 9 or 10 12. (Non-pharmaceutical or NPI).mp. 13. Prevent*/ or control/or exp measures/ 14. Vaccinations.mp or exp Vaccines/or exp Vaccine/or exp pharmaceutical/ 15. 12 or 13 or 14 16. Immunological.mp 17. Immunity.mp 18. 16 or 17 19. ep.fs. 20. 6 or 11 or 15 or 18 21. 3 and 20 22. Limit 21 to humans	3620 studies
Global Health	1. Respiratory syncytial.mp or Human respiratory syncytial virus.od. 2. Coronavirus.mp. or SARS-CoV-2/ or COVID-19/or exp Coronavirus / 3. 1 and 2	1246 studies

	<ol style="list-style-type: none"> 4. burden.mp. or respiratory diseases.sh. or exposure.sh. or disease incidence.sh. or disease prevalence.sh. or human diseases.sh. 5. healthcare burden.mp. 6. 4 or 5 7. Spread.mp 8. Infection.mp. or exp Infections/or exp co-infection/ 9. Interaction.mp 10. Transmission.mp 11. 7 or 8 or 9 or 10 12. (Non-pharmaceutical or NPI).mp 13. Prevent*/ or control/or exp measures/ 14. Vaccinations.mp or exp Vaccines/or exp Vaccine/or exp pharmaceutical 15. 12 or 13 or 14 16. Immunological.mp 17. Immunity.mp 18. 16 or 17 19. 6 or 11 or 15 or 18 20. 3 and 19 	
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ANNEX II.

Table 1: Description of published studies reporting RSV epidemiology changes before, during, and after the COVID-19 pandemic. This table displays the characteristics of each study (country, study design, population, and period) and the main findings these studies presented.

Source (Author/Year)	Study characteristics	Discussion	Main findings
<p>Hönemann <i>et al.</i>, 2023 ¹⁰³⁴³³⁹</p>	<p>Country Germany <small>–PROMISE – D1.7</small></p> <p>Population <18 and >18 years</p> <p>Period October 2017-September 2022</p> <p>Design Retrospective observational</p>	<p>Reports on RSV detection, seasonality, and subtypes between 2017-2022</p>	<p>Seasonality:  In 2017-2019, the majority of RSV cases were observed between week 41 (October) and week 22 (May). In 2018/2019, between weeks 47 (November) and week 22 (May). In 2019/2020, between week 45 (November) and week 14 (April). During all these pre-pandemic years, RSV peak was in February. In the 2021/2022 season, RSV cases were observed between week 27 (June) and week 9 (February) with a peak in week 40, representing an atypical seasonality compared to typical winter RSV seasons.</p> <p>RSV incidence: Reported overall RSV RT-PCR positivity. Brackets represent positivity rates for adults and paediatric patients, respectively. 2017/2018=6.4% (3.8% and 25.6%) 2018/2019=8.3% (6.8% and 30.7%) 2019/2020= 4.0% (3.8% and 27.7%) 2021/2022=11.5% (9.4% and 48.9%)</p> <p>RSV Subtypes: Reported a shift in dominant RSV subtypes during the study period. RSV-B was mainly seen in 2017/2018, however, all later seasons were mainly attributed to RSV-A.</p> <p>Age demographics: Compared to pre-pandemic seasons, significantly more paediatric cases were observed in 2021/2022</p> <p>2021/2022 88.9% (208/234) vs 11.1% (26/234) (p<0.001)</p>

			<p><u>2019/2020</u> 69.5% (89/128) vs 30.5% (39/128)</p> <p><u>2018/2019</u> 68.3% (151/221) vs 31.7% (70/221)</p>
Çağlar <i>et al.</i> , 2023	<p>Country Turkey</p> <p>Population <18 years</p> <p>Period April 2018- March 2023</p> <p>Design Retrospective observational</p>	<p>Reports on RSV incidence rates between 2018 and 2023. This study also reports on demographic changes between three pandemic groups such as age, sex, and comorbidities</p>	<p><u>RSV incidence</u> This study reported peak annual RSV cases as reported below with peak months shown in brackets:</p> <ul style="list-style-type: none"> • 2018/2019 = 102 (January) • 2019/2020 = 70 (January) • 2020/2021 = 0 (all) • 2021/2022 = 56 (November) • 2022/2023 = 133 (January) <p><u>Seasonality</u> Reported peaks of RSV cases in January in 2018/2019, 2019/2020, 2022/2023 periods. Peak in RSV cases was observed in November of 2021/2022.</p> <p><u>Demographics:</u> No statistically significant difference in age, sex, and comorbidities between the three pandemic groups. However, this study reported statistically significantly worse clinical outcomes in the post-COVID-19 group than the other two groups. ICU admission was higher (p=0.023), length of stay was longer (p=0.031), SpO2 was lower (p<0.001), and inhaled salbutamol requirement was higher (p<0.001).</p>

Pérez-López <i>et al.</i> , 2022)	<p>Country Qatar</p> <p>Population Not stated.</p> <p>Period March 2020 to December 2021</p> <p>Design Retrospective observational</p>	<p>Reports on RSV detection rate between July 2019 and January 2022 and investigates the correlation between NPI stringency index and RSV cases</p>	<p><u>RSV incidence</u></p> <p>RSV was detected in 0.7% of specimens in October-December 2020 compared to 21.2% in October-December 2019. In October-December 2021, RSV was detected in 22.3% of specimens.</p> <p>The likelihood of RSV related disease (RSVRD) decreased >78-fold in October 2020 compared to 2019. The likelihood of RSVRD decreased 2.5-fold in October 2021 compared to 2019.</p> <p><u>Age demographics:</u></p> <p>Median age of RSVRD patients did not vary.</p> <p><u>Stringency index (SI)</u></p> <p>Reported a strong negative correlation between RSV infections and stringency index. Also reported strong positive correlations between international visitors and RSV infections with the number of international visitors in October-December 2020 and 2021 declining by 96 and 47%, respectively.</p>
Wagatsuma <i>et al.</i> , 2021	<p>Country China</p> <p>Population All ages</p> <p>Period January 2014-December 2020</p> <p>Design Ecological time series analysis</p>	<p>Reports on RSV incidence January 2014 and November 2020. Also reports on NPI indicators and assesses their relationship with RSV cases.</p>	<p><u>RSV incidence</u></p> <p>The average monthly HRSV activity was relatively similar each year reporting;</p> <ul style="list-style-type: none"> • 3.69 cases in 2019 • 3.19 cases in 2018 • 3.68 cases in 2017 • 2.83 cases in 2016 • 3.18 cases in 2015

			<ul style="list-style-type: none"> • 2.66 cases in 2014 <p>In 2020 there was a sharp decline in incidence of 0.47 cases. The study reported that the average number of HRSV cases during January-December 2020 decreased by approximately 85% in comparison to the preceding 6 epidemiological years. (2014-2019). No major epidemic peaks of RSV were observed between January to May 2020 compared to previous years.</p> <p><u>NPI indicators</u></p> <p>International travel</p> <p>From 2014-2020, the monthly average number of domestic and international passenger arrivals were approx. 8.3 million and 1.7 million which significantly declined in 2020 as both number of domestic and international flights was low.</p>
Delestrain <i>et al.</i> , 2021	<p>Country France</p> <p>Population >2 years of age</p> <p>Period 2018-2021</p> <p>Design Retrospective observational</p>	<p>Reports on the timing of RSV epidemics, Percentage of RSV positive tests, and Incidence rates of bronchiolitis</p>	<p><u>RSV incidence</u></p> <p>At the end of March 2021, the percentage of RSV positive tests rose from 3% in week 4 to 11% in week 13. This was higher than what had been observed in week 13 in 2019 and 2020. During the peak week of 2021, 2436 acute bronchiolitis cases in children <2 years of age presented at ED (week 13), compared with 4943 case in the peak week of 2019–2020 (Week 52) and 5478 cases in the peak week of 2018–2019 (Week 51).</p> <p>In Week 15, RSV rates began to decline, and the endemic ended in Week 18 at the end of</p>

			the third lockdown. In Week 19, 3% of specimens were positive for RSV, similar to the two previous seasons which reported 2% (Week 10) in 2019–2020, and 3% (Week 9) in 2018–2019.
Fourgeaud <i>et al.</i> , 2021	<p>Country France</p> <p>Population Adult and paediatric patients. Specific ages not described.</p> <p>Period August 2018-April 2021</p> <p>Design Retrospective observational</p>	<p>Reports on RSV epidemic timing, age distributions of cases, and incidence rates. This study also gave epidemiological context.</p>	<p><u>Seasonality</u></p> <p>During the 2018/2019 and 2019/2020 outbreaks, more than 90% of RSV infections occurred between October and January, with the epidemic peak lying between the end of November and mid-December. This study reported that after the beginning of the March 2020 lockdown, no patient was admitted with community-acquired RSV-associated ALRI and that RSV cases had begun declining before the lockdown.</p> <p><u>Age demographics</u></p> <p>Compared to those admitted during the 2018/2019 and 2019/2020 outbreaks, during the 2020/2021 interseasonal epidemic patients were more frequently aged 6 to 11 months (25.8% vs 13.1%) ($p < 0.0001$) and less frequently were there infants aged less than 6 months being admitted (41.3% vs 56.6%) ($p < 0.0001$)</p>
Reyes-Dominguez <i>et al.</i> , 2021	<p>Country Spain</p> <p>Population Patients aged 0-14 years.</p> <p>Period January 2016-June 2021</p>	<p>Reports on correlation between the OxCGRT index and RSV and also reports on RSV incidence changes.</p>	<p><u>RSV incidence</u></p> <p>Diagnoses of acute bronchiolitis by RSV ranged from 6,743 to 8,608 in pre-pandemic years, before dropping to 2,489 in 2020.</p> <p><u>Stringency index correlation</u></p> <p>Reported an average index of 59.7 from March 2020 to June 2021. OxCGRT</p>

	Design Interrupted time series analysis.		implementation was associated with an immediate reduction in rate of visits to the PED (19.5 decrease). This implementation was also correlated with an initial reduction in diagnoses and admission rates for RSV acute bronchiolitis, but this only had a short-term effect.
Jiang <i>et al.</i> , 2022	<p>Country China</p> <p>Population Not explicitly stated.</p> <p>Period July 2017-December 2021</p> <p>Design Retrospective observational</p>	Reports on RSV incidence and RSV subtype	<p><u>RSV seasonality and incidence</u></p> <p>Reported peak month RSV positivity rates;</p> <ul style="list-style-type: none"> ○ 2017= 52% December peak ○ 2018=44% December peak ○ 2019=38% December peak ○ 2020=no peak ○ 2021=15% January peak <p><u>RSV seasonality</u></p> <p>From 2017-2019, endemic season started in October or November and ended in February or March, lasting for approximately 5-6 months. However, in 2020, RSV positive rates decreased from 31.93% in January 2020 to 4.39% in February 2020. Following this, monthly RSV positivity rates increased from 22.34% in December 2020 and 23.71% in January 2021 decreasing to 12.03% in February and 10.4% in March 2021. RSV positive rates increased again in April and May 2021, staying abnormally at 10% from June to September 2021, followed by a low RSV epidemic from October.</p>

<p>Lee <i>et al.</i>, 2023</p>	<p>Country Taiwan</p> <p>Population Hospitalised children (no specific ages stated)</p> <p>Period 2020-2022</p> <p>Design Prospective surveillance</p>	<p>Reports on RSV incidence in terms of case numbers between 2020 and 2022 and discusses demographic characteristics.</p>	<p><u>RSV incidence of hospitalised patients</u></p> <ul style="list-style-type: none"> • Peak of 53 cases in December 2020 • No RSV peak/no RSV cases in 2021 • RSV peak cases of 58 in October 2022 <p>This study highlighted these peaks in line with implemented NPIs, recognising that the paucity observed in 2021 is linked to the return of intense NPIs (lockdown). Following, in line with easing of NPIs, saw an RSV resurgence in September 2022 and peaking in October.</p> <p><u>Demographic characteristics</u></p> <p>Observed no statistically significant differences in most clinical parameters.</p>
<p>Yeoh <i>et al.</i>, 2020</p>	<p>Country Australia</p> <p>Population <16 years old</p> <p>Period January 2012- August 2020</p> <p>Design Retrospective observational</p>	<p>Reports on RSV incidence rate.</p>	<p><u>RSV incidence rate</u></p> <p>Annual number of RSV cases ranged from 527 to 707 (mean of 629) during 2012-2019. For the first 13 weeks of 2020, RSV detections were comparable to averages from previous seasons. Following COVID-19 preventive measure implementation, RSV activity declined and stayed low even despite the relaxation of local COVID-19 restrictions. RSV detections in 2020 were 98.0% lower than average detections from week 14 to week 35 in pre-pandemic years.</p> <p><u>Seasonality</u></p> <p>In pre-pandemic years, the average RSV cases peaked at around 44 cases in week 28</p>

			of the year (July), whereas in 2020, peak RSV cases of 7 were observed in week 10 (March).
Bardsley <i>et al.</i> , 2023	<p>Country England</p> <p>Population <5 years of age</p> <p>Period December 2014 to March 2022</p> <p>Design Retrospective observational</p>	Reports on RSV incidence and RSV positivity rate.	<p><u>RSV incidence</u></p> <ul style="list-style-type: none"> • 2015-2016 = 1000 cases (week 51) • 2016-2017= 800 cases (week 49) • 2017-2018 = 900 cases (week 48) • 2018-2019 = 1050 cases (week 49) • 2019-2020 = 1350 cases (week 2 of 2020) • 2020-2021 = 150 cases (week 25 of 2021) • 2021-2022 = 1175 cases (week 32 of 2021) <p><u>RSV test positivity (%) - peak week</u></p> <ul style="list-style-type: none"> • 2015-2016= 52% (week 51) • 2016-2017 = 54% (week 47) • 2017-2018= 40% (week 47) • 2018-2019= 47% (week 49) • 2019-2020 = 38% (week 51) • 2020-2021= 5% (week 25 of 2021) • 2021-2022= 28% (week 31 of 2021) <p><u>Seasonality</u></p> <p>RSV case peaks were observed between weeks 47 and 50 with a mean of 8697 cases reported in each winter season. No winter peak was observed in 2020-2021. This study reported seeing an atypical peak in summer 2021 with 12150 cases reported during weeks 11-39 compared to the predicted 895 cases, constituting a 1258.3% increase. This was followed by a missing winter peak in</p>

			2021/2022, a change of 26.9% from predicted values. This study also reported no observed seasonal increase in winter 2020/2021, representing a 99.6% reduction in test positivity. In 2021/2022, test positivity was 527.3% higher than expected declining throughout the year until no epidemic activity was observed in winter 2021/2022.
Hu <i>et al.</i> , 2023	<p>Country China</p> <p>Population 0-18 years</p> <p>Period January 2019 to June 2023</p> <p>Design Retrospective observational</p>	Reports on RSV seasonal changes in RSV infection rates, and correlations between age and RSV positivity rates.	<p><u>Seasonality</u></p> <p>In 2019, RSV positive rates decreased to low levels since April and started to rise in November with typical winter peaks (December/January). Trend of RSV positivity in 2020 was similar to that in 2019, however there were slightly higher rates in 2020 from October-December compared to 2019. In 2021, RSV positivity increased sharply since July with a peak in October. 2022 saw increases from July with peaks in December. 2023 saw out-of-season outbreaks of RSV in spring, with peaks in May (significantly higher than previous years).</p> <p><u>Age demographics</u></p> <p>Among children under 12 months old, RSV positivity rates were high in all phases of the pandemic, with cases being particularly high during winter seasons. However, in phase III (After December 19, 2022), an atypical observation was seen observing the highest RSV positivity rate in those 1-3 years old during the summer months.</p>
Saravanos <i>et al.</i> , 2022	Country Australia	Reports on seasonality and	<p><u>Seasonality</u></p> <p>From 2015-2019, there was peak of</p>

	<p>Population <16 years old</p> <p>Period January 2014-December 2020</p> <p>Design Retrospective multicentre analysis</p>	<p>hospitalisations.</p>	<p>infections occurring during autumn and winter, and in 2020, peak of infections occurred in early summer (December)</p> <p><u>Age demographics</u></p> <p>Observed an increase in frequency of infections in children aged 2 to 4 years compared with the expected value based on observed numbers in previous years (83.91% vs 34.21%, p<.01). Median age of children with an RSV infection in 2020 was higher in 2020 than previous years (14 vs 7 months). RSV test percent positivity was higher for children aged 2-4 years and lower for all other age groups compared with previous years.</p> <p><u>Hospitalisations/ age demographics</u></p> <p>An overall decrease in hospitalisations was observed in 2020 compared with the expected value (decrease of 31.8%) increase in peak hospitalisations was mainly seen in 2- to 4-year-olds. Hospitalisation frequency for age groups 12 months to 5 years fell within expected ranges for 2015-2019 trends. However, in children aged 0-5 months, 6-11 months, and 5-15 years, the frequency of hospitalisations in 2020 compared with the expected value decreased. Median age of hospitalisations was higher in 2020 than previous years. This study also reported a decrease in frequency of ICU admissions in</p>
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			2020 compared with the expected values (decrease of 44.63%)
Eden <i>et al.</i> , 2022	<p>Country Australia</p> <p>Population Not explicitly stated.</p> <p>Period January 2017- March 2021</p> <p>Design Retrospective observational</p>	Reports on RSV incidence, and seasonality across 3 different Australian Territories.	<p><u>RSV incidence</u></p> <p>Reported as % positive per month. Numbers in brackets represent the 2017-2019 mean positivity for that month.</p> <p>New South Wales</p> <ul style="list-style-type: none"> • April- August 2020- 0% (8%) • September 2020- 1% (5%) • October 2020 – 6% (3%) • November 2020- 20% (2%) • December 2020- 17% (0%) • January 2021- 20% (0%) • February 2021- 5% (4%) • March 2021- 4% (4%) • April 2021- 3% (8%) <p>Western Australia</p> <ul style="list-style-type: none"> • April-September 2020- 0 (8-18%) • October 2020 – 1% (5%) • November 2020- 6% (4%) • December 2020- 15% (3%) • January 2021- 35% (1%) • February 2021- 20% (1%) • March 2021- 15% (1%) • April 2021- 11% (4%) <p>Victoria</p> <ul style="list-style-type: none"> • April 2020- 7% (10%) • May 2020- 4% (18%) • June 2020- 8% (28%) • July 2020- 3% (28%) • August 2020- 1% (15%) • September-December 2020- 0% (4-

			10%) <ul style="list-style-type: none"> • January 2021- 10% (5%) • February 2021- 21% (8%) • March 2021- 43% (7%) • April 2021- 40% (8%)
Wang <i>et al.</i> , 2023	<p>Country United states</p> <p>Population Ages 0-5 years</p> <p>Period January 2010- January 2023</p> <p>Design Retrospective cohort</p>	Reports on RSV seasonality and incidence.	<p><u>Seasonality</u></p> <p><u>0-5-year old-cohort</u></p> <p>From 2010 to 2019, monthly incidence rate of medically attended RSV infection followed a consistent seasonal pattern with RSV cases rising from between September-November, typically peaking in December-January, before dropping from February-April. However, in 2020, this seasonality changed with this study reporting the seasonal variation of RSV cases disappeared, reporting a 97.4% decrease in RSV cases during the December peak in 2020 compared to pre-pandemic averages. However, in 2021, seasonality returned but earlier than expected in August. In 2022 and 2023, seasonal pattern returned to be similar to that of pre-pandemic years with a winter peak in November.</p> <p><u>0-1-year-old cohort</u></p> <p>This age group followed the same seasonal pattern as the 0–5-year cohort just at higher rates. This study reported that in 2022, incidence rate peaked at 3077 cases per 1,000,000 person-days in November which corresponded to a 96.4% increase from the expected December peak rate of 1569 cases</p>

			<p>per 1,000,000 person-days.</p> <p><u>RSV Incidence</u></p> <ul style="list-style-type: none"> ○ Incidence rate peaked in August 2021 with an incidence rate of 753 cases per 1,000,000 person-days corresponding with a relative decrease of 9.6% from the expected peak incidence rates. ○ In 2020, incidence rate was consistently low from April through to December ranging from 13-20 cases/1,000,000 person-days compared with an expected December peak incidence rate of 770 cases per 1,000,000 person-days from the pre-pandemic trend, ○ Incidence rates in December 2020 corresponded with a relative decrease of 97.4%. ○ In 2021, Incidence rate peaked in August of 753 cases per 1,000,000 person-days corresponding with a relative decrease of 9.6% from the expected peak incidence rates. ○ In 2022 and 2023, a winter peak in November at 2182 cases per 1,000,000 person-days, that was one month earlier and 143% higher than the expected December peak.
Billard <i>et al.</i> , 2022	Country South Africa, South Korea, France, Israel, Japan, Canada, Taiwan, Brazil, Chile, United	Reports on the correlation between OxCGRT stringency index	<p><u>RSV seasonality</u></p> <p>In tropical countries, RSV season was in rainy or humid periods, in temperate countries, RSV peaks were in winter</p>

	<p>States, the Netherlands</p> <p>Population Not explicitly stated.</p> <p>Period Week 12 2020-W44 2021</p> <p>Design Retrospective observational</p>	<p>and RSV trends. Also reports on changes in RSV seasonality and observed epidemic changes.</p>	<p>seasons. Upon pandemic onset, seasonality changed, with a reported average delay in onset of the first RSV epidemic of 39 weeks being reported over 10 countries, with an average peak delay of 28 weeks across 7 countries. South Africa which previously only saw one RSV peak experienced two peaks in 2020/2021.</p> <p><u>Stringency index and RSV association</u></p> <p>Most commonly downgraded NPIs were school closures, workplace closures, and stay at home requirements. This study reported that multiple NPIs were generally downgraded at the same time. The study reported that lower NPI levels were associated with higher difference between observed and expected RSV activity. Stringency index was negatively associated with the difference in RSV activity. Reported that a 10-point decrease in the stringency index was associated with an average absolute increase in the difference between observed and expected RSV positivity rate of 0.8%. School closures, stay-at-home requirements, and public transport closures were associated with the difference between observed and expected RSV positivity rates.</p>
<p>AlBahrani <i>et al.</i>, 2024</p>	<p>Country Saudi Arabia</p> <p>Population Hospitalised paediatric patients. Specific age group not explicitly stated.</p>	<p>Reports on RSV incidence and on age demographics.</p>	<p><u>RSV incidence</u></p> <p>Between January 2019 to December 2022, 18.7% of tested patients were positive for RSV.</p> <ul style="list-style-type: none"> - 35.6% tested positive in 2019 - 33.3% in 2020

	<p>Period January 2019-December 2022</p> <p>Design Retrospective mixed cross-sectional analysis</p>		<ul style="list-style-type: none"> - 18.5% in 2021 - 14% in 2022 <p>Reported significant declines in RSV cases during the period of 2020–2021, followed by a resurgence of RSV infections in October 2022 subsequent to the COVID-19 pandemic.</p> <p><u>Age demographics</u></p> <p>Over the study period there was an observed increase in the mean age of patients from 0.50 (+0.70) to 1.08 (+2.22) years, however, this finding was not statistically significant.</p>
Reicherz <i>et al.</i> , 2022	<p>Country Canada</p> <p>Population Women of childbearing age (18-51 years) and infants (4-12 months)</p> <p>Period April 2018-June 2021</p> <p>Design Retrospective observational</p>	<p>Reports on levels of Prefusion RSV F IgG levels before vs after the pandemic. They also looked at neutralising titres.</p>	<p><u>Women</u></p> <p>Prefusion RSV F IgG levels significantly decreased in women of childbearing age in the spring 2021 compared with the same individuals in 2020 ($148\,858 \pm 2.4$ vs 197806 ± 2.2 AU/ml, $p=.0232$). No statistical difference was observed when compared to age matched women in 2018 or 2019.</p> <p>RSV neutralising antibody titres were 12-fold lower in 2021 compared to women in 2020 (10.3 ± 2.0 vs 120.9 ± 2.9, $p<.0001$) and were lower compared to women in 2019 (28.7 ± 2.8, $P=.0026$) and 2018 (78.4 ± 2.9, $P<.0001$).</p> <p><u>Infants</u></p> <p>Prefusion RSV F IgG levels were approximately 15-fold lower in infants sampled in 2021 compared to those sampled</p>

			<p>in 2020 (4258 ± 8.8 vs 63530 ± 4.4. AU/ml, $p < .0001$).</p> <p>RSV neutralisation titres in infants in 2021 were 3.4-fold lower compared to infants in 2020 (6.7 ± 1.8 vs 22.8 ± 2.0, $P < .0001$). Both prefusion RSV F IgG levels and neutralising titres remained significantly lower in infants in 2021 compared to 2020</p>
Grobben <i>et al.</i> , 2022	<p>Country The Netherlands</p> <p>Population Lactating mothers. Ages not explicitly specified.</p> <p>Period April -November 2020</p> <p>Design Longitudinal observational</p>	<p>Reported on IgG and IgA levels in both human milk and serum before and after the pandemic. They also explored the effect of COVID-19 infection on IgG and IgA levels.</p>	<p>Reported significantly reduced IgG to RSV in human milk by a factor of 1.7 following the pandemic, however, this was not observed for IgA levels. In contrast, maternal serum antibodies increased during the pandemic by a factor of 1.7 ($p < 0.01$). Of mothers who had previously experienced COVID-19 infection, they had significantly higher milk IgG and IgA levels than mothers who had not had previous COVID-19 infection, with an increase of 1.7 for IgG ($p < 0.001$) and 4.3 for IgA ($p < 0.001$).</p>
Hartog <i>et al.</i> , 2022	<p>Country The Netherlands</p> <p>Population Ages 1 to 89 years</p> <p>Period June 2020-June 2021</p> <p>Design Prospective observational</p>	<p>Reports on RSV-specific antibody levels during the COVID-19 pandemic.</p>	<p>This study reported that post fusion F IgG antibody concentrations saw a decline from 2020 to 2021 ($p < 0.001$). This antibody decrease was found to be significant in all age groups except for the 31-40 years. Across all three time points, ages 71 years and older had higher antibody concentrations than participants aged 1-10 years ($p = 0.019$), 21-30 years ($p < 0.001$), 31-40 years ($p = 0.021$), 41-50 years ($p < 0.001$), and 51-60 years ($p = 0.034$). However, this study found no differences in decay rates between age</p>

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ANNEX III

Table 1: The available and imputed weeks in Spain-Valencia

Year	Active surveillance (Start-End)	Imputed weeks Start	Imputed weeks End	N weeks available	N weeks imputed
2016	2016-W01 to 2016-W17 & 2016-W45 to 2016-W52	2016-W18	2016-W44	25	27
2017	2017-W01 to 2017-W16 & 2017-W36 to 2017-W52	2017-W17	2017-W35	33	19
2018	2018-W01 to 2018-W26 & 2018-W36 to 2018-W52	2018-W27	2019-W35	43	9
2019	2019-W01 to 2019-W32 & 2019-W36 to 2019-W52	2019-W33	2019-W35	49	3