Estimates of effectiveness and impact of nirsevimab on hospitalisations for RSV bronchiolitis in metropolitan France, 2023-2024 : a modelling study

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Summary

Background

Respiratory Syncytial Virus (RSV) is a major cause of hospitalisations and deaths among infants worldwide. France was one of the first countries to administer nirsevimab, a single-dose long acting monoclonal antibody treatment to prevent lower respiratory tract infection caused by RSV. Effectiveness in real-world settings and impact in terms of hospitalisations averted are not well known.

Methods

We developed an age-structured deterministic model characterising RSV transmission as well as plausible scenarios for the administration of nirsevimab doses based on delivery data to maternity wards and pharmacies. We estimated nirsevimab effectiveness and the number of hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV) averted, by calibrating the model to hospital and virological surveillance data from mid-2017 to February 4, 2024, alongside serological data.

Findings

We estimated that nirsevimab administration prevented 5,800 (95% CI: 3,700-7,800) HBER-RSV, including 4,200 (2,900-5,600) among those aged 0-2 months, between September 15, 2023 and February 4, 2024. This corresponds to a 23% (16%-30%) reduction in the total number of HBER-RSV (35%, 25%-44%, among 0-2 months) compared to the scenario without administration. In our baseline scenario with 215,000 doses administered by January 31, 2024, the effectiveness of nirsevimab against HBER-RSV was estimated at 73% (61%-84%), which corresponds to 1 HBER-RSV case prevented for every 39 (26-54) doses administered. The estimated number of HBER-RSV averted was insensitive to the assumed administration scenario; but effectiveness varied slightly.

Interpretation

With 1 HBER-RSV averted for about every 40 children treated, our study highlights the relevance of nirsevimab administration to reduce RSV hospitalisations.

Funding

DURABLE, IBEID, INCEPTION.

Research in context

Evidence before this study

We searched on PubMed all articles published after January 1, 2023 estimating the impact of nirsevimab or its effectiveness in real-world settings with the following search terms: “(nirsevimab OR Beyfortus) AND (impact OR effectiveness)”. We found 25 publications associated with this query. We excluded off-topic studies, clinical trials measuring efficacy (not effectiveness in real-world settings), modelling studies that did not use data from after the start of a treatment campaign with nirsevimab. We found two relevant studies. López-Lacort et al. 2024 estimated the effectiveness of nirsevimab against lower respiratory tract infection with RSV in Spain to be 70% (38%–86%), using a test-negative design. Ernst et al. 2024 observed a reduction of 38% in RSV-related hospitalisations for children under 5 years compared to the previous season in Luxembourg.

Added value of this study

This study used a mathematical model to simulate the epidemiological dynamics of RSV across seven consecutive epidemic seasons. Incorporating data on nirsevimab delivery to maternal wards and community pharmacies during the French season in 2023-2024, we constructed plausible administration scenarios for the treatment. This approach enabled us to assess the effectiveness and population level impact of nirsevimab administration on hospitalisations for RSV bronchiolitis.

Implications of all the available evidence

All studies point to an important impact of nirsevimab on RSV hospitalisations. These studies inform the design of interventions to reduce the burden of RSV during future RSV seasons.

Introduction

Respiratory Syncytial Virus (RSV) is a major cause of lower respiratory tract infections (LRTI) in young children.[1] Globally, it led to between 2.9 and 4.6 million hospital admissions and 100,000 deaths among children under the age of 5 in 2019. The burden of this disease disproportionately affects low and middle income countries, where 97% of these deaths occur. However, even in high-income countries, RSV constitutes an important healthcare challenge.[2,3]

In France, RSV typically circulates in the winter months. The consequences of this widespread circulation are particularly observed in paediatric wards, which may necessitate substantial reorganisation to admit children requiring hospitalisation for bronchiolitis, a condition mostly induced by RSV.[4,5] Following the emergence of SARS-CoV-2, RSV epidemic and hospitalisations for bronchiolitis have been severely disrupted.[6,7]

In October 2022, the European Union granted approval for nirsevimab (Beyfortus®), a single-dose long-acting monoclonal antibody designed for neonates and infants to prevent RSV LRTI during their first year of exposure. In clinical studies, the efficacy against hospitalisation for RSV LRTI was estimated between 77% (49%-89%) and 83% (68%-92%).[9,10] A real-world study estimated the effectiveness against hospital admissions for RSV LRTI at 70% (38%-89%).[11] In September 2023, France was one of the first countries to organise a national immunisation campaign with this preventive treatment.[12] At the end of January 2024, about 232,000 doses had been delivered to maternity wards and community pharmacies. Given the limited availability of doses and high adherence to the treatment, priority was given to neonates in maternity wards.[13]

Here, we leveraged France's early delivery of nirsevimab to measure its impact on the dynamics of hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV). This was achieved by developing a mathematical model characterising French RSV epidemics calibrated to French hospitalisation, virological and serological data. This

modelling framework made it possible to estimate the effectiveness of nirsevimab administration against HBER-RSV, as well as the number of HBER-RSV averted.

Methods

Reconstruction of hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV)

The French syndromic surveillance network of emergency rooms (OSCOUR®[14]), coordinated by Santé publique France, records daily numbers of hospitalisations with bronchiolitis following emergency room visits (HBER) per age group. Annually, an increasing number of healthcare facilities contribute to OSCOUR®. To calculate the number of HBER in metropolitan France, we divided the number of HBER by an annual factor that is the product of the proportion of healthcare facilities and the number of emergency room visits coded in the system. Given that bronchiolitis only affects infants < 24 months, we excluded individuals aged 2 and over.[15]

The number of HBER related to RSV (HBER-RSV) is unknown. We reconstructed the weekly number of HBER-RSV by combining data from the syndromic hospital surveillance (OSCOUR®) and virological surveillance. The data on virologically confirmed RSV cases were obtained from the hospital virological surveillance network (RENAL), comprising volunteer hospital laboratories. This dataset lacks age stratification, and the subset of patients tested for RSV does not exclusively include those diagnosed with bronchiolitis.

We developed an age-specific indicator reflecting the weekly number of HBER-RSV for the following age groups: 0-2 months, 3-5 months, 6-8 months, 9-11 months, and 1 year. A key assumption underpinning the estimation of HBER-RSV was that for each season (from week 34 of one year to week 33 of the following year) and within each age group, the peak of HBER-RSV reached 90% of the peak incidence of HBER. We give a detailed derivation of the indicator in supplementary materials.

Serological data

Between February and August 2020, the SeroPed study, a cross-sectional serological survey, was carried out among 2,499 patients admitted to French hospitals for reasons other than COVID-19[16] with extensive sampling among children under 10 years of age (804 of 2,499). For this study 1,132 samples were available for serological testing, with 275 from children under 10 years of age. IgG antibody levels were measured using a bead-based multiplex serological assay, with technical details presented in supplementary materials. Patients under 1 year were excluded due to the potential confounding effect of rapidly declining maternal antibodies post-birth, which could bias seropositivity interpretations in this age group.

Nirsevimab dose administration scenarios

Nirsevimab administration in France officially started on September 15, 2023, with a focus on maternity wards. The daily number of nirsevimab doses delivered to maternity wards and community pharmacies is presented in Figure 1A, with a total of 232,000 doses delivered by January 31, 2024. Two types of single dose formulations of nirsevimab exist: 50 mg for infants weighing < 5 kg and 100mg for those weighing more. In maternity wards, 167,000 50 mg doses and 11,000 100mg doses were delivered. Community pharmacies received 54,000 100 mg doses. In January 2024, reports from a subset of 160 maternity wards indicated that their remaining stocks constituted only 4% of the 50 mg doses but 63% of the 100mg doses reflecting the typical weight of neonates in these settings. In community pharmacies data on their remaining stock was not available for 2024. Given the high uptake of the medication, we assumed that i) 6% of the doses allocated to pharmacies remained unused and that ii) stock levels were similar in maternity wards that did and did not report their stocks in January 2024. Under these assumptions, we estimated in our baseline scenario that approximately 215,000 doses (74% of 50 mg doses and 26% of 100 mg doses) of nirsevimab had been administered by the end of January 2024. We also explored

scenarios with 205,000 and 220,000 doses administered by 31 January 2024. We presumed that neonates received 50 mg doses at birth, while infants aged 0-2 months and 3-5 months each received 50% of the 100 mg doses, respectively, with a constant number of doses administered daily between September 15, 2023 and January 7, 2024. We assumed that the number of doses administered daily was twice lower between January 8 and 31, 2024 (i.e. after the intense epidemic period had passed) than between September 15, 2023 and January 7, 2024.

Transmission model

We adapted a deterministic compartmental model previously employed for describing the transmission dynamics of RSV[17–19] to assess the impact of nirsevimab administration. The model is structured in 7 age groups: 0-2 months, 3-5 months, 6-8 months, 9-11 months, 1 year old, 2 years, ≥ 3 years. It accounts for the ageing of individuals, with the rate of transition between age groups corresponding to the size of each age group. An age-dependent rate was implemented to account for both natural mortality and migrations.

We calculated the average number of daily contacts between age groups (Figure S1) using the contact matrix provided in Mistry et al.[20] for individuals ranging from 0 years old to those aged 84 and above. To determine the contacts in the age groups under 1 year old, we presumed that individuals within age groups 0-2 months, 3-5 months, 6-8 months, 9-11 months had the same number of contacts with other age groups. A detailed derivation is provided in supplementary materials.

The population was partitioned in compartments M, S, I and R (Figure S2). Neonates are initially placed into one of two compartments: a portion receives maternal immunity against RSV (M), which wanes after an average duration $1/\omega_M$, leading to their transition to the susceptible state (S). Neonates not receiving maternal immunity are directly classified as susceptible. Upon exposure to RSV, susceptible individuals become infectious (I) for an average duration $1/\gamma$, after which they move to the temporarily immune compartment (R).

Immunity lasts for an average duration of $1/\omega$, after which individuals revert to susceptibility. The model accounts for reduced susceptibility following sequential infections, with susceptibility multiplied by a factor λ_1 after the first infection and a factor $\lambda_2 \cdot \lambda_1$ after the second infection.

We hypothesised that the transmission rate varies seasonally (cosine function), with an additional effect during the summer holidays (from July 1 to August 31). During the COVID-19 period, we explicitly modelled the impact on the transmission rate of lockdowns, curfews, and periods when other protective measures (mask-wearing, physical distancing) were implemented. We also modelled potential changes in the transmission rate during the 2022-2023 and 2023-2024 seasons.

The probability of HBER-RSV during an RSV infection was parameterized as a decreasing exponential function with respect to age for the four distinct age categories within the first year of life, and by an independent parameter for the age group 1 year old. For individuals receiving nirsevimab treatment the relative risk of HBER-RSV during an RSV infection is multiplied by $1 - TE$, where TE is treatment effectiveness.

Model calibration

The model was initialised in January 1, 2005, with 1 infection per age group so that it could reach a steady state before being compared to the data. It was calibrated jointly on reconstructed weekly HBER-RSV data spanning from August 2017, to February 4, 2024 for the age group under 2 years old and serological data for the age groups older than 1 year old. The likelihood is expressed as:

$$\prod_{a=0-2\ months}^{1\ year} \prod_{t=t_1}^{t_f} Neg(HBER_{RSV}(t,a) \mid HBER_{RSV}^{model}(t,a)) \cdot \prod_{a=1\ year}^{\geq 3\ years} Binom(\ Pos(a)\ \mid N(a),\ p_{sero}^{model}(a)),$$

where $Neg(\cdot\ |x)$ is the negative binomial distribution of mean x and variance $x + x^{2-\kappa}$, where κ is being estimated, $Binom(\ \cdot\ |N,\ p)$ is the binomial distribution with parameter N and p. The terms $HBER_{RSV}(t,a)$ and $HBER_{RSV}^{model}(t,a)$ are respectively the reconstructed and modelled number of HBER-RSV during week t in age group a, t_1 is week 34 of 2017 and t_f week 5 of 2024. For age group a, $N(a)$ represents the total number of individuals screened for RSV seropositivity, while $Pos(a)$ denotes the count of those who tested positive in the data. Then, $p_{sero}^{model}(a)$ is the modelled proportion of individuals in age group a who either underwent at least one RSV infection or retained maternal immunity during the period from February 2020 to August 2020, coinciding with the timeframe of the serological study.

In a Bayesian framework, the posterior distribution of model parameters was explored by Markov Chain Monte Carlo sampling. A comprehensive breakdown of both fitted and fixed parameters, along with their corresponding priors, is provided in Table S1. In the results section, we give the mean and 95% credible interval (CI) of the posterior distribution of the parameters, using the highest posterior density interval method.

Estimating HBER-RSV averted due to nirsevimab

To estimate the number of HBER-RSV averted, we compared the number of HBER-RSV in the simulation scenario where nirsevimab is administered to the counterfactual scenario where it is not, sampling 1,000 epidemic trajectories for each scenario.

Sensitivity analysis

In a first sensitivity analysis, we hypothesised that the peak incidence of HBER-RSV equates to 100% (instead of 90%) of the HBER peak. We also explored the sensitivity to assumptions about immunity. Compared to our baseline scenario with medium duration of immunity (i.e. $1/\omega$=9 months of immunity following infection and $1/\omega_M$=2 months of maternal

immunity), we evaluated a scenario with short ($1/\omega$=6 months, $1/\omega_M$=1 month) and long ($1/\omega$=12 months, $1/\omega_M$=4 months) duration of immunity.

Implementation

All analyses were conducted using R software (version 4.3.2). The *odin* package was used to run the RSV dynamical models.

Role of the funding source

The funding source of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Dynamics of hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV)

The annual number of hospitalisations for bronchiolitis following emergency room visits (HBER) in children under 2 years old ranged from 37,700 (2017-2018) to 39,000 (2018-2019) in the pre-COVID period. Following the emergence of SARS-CoV-2, it decreased to 30,100 (2019-2020), 23,300 (2020-2021), 36,700 (2021-2022) before increasing to 44,700 HBER in 2022-2023. For the ongoing 2023-2024 season, there were 26,200 HBER recorded as of January 31, 2024 (Figure 1B).

The behaviour of our reconstructed indicator for hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV) aligns with our expectations and synthesises data from both the hospital and virologic surveillance networks (Figure 1B). During epidemic periods, the majority of HBER are attributed to RSV, whereas outside of the season, HBER are generally not related to RSV. Based on this indicator, we estimate that in the pre-COVID-19 era, there were between 25,200 and 29,400 HBER-RSV annually; around 14,200 to 25,300 during the COVID-19 period (between mid-2019 and mid-2022); and then

32,600 in 2022-2023. There have been 19,500 HBER-RSV in the first part of the 2023-2024 season (up to February 4, 2024), (Figure 1B).

The model was able to accurately reproduce the dynamics of HBER-RSV across different age groups (Figure 2A) as well as age-specific seroprevalence data (Figure 2B). It captured the important disruptions associated with the implementation of non-pharmaceutical interventions (NPIs) during the COVID-19 pandemic, leading to a delayed peak and a reduction in HBER-RSV during the 2020-2021 season, and a rebound in 2022-2023.

We estimated that RSV transmission was reduced by 18% (95% CI: 17%-20%), 29% (28%-32%), 10% (9%-11%), 5% (5%-6%) respectively during summer holidays, lockdowns, curfews, and other periods with protective measures (Figure 3A). Conversely, we estimated a slight rise in transmission rates during the 2022-2023 (5%, 4%-6%) and 2023-2024 (8%, 7%-9%) seasons. The probability of HBER-RSV upon RSV infection is estimated to rapidly decrease with age from 14% in 0-2 months to 7% in 3-5 months, 4% in 6-8 months, 2% in 9-11 months, and 0.5% in 1 year old infants (Figure 3B).

We assessed the seasonal incidence of RSV across different age groups defined as the ratio of the number of infections to the population size within each specific age group over a season. During the pre-COVID period, seasonal incidence was highest in the 0-5 months age group (around 60%). It fell to 44% in the 2 years age group, before rising again to around 54% in the ≥3 years age group, due to the greater number of contacts in this age group (Figure 3C). In 2020-2021, due to NPIs implemented to mitigate the impact of COVID-19, the seasonal incidence dropped sharply in all age groups (e.g. 35% in the age group 0-5 months and 36% in the ≥3 years age group). After the relaxation of NPIs, there was a rebound in infections, partly due to the decline in immunity in the population, with a seasonal incidence of 67% in the 0-5 months age group in 2022-2023.

Effectiveness of nirsevimab and number of HBER-RSV averted

In the age groups to which nirsevimab was not or scarcely administered (3-5 months, 6-8 months, 9-11 months, 1 year), the peak of HBER-RSV was of the same magnitude in 2023-2024 as in 2022-2023 (Figure 2A). However, for children aged 0-2 months, the peak of HBER-RSV was 47% lower in 2023-2024 (with nirsevimab administration) than in 2022-2023 (without nirsevimab administration). These age group differences suggest a significant impact of nirsevimab on HBER-RSV in the target group in 2023-2024.

These observations were confirmed by the mathematical model (Figure 2A), which predicted that the number of HBER-RSV observed in the 0-2 months age group was 35% (25%-44%) lower than what would have been expected without nirsevimab administration. This corresponds to a 23% (16%-30%) reduction in the total number of HBER-RSV thanks to nirsevimab administration.

The model estimated that nirsevimab administration averted 5,800 (3,700-7,800) HBER-RSV in metropolitan France, including 4,200 (2,900-5,600) among those aged 0-2 months, between September 15 (start of treatment administration) and February 4, 2024. In our baseline scenario with n=215,000 doses administered by January 31, 2024, the effectiveness of nirsevimab against HBER-RSV was estimated at 73% (61%-84%) (Figure 4A), corresponding to 1 HBER-RSV case prevented for every 39 (26-54) doses administered (Figure 4B).

Sensitivity analysis

The estimate of the number of HBER-RSV averted was robust to assumptions about the number of doses administered (Figure S3). The estimate of the effectiveness of nirsevimab against HBER-RSV changed slightly with the scenario of administration, from 73% (61%-84%) in our baseline scenario (n=215,000 doses administered) to 71% (59%-82%) (n=220,000 doses) and 76% (64%-90%) (n=205,000 doses) (Figure 4A). This corresponds to 1 HBER-RSV case prevented for every 39 (26-54), 40 (27-56) and 37 (26-54) doses administered, respectively (Figure 4B).

The number of HBER-RSV averted also exhibited small fluctuations with the assumed duration of immunity: 6,000 (4,000-8,000), 5,800 (3,700-7,800) and 5,400 (3,200-7,600) HBER-RSV averted in scenarios with short, medium (baseline) and long durations of immunity (Figure S3). Small fluctuations were also observed for estimates of treatment effectiveness: 74% (62%-85%), 73% (61%-84%) and 70% (57%-83%) in scenarios with short, medium (baseline) and long durations of immunity (Figure S4).

A minor increase in the number of HBER-RSV averted was observed when the peak of HBER-RSV was assumed to be 100% of the HBER peak (Figure S3). The probability of HBER-RSV upon infection increased when duration of immunity and size of HBER-RSV peak increased (Figure S5).

Discussion

In this study, we capitalised on France's early administration of nirsevimab, along with strong population adherence, to evaluate its real-world population-level impact and effectiveness in reducing HBER-RSV. Our findings reveal an important reduction in HBER-RSV in metropolitan France in 2023-2024, among infants aged 0-2 months who were mostly targeted by the treatment campaign. With 1 HBER-RSV averted for about every 40 children treated, our study highlights the relevance of nirsevimab administration to reduce RSV hospitalisations.

A previous study[21] in Luxembourg highlighted the impact of nirsevimab at the beginning of the 2023-2024 season, with a 38% decrease in RSV-related hospitalisations compared to the previous season. This reduction was particularly notable among infants under 6 months of age, where a 69% decrease was recorded. However, given the important disruptions of RSV epidemic patterns during and post COVID-19, inter-seasonal variations might be caused by a multitude of factors. To address this challenge, we developed a mathematical model that we used to construct counterfactual scenarios simulating what would have happened in the absence of nirsevimab administration. In clinical trials, efficacy against

hospitalisation for RSV LRTI was estimated between 77% (49%-89%) and 83% (68%-92%).[9,10] López-Lacortet et al[11] estimated the real-world effectiveness of nirsevimab against hospitalisation for RSV LRTI at 70% (38%-89%). Our point estimate of effectiveness against HBER-RSV, a specific category of RSV LRTI, was in line with those previous studies.

The high level of adherence to nirsevimab uptake was driven by past RSV outbreaks that strongly strained French hospitals. In response, health care workers proactively advocated for nirsevimab in infants to prevent the challenging scenario witnessed during 2022-2023. Moreover, the single-dose format of nirsevimab, in contrast to the multi-dose regimen of palivizumab - a monoclonal antibody prescribed for high-risk infants - simplified administration and increased parental acceptance.

In our study, we estimated a seasonal incidence of 54% for RSV in ≥3 years age group. These results are compatible with a longitudinal household study conducted in South Africa reporting attack rates of 49% in the 5-12 year age group and 30% among those aged 19-44 years, the majority of whom were asymptomatic.[22] Conducting similar types of studies in France would help quantifying infants risk of contracting RSV according to household composition, and thus designing effective preventive measures.

It is important to note that HBER-RSV are a subset of hospitalisations for RSV bronchiolitis, which form a part of the wider spectrum of RSV-related hospitalisations. As a result, the total number of RSV-related hospitalisations averted thanks to nirsevimab is greater than the number of HBER-RSV averted that we estimate here.

Our work has a number of limitations. Although there were no age-specific data on nirsevimab administration, we used data on doses delivered to maternity wards and pharmacies to develop credible administration scenarios. Nevertheless, uncertainty remains about the exact number of children treated in the different age groups as well as the timing of administration. Estimates of the number of HBER-RSV averted were robust to the

administration scenario but those for effectiveness were slightly affected. We might underestimate nirsevimab effectiveness if we assumed that too many children were treated or if we assumed that they were treated at a faster pace than what effectively happened. In France, data on RSV hospitalisations by age group are lacking. As a consequence, we constructed an indicator to capture age-stratified dynamics of HBER-RSV, derived from hospital surveillance for bronchiolitis hospitalisations and hospital laboratory surveillance for confirmed RSV cases. Given uncertainty about our indicator, we explored sensitivity of our results to assumptions about the proportion of RSV bronchiolitis hospitalisations during peak periods. Nonetheless, establishing a comprehensive virological surveillance network in French hospitals, incorporating key covariates such as age, would be instrumental to obtain more accurate and reliable data for future research. In the model, individuals move between age groups with a constant ageing rate. As a result, the age distribution of treated individuals may not perfectly match what might be expected when following up birth cohorts. However, we expect the phenomenon to be relatively limited given the short time period we consider here. In our study, we did not account for the use of palivizumab, a monoclonal antibody recommended for infants at high-risk for RSV. During the 2023-2024 season, it is conceivable that a subset of these high-risk infants might have received nirsevimab as an alternative to palivizumab. Such substitution could lead to underestimating nirsevimab effectiveness in our analysis. We assumed that nirsevimab reduced severity upon infection, not the susceptibility to infection. To our knowledge, the efficacy of nirsevimab against susceptibility is largely unknown. Nonetheless, given that the majority of contacts of individuals under 1 year old come from contacts with the age group ≥3 years old, a reduction in susceptibility after treatment should not dramatically modify RSV dynamics and the number of HBER-RSV averted.

This study demonstrates the relevance of nirsevimab administration to mitigate the hospital burden associated with RSV bronchiolitis. Further research should explore the most effective allocation of nirsevimab,[23–25] particularly when used alongside emerging treatments like the

maternal vaccine, which is already recommended in the United States. This could provide valuable insights into strategies for reducing the burden of RSV.

Data sharing

The code and data will be made available online.

Contributors

AB, SV and SC conceived the study. AB developed the code. JP, IPC, JSC, SV, and SC supervised the project. IP, VE, CD collected data. EB, GB and MW generated and analysed serological data. AB and SC wrote the initial draft of the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

The authors declare no competing interests.

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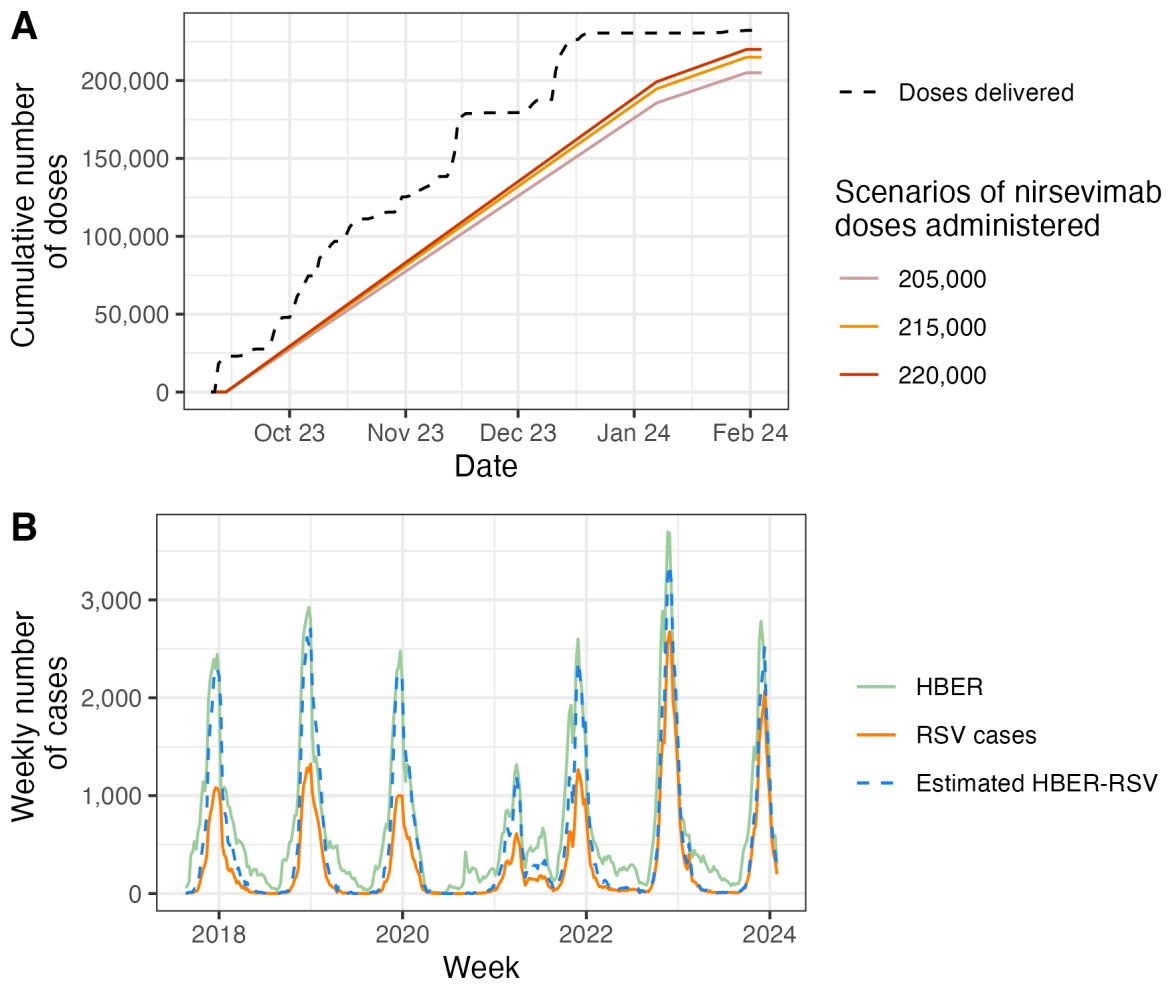

Figure 1: Nirsevimab doses administered, hospital and virologic surveillance. (A) Cumulative number of nirsevimab doses delivered to maternity wards and community pharmacy (dashed black) and scenarios for the cumulative number of nirsevimab doses administered by January 31, 2024: 205,000 (pink), 215,000 (orange) and 220,000 (red) doses. (B) Number of hospitalisations for bronchiolitis following emergency room visits (HBER; OSCOUR® data - green), number of RSV positive tests in the RENAL hospital laboratory network (RSV cases in RENAL - orange), and reconstructed number of hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV - dashed blue).

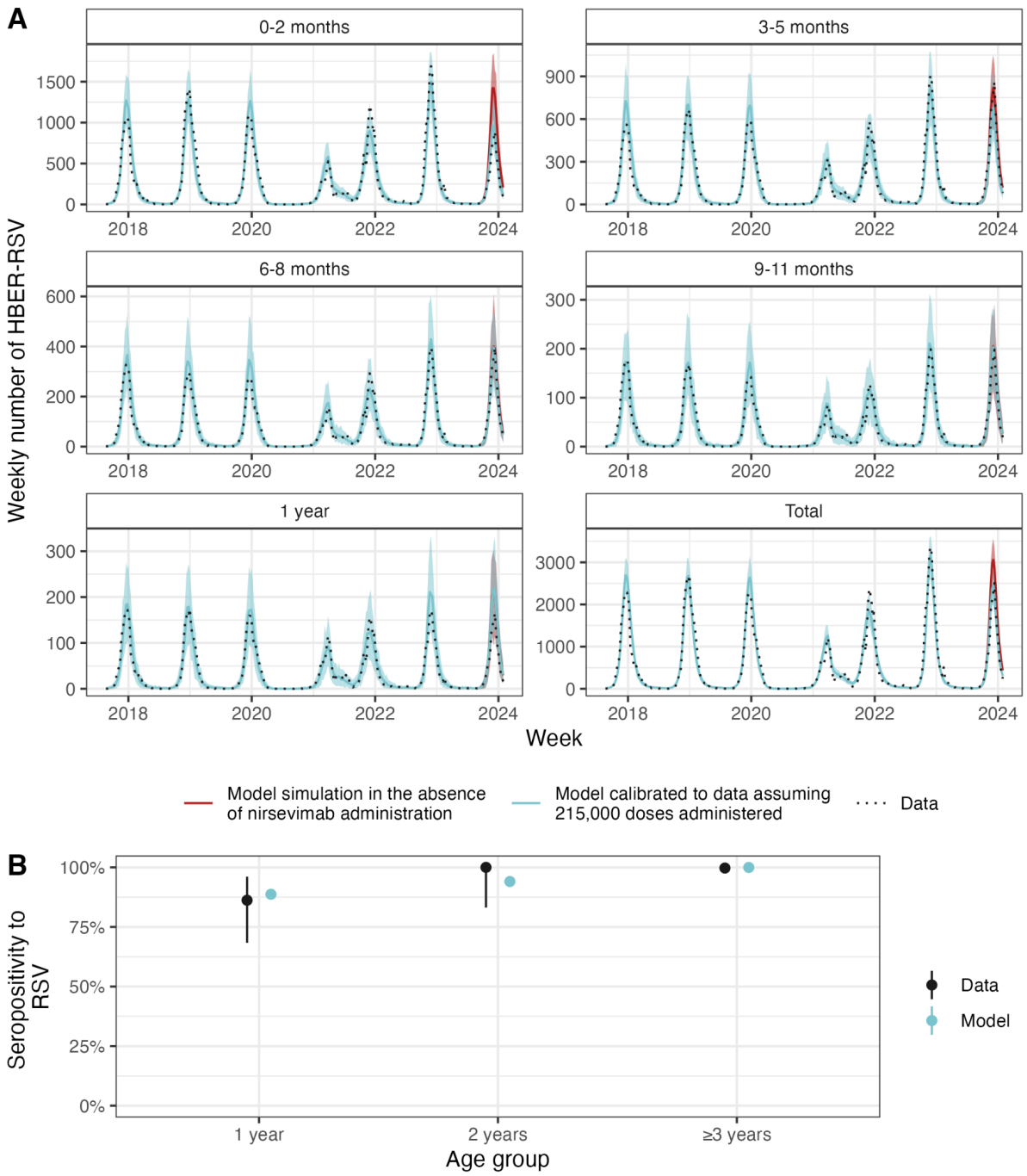

Figure 2: Model calibration to data. (A) Observed (black dots) and predicted (blue curves) dynamics of hospitalisations for RSV bronchiolitis following emergency room visits (HBER-RSV) in different age groups, assuming that 215,000 doses of nirsevimab were administered by 31 January 2024. The red curves correspond to model simulations in the absence of nirsevimab administration. (B) Observed (black) and predicted (blue) RSV

seroprevalence between February and August 2020, in 1 year, 2 years, and over 3 years old, respectively.

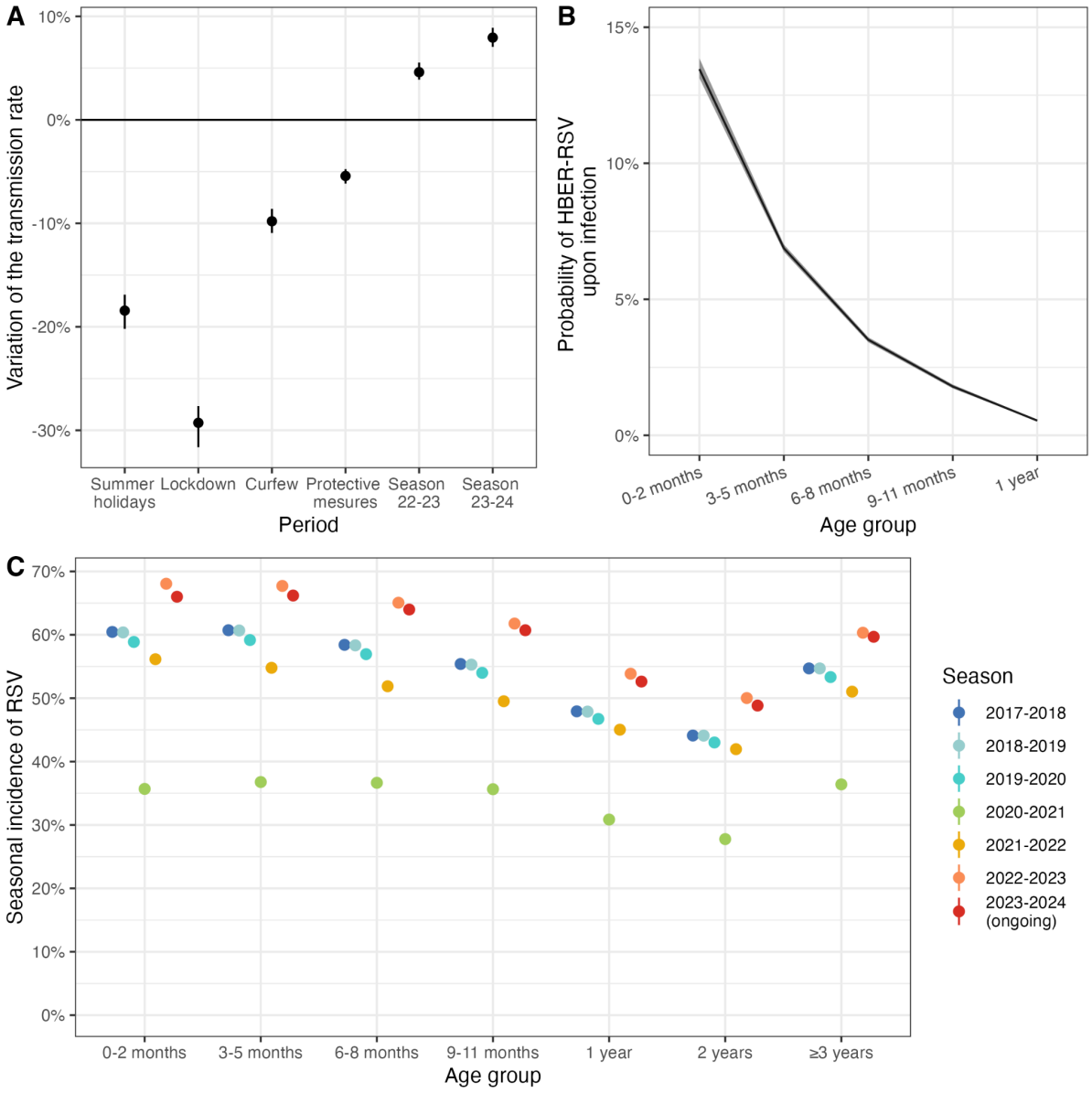

Figure 3: Variations in transmission, severity by age and proportion of infections by age and season. (A) Variations in transmission rates estimated during summer holidays, lockdown, curfew, protective measures (mask, physical distancing,...), season 2022-2023 and season 2023-2024. (B) Estimation of the probability of hospitalisation for RSV bronchiolitis following an emergency room visit (HBER-RSV) upon RSV infection in individuals with no prior infection or maternal immunity, categorised by age group. (C) Seasonal incidence of RSV by age and season. The seasonal incidence is defined as the

ratio of the number of infections within an age group during a season to the average population size of that age group throughout the season. A season period is defined as spanning from week 34 of one year to week 33 of the following year. The season 2023-2024 is not over.

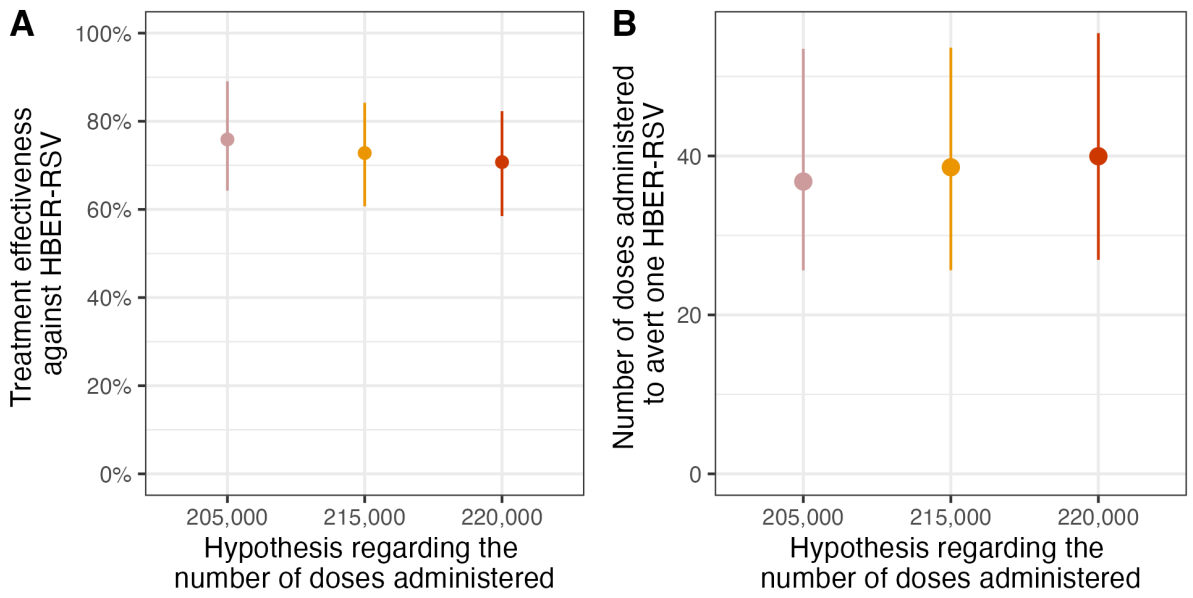

Figure 4: Estimates of nirsevimab effectiveness and number of doses administered required to avert one hospitalisation for RSV bronchiolitis following emergency room visits (HBER-RSV). (A) Estimates of nirsevimab effectiveness against HBER-RSV depending on the hypothesis about the number of doses administered by January 31, 2024. (B) Number of doses to be administered in infants to prevent one HBER-RSV, depending on the hypothesis about the number of doses administered by January 31, 2024.

Supplementary Materials

Estimates of effectiveness and impact of nirsevimab on hospitalisations for RSV bronchiolitis in metropolitan France, 2023-2024 : a modelling study

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Reconstruction of the number of hospitalisations for RSV bronchiolitis following emergency room visits

A season period is defined as spanning from week 34 of one year to week 33 of the following year. Let $HBER(t,a)$ the number of hospitalisations for bronchiolitis following emergency room visits (HBER) in week t, in age group a (observed), $HBER_{RSV}(t,a)$ the number of hospitalisations for RSV bronchiolitis following emergency room visits in week t, in age group a (unobserved), $RSV_{renal}(t)$ the number of RSV positive hospital cases in the RENAL network in week t (observed), $RSV_{renal,B}(t)$ the number of bronchiolitis tested positive to RSV in the RENAL network in week t (unobserved), and $B_{renal}(t)$ the number of patients with bronchiolitis tested for RSV in the RENAL network in week t (unobserved). OSCOUR and RENAL data provided $HBER(t,a)$ and $RSV_{renal}(t)$ values, respectively; the other quantities cannot be directly measured from the available data.

We make the following assumptions to estimate $HBER_{RSV}(t,a)$:

1. The proportion of individuals infected by RSV among HBER is equal to the proportion of individuals testing positive to RSV among patients hospitalised with bronchiolitis tested for RSV in the RENAL network:
$\frac{HBER_{RSV}(t,a)}{HBER(t,a)} = \frac{RSV_{renal,B}(t)}{B_{renal}(t)}$.

2. During each season, $HBER(t,a)$ is proportional to the number of patients hospitalised with bronchiolitis tested for RSV in the RENAL network, i.e. for t a week in season s:

$$HBER(t,a) = \rho_1(s,a) \cdot B_{renal}(t),$$

where $\rho_1(s,a)$ is a factor depending only on the season s and age group a.

3. In RENAL network, the proportion of patients with bronchiolitis who test positive for RSV among patients tested positive for RSV is constant:

$\frac{RSV_{renal,B}(t)}{RSV_{renal}(t)} = \rho_2$ where ρ_2 is a constant.

4. For each season and in each age group, the peak of HBER-RSV cases corresponds to *p*=90% of the peak of HBER cases.

We decompose:

$$\frac{RSV_{renal,B}(t)}{B_{renal}(t)} = \frac{RSV_{renal}(t)}{B_{renal}(t)} \cdot \frac{RSV_{renal,B}(t)}{RSV_{renal}(t)}.$$

Then according to hypothesis 1,

$$\frac{HBER_{RSV}(t,a)}{HBER(t,a)} = \frac{RSV_{renal,B}(t)}{B_{renal}(t)} = \frac{RSV_{renal}(t)}{B_{renal}(t)} \cdot \frac{RSV_{renal,B}(t)}{RSV_{renal}(t)}.$$

It follows from hypothesis 2 that

$$\frac{HBER_{RSV}(t,a)}{HBER(t,a)} = \frac{RSV_{renal}(t)}{HBER(t,a)} \cdot \rho_1(s,a) \cdot \frac{RSV_{renal,B}(t)}{RSV_{renal}(t)},$$

and from hypothesis 3 that

$$\frac{HBER_{RSV}(t,a)}{HBER(t,a)} = \frac{RSV_{renal}(t)}{HBER(t,a)} \cdot \rho_1(s,a) \cdot \rho_2.$$

We then obtain that

$$HBER_{RSV}(t,a) = \rho(s,a) \cdot RSV_{renal}(t),$$

where $\rho(s,a) = \rho_1(s,a) \cdot \rho_2$. According to hypothesis 4, during each season s and each week t in the season s,

$$\max_{u\ weeks\ in\ s}(HBER_{RSV}(u,a)) / \max_{u\ weeks\ in\ s}(HBER(u,a)) = p = 0.9.$$

We deduce that for each season s, each week t in season s:

$$HBER_{RSV}(t,a) = p \cdot \frac{\max_{u\ weeks\ in\ season\ s}(HBER(u,a))}{\max_{u\ weeks\ in\ season\ s}(RSV_{renal}(u))} \cdot RSV_{renal}(t).$$

This last formula allows us to reconstruct the number of hospitalisations for RSV bronchiolitis following emergency room visits.

Contact matrix

From the contact matrix provided in Mistry et al.[1] for age groups 0 year, 1 year, ..., 84 years and over, we constructed a contact matrix for age groups of our RSV model (0-2 months, 3-5 months, 6-8 months, 9-11 months, 1 year, 2 years, ≥ 3 years) as follows. Let us denote $c'_{k,l}$ the average number of daily contacts of an individual in age group k with the individuals in age group l, given by Mistry et al., with $k, l \in \{0, ..., 84\}$. We will determine $c_{i,j}$ the average number of daily contacts of an individual in age group i with the individuals in age group j, with $i, j \in \{0-2m, ..., 2y, \geq 3y\}$ (with abbreviation m for months and y for years).

We define a matrix $\hat{c}$ by: $\hat{c}_{1y,1y} = c'_{1,1}$, $\hat{c}_{1y,2y} = c'_{1,2}$, $\hat{c}_{2y,1y} = c'_{2,1}$, $\hat{c}_{2y,2y} = c'_{2,2}$.

Let pop'_k the population in age group $k \in \{0, ..., 84\}$. The average number of daily contacts between age groups k and l is $K'_{k,l} = c'_{k,l} pop'_k$. We set:

$$\hat{c}_{\geq 3y,\geq 3y} = \sum_{k,l\geq 3} K'_{k,l} / \sum_{k\geq 3} pop'_k,\ \hat{c}_{1y,\geq 3y} = \sum_{l\geq 3} K'_{1,l}/pop'_1,\ \hat{c}_{2y,\geq 3y} = \sum_{l\geq 3} K'_{2,l}/pop'_2,$$

And for $i, j \in \{0-2m, ..., 9-11m\}$, $\hat{c}_{i,j} = \frac{c'_{0,0}}{4}$, $\hat{c}_{i,1y} = \frac{c'_{0,1}}{4}$, $\hat{c}_{i,2y} = \frac{c'_{0,2}}{4}$,

$\hat{c}_{i,\geq 3y} = \sum_{l\geq 3} K'_{0,l}/(4\,pop'_0)$. Note that a contact matrix c must verify the condition $pop_i c_{i,j} = pop_j c_{j,i}$ for all i, j, i.e. the number of contacts between age groups i and j is the same as the number of contacts between age groups j and i. To ensure that the contact matrix c verify this property we set for all $i, j \in \{0-2m, ..., 9-11\,m, 1y, 2y, \geq 3y\}$:

$$c_{i,j} = \frac{pop_i \hat{c}_{i,j} + pop_j \hat{c}_{j,i}}{2pop_i}.$$

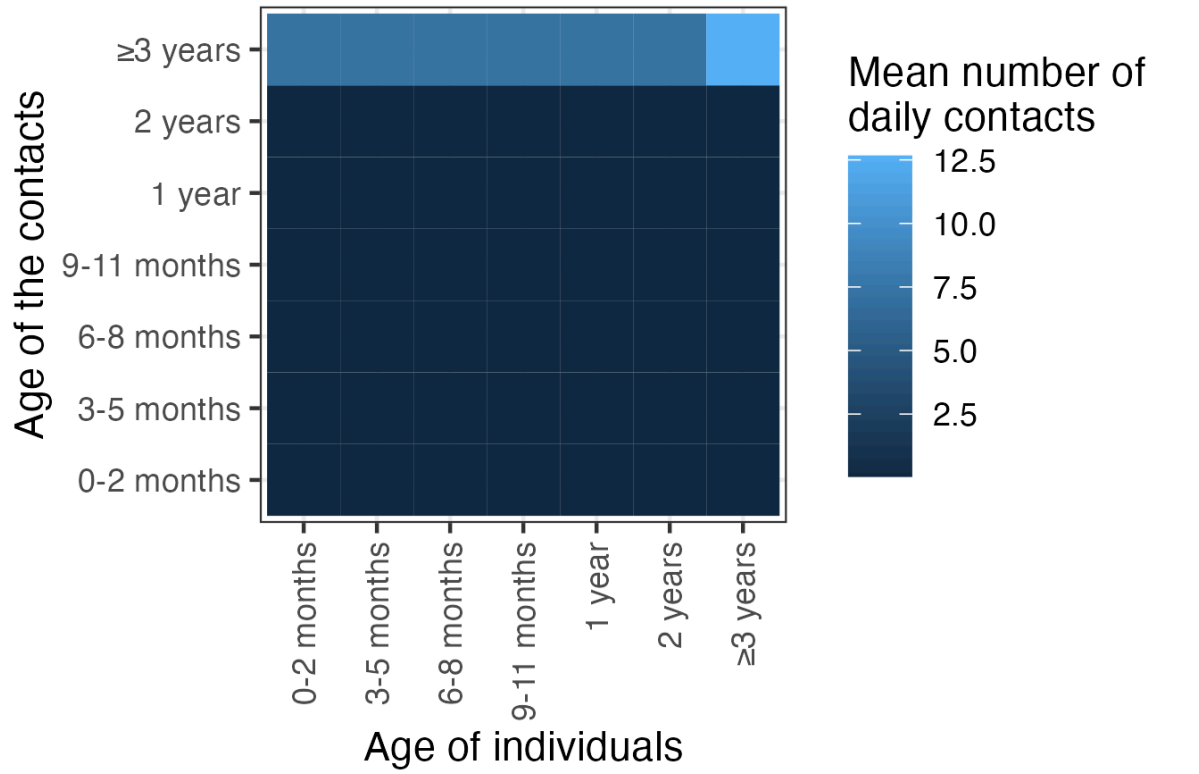

Figure S1: Contact matrix. Contact matrix used in the RSV model. The gradient of colour represents the average daily number of contacts an individual in each age group has with individuals in other age groups.

Model flow chart

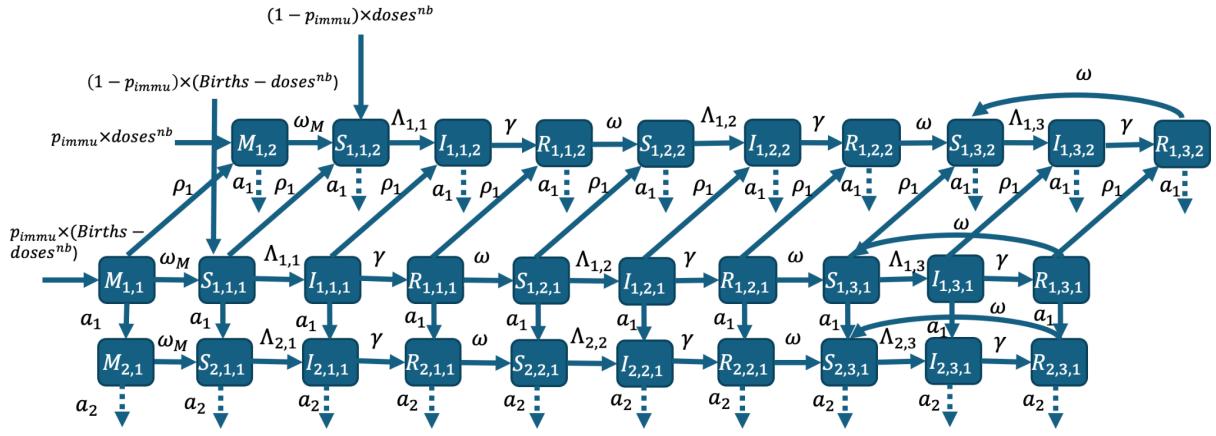

Figure S2: Model flow chart.

Ordinary differential equations of the transmission model

We refer to:

- age groups 0-2 months, 3-5 months, 6-8 months, 9-11 months, 1 year, 2 years, ≥ 3 years using indices 1 to 7,
- the levels of exposure with indices 1 to 3 with indice 1 stands for no previous infection, indice 2 stands for 1 previous infection, and indice 3 at least 2 previous infections,
- treatment status with indice 1 for individuals not treated, and indice 2 for individuals treated with nirsevimab.

The population is split in the following compartments:

- $M_{i,k}$: number of individuals in age group i and treatment group k protected from infection by maternal immunity;
- $S_{i,j,k}$: number of susceptible individuals in age group i, exposed group j and treatment group k;
- $I_{i,j,k}$: number of infectious individuals in age group i, exposed group j and treatment group k;
- $R_{i,j,k}$: number of immunised individuals in age group i, exposed group j and treatment group k.

The seasonal variation of the transmission rate is defined as:

$$\beta_{seas}(t) = \mu(t)\left(\beta_{min} + \left(\beta_{max} - \beta_{min}\right) 0.5\left(1 + \cos\left(\frac{t - t_{peak}}{2\pi}\right)\right)\right),$$

Where $\mu(t)$ is equal to a parameter of reduction of transmission μ_{school} between July 1 and August 31 of each year, otherwise $\mu(t)$ is equal to 1; β_{min} and β_{max} are the minimum and maximum of the transmission rate ;t_{peak} is the timing in the peak of transmissibility.

We denote respectively λ_1 the reduction of susceptibility following a first infection with respect to no previous infection and λ_2 the reduction of susceptibility following two or more infections with respect to the first infection. Then the relative reduction of susceptibility with respect to no previous infection is:

$$\lambda'_j = \begin{cases} 0, \text{ for } j = 1 \\ \lambda_1, \text{ for } j = 2 \\ \lambda_1\lambda_2, \text{ for } j = 3 \end{cases}$$

We denote $c_{i,j}$ the average number of daily contacts between an individual in age group i and individuals in age group j and $\bar{c}_{i,j} := c_{i,j}/c_{max}$, the contact matrix normalised by its spectral radius c_{max} (maximum absolute value of the eigenvalues of the contact matrix). The number of individuals in age group i is denoted $N_i(t)$.

The force of infection applied to individuals in $S_{i,j,k}$ is:

$$\Lambda_{i,j}(t) = \lambda'_j \eta(t) \beta_{seas}(t) \sum_{l=1}^{n_{age}} \bar{c}_{i,l} \sum_{m=1}^{3} \sum_{m'=1}^{2} \frac{I_{l,m,m'}(t)}{N_l(t)},$$

where $\eta(t)$ is the change in the transmission rate during summer holiday, lockdown, curfew, protective measures, 2022-2023, 2023-2024.

The model is characterised by the the following ordinary differential equations: for $i \in \{1,\ldots,n_{age}\}$, $j \in \{1,2,3\}$, $k \in \{1,2\}$,

$$\frac{dM_{i,k}(t)}{dt} = \delta_{i=1,k=1} p_{immu}(t)\,(Births(t) - doses^{nb}(t)) + \delta_{i=1,k=2} p_{immu}(t)\,doses^{nb}(t)$$
$$- \omega_M M_{i,k}(t) - m_i M_{i,k}(t) - \delta_{k=1}\rho_i(t)\,M_{i,k}(t) + \delta_{k=2}\rho_i(t)\,M_{i,k-1}(t) - \delta_{i<n_{age}} a_i M_{i,k}(t)$$
$$+ \delta_{i>1} a_{i-1} M_{i-1,k}(t)$$

$$\frac{dS_{i,j,k}(t)}{dt} = -S_{i,j,k}(t)\,\Lambda_{i,j}(t) - m_i S_{i,j,k}(t) + \delta_{j=1}\omega_M M_{i,k}(t)$$
$$+ \delta_{i=1,j=1,k=1}\left(1 - p_{immu}(t)\right)(Births(t) - doses^{nb}(t)) + \delta_{i=1,j=1,k=2}\left(1 - p_{immu}(t)\right)doses^{nb}(t)$$
$$- \delta_{k=1}\rho_i(t)\,S_{i,j,k}(t) + \delta_{k=2}\rho_i(t)\,S_{i,j,k-1}(t) - \delta_{i<n_{age}} a_i S_{i,j,k}(t)$$
$$+ \delta_{i>1} a_{i-1} S_{i-1,j,k}(t) + \delta_{j\in\{2,3\}}\,\omega R_{i,j-1,k}(t) + \delta_{j=3}\,\omega R_{i,j,k}(t)$$

$$\frac{dI_{i,j,k}(t)}{dt} = S_{i,j,k}(t)\,\Lambda_{i,j}(t) - \gamma I_{i,j,k}(t) - m_i I_{i,j,k}(t) - \delta_{k=1}\rho_i(t)\,I_{i,j,k}(t)$$
$$+ \delta_{k=2}\rho_i(t)\,I_{i,j,k-1}(t) - \delta_{i<n_{age}} a_i I_{i,j,k}(t) + \delta_{i>1} a_{i-1} I_{i-1,j,k}(t)$$

$$\frac{dR_{i,j,k}(t)}{dt} = \gamma I_{i,j,k}(t) - \omega R_{i,j,k}(t) - m_i R_{i,j,k}(t) - \delta_{k=1}\rho_i(t)\,R_{i,j,k}(t)$$
$$+ \delta_{k=2}\rho_i(t)\,R_{i,j,k-1}(t) - \delta_{i<n_{age}} a_i R_{i,j,k}(t) + \delta_{i>1} a_{i-1} R_{i-1,j,k}(t)$$

where:

- $\delta_{i=v} = 1$ if and only if $i = v$, 0 otherwise
- γ is the recovery rate,
- ω is the waning rate of immunity after an infection,
- ω_M is the waning rate of maternal immunity,
- $Births(t)$ is the daily number of birth in metropolitan france
- m_i is a rate that takes into account the mortality and the negative net migration in age group i
- $a_i = 1/(30.5 * number\ of\ months\ in\ age\ group\ i)$ is the daily ageing rate in age group i
- $doses^{nb}(t)$ is the daily number of doses administered to neonates.
- $\rho_i(t) = doses_i(t)/N_i(t)$ is the daily treatment rate in age group i, with $doses_i(t)$ with the daily number of doses administered in age group i.
- $p_{immu}(t) = \sum_{j=1}^{3}\sum_{k=1}^{2} R_{7,j,k}(t)/N_7(t)$ is the proportion of neonates immunised with maternal immunity.

For individuals not treated, the probability of hospitalisation upon infection is parameterised as:

$$\begin{cases} exp\left(-\left(\varepsilon_0 + \varepsilon_{age} \cdot i\right)\right), & \text{for } i \in \{1,2,3,4\} \\ h, \text{ for } i = 5 \end{cases}$$

The probability of hospitalisation upon infection is multiplied by $1 - TE$ for individuals treated, where TE is the treatment effectiveness against hospitalisation.

Demographic data

Daily births in metropolitan France were computed by interpolating monthly births in metropolitan France.[2] We derived the age-specific population for metropolitan France, spanning from 2005 to 2022, using the annual, department-level age data supplied by the Institut National de la Statistique et des Études Économiques (INSEE) to Santé Publique France. Additionally, we assumed there was the same number of individuals in age groups 0-2 months, 3-5 months, 6-8 months, 9-11 months.

Description of transmission model parameters

Name	Symbol	Value / Priors	Estimation with calibration
Duration infectiousness	$1/\gamma$	7 days	Fixed[3]
Waning of immunity after infection	$1/\omega$	9 months (sensitivity analysis: 6 months, 12 months)	Fixed[4,5]
Waning maternal immunity	$1/\omega_M$	2 months (sensitivity analysis: 1 month, 4 months)	Fixed
Reduction of susceptibility after 1 and 2 infections	λ_1, λ_2	0.76, 0.88	Fixed[6]
Transmission rate minimum and maximum of the forcing seasonality	β_{min}, β_{max}	Uniform prior (0,3]	0.34 (0.337-0.344), 0.414 (0.411-0.417)
Date of the peak of the forcing seasonality	t_{peak}	320 days	Fixed
Reduction transmission during summer holidays July 1 to August 31	μ_{school}	Uniform prior (0,1]	0.816 (0.798-0.831)
Reduction of transmission during lockdown corresponding to periods: - March 17-May 10, 2020 - Oct. 30 - Dec. 14, 2020 - April 3 - May 2, 2021	η_{lock}	Uniform prior (0,1]	0.707 (0.684-0.723)

Reduction of transmission during curfew corresponding to periods: - Dec.15, 2020-April 2, 2021 - May 3- June 19, 2021	η_{curfew}	Uniform prior (0,1]	0.902 (0.891-0.914)
Reduction of transmission during protective measure corresponding to periods between May 11, 2020 and June 30, 2022 outside lockdown and curfew periods	$\eta_{protect}$	Uniform prior (0,1]	0.946 (0.938-0.952)
Variation of transmission between September 1, 2022 and June 30, 2023	$\eta_{2022-2023}$	Uniform prior [0.9,1.5]	1.05 (1.04-1.06)
Variation of transmission between September 1, 2023 and June 30, 2024	$\eta_{2023-2024}$	Uniform prior [0.9,1.5]	1.08 (1.07-1.09)
Exponential decrease of severity under 1 year old	ϵ_0, ϵ_{age}	Uniform (0,10]	1.33 (1.29-1.37) 0.672 (0.654-0.689)
Severity in age group 1 year old	h	Uniform (0,1]	0.0054 (0.0051-0.0057)
Daily mortality/migration rates	m_1 m_2 m_3 m_4 m_5 m_6 m_7	0.000411 0.0000137 0.0000137 0.00000822 0 0 0.0000205	Determined before calibration using births and age-specific population data (Section Demographic Data).
Treatment effectiveness against hospitalisation	TE	Uniform (0,1]	0.73 (0.61-0.84)
Coefficient of adjustment of dispersion in likelihood	κ	Uniform (0,10]	0.54 (0.52-0.56)

Table S1: Parameters fixed and estimated in the RSV transmission model. The first column provides a description of the role of parameters, the second column the associated symbols, the third the value of the parameter when it is fixed or the prior of the parameter when it is calibrated to the data. The estimation of parameters is presented in the fourth column.

Serological data

For the serological study 1,132 samples were available for serological testing, with 275 from children under 10 years of age. IgG antibody levels were measured using a bead-based multiplex serological assay. Samples were run at a final dilution of 1:200. Plates were read using the Intelliflex® technology from Luminex®, and the median fluorescence intensity was used for analysis. Participants were

classified as seropositive for RSV based on measurements of IgG antibodies against viral lysates specific to the RSV-A subtype (purchased from The Native Antigen Company, UK). The threshold for seropositivity was established for paediatric patients by subtracting two standard deviations from the average antibody titers observed in the adult cohort.

Monte Carlo Markov Chain calibration

We used the Metropolis within Gibbs algorithm, running two chains with the same initialisation each comprising 10,000 iterations. The algorithm was configured with a log-normal proposal distribution. To optimise the sampling efficiency, the standard deviation of this proposal was adaptively adjusted to target an acceptance rate of 0.24 over the first 5,000 iterations. We selected a burin-in of 2,500 iterations.

The credible intervals (CI) of the parameters were computed using the highest posterior density interval method.

Sensitivity analysis

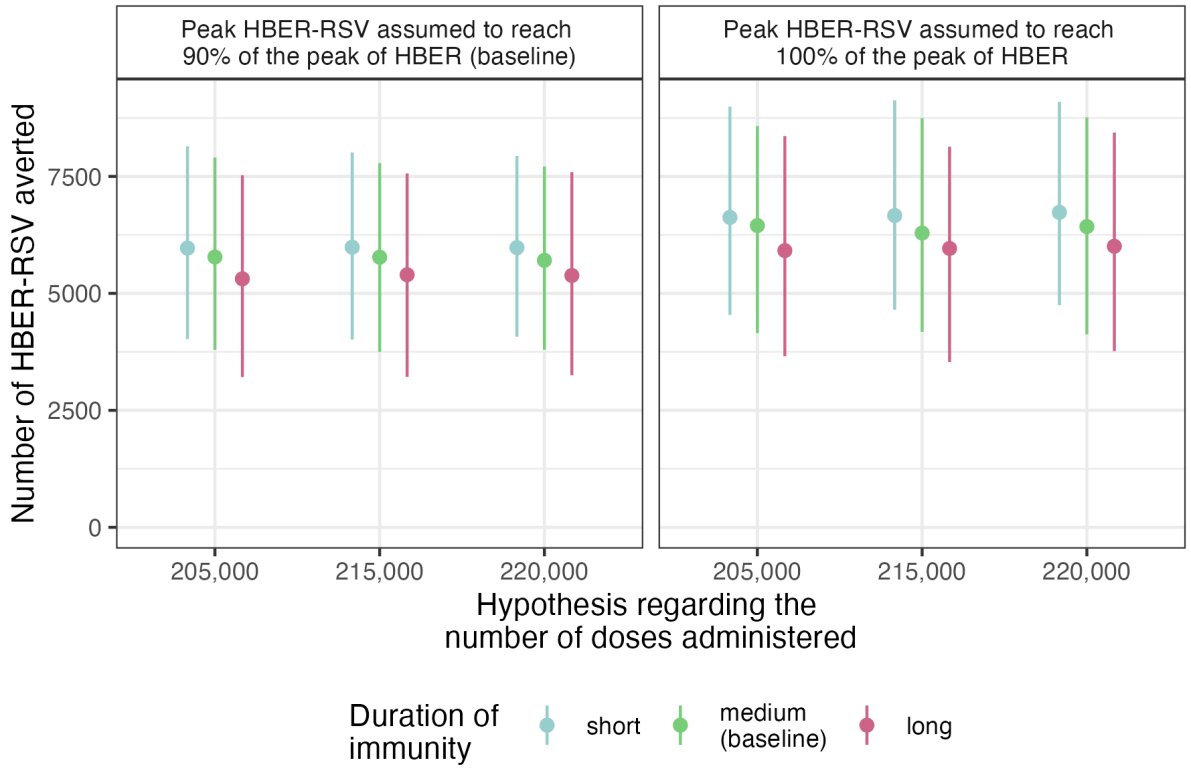

Figure S3: Sensitivity of estimates for the number of HBER-RSV averted. (Left panel) Number of HBER-RSV averted with respect to the hypothesis on the number of doses administered and the duration of immunity, assuming that the peak of HBER-RSV reaches 90% of the peak of HBER. **(Right panel)** Number of HBER-RSV averted with respect to the hypothesis on the number of doses administered and the duration of immunity, assuming that the peak of HBER-RSV reaches 100% of the peak of HBER. The scenarios of short, medium and long immunity correspond respectively to an immunity post-infection of 6, 9, 12 months combined with a maternal immunity of 1, 2 and 4 months.

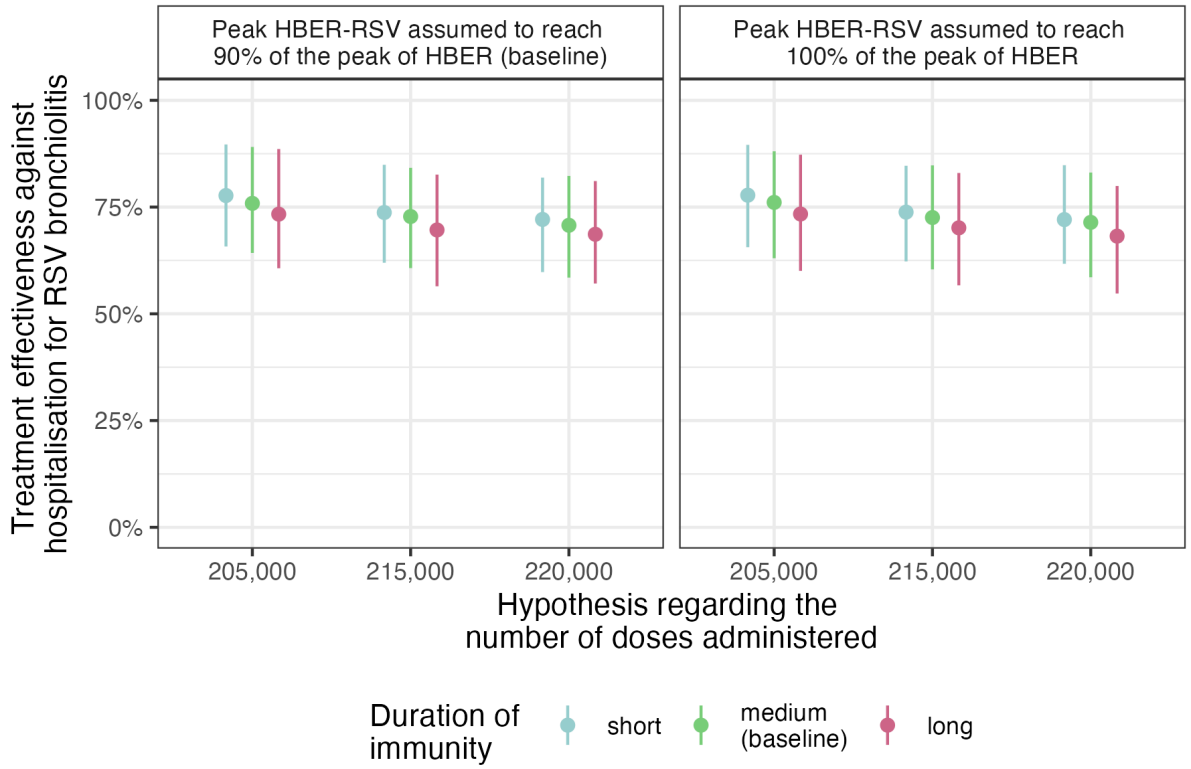

Figure S4: Sensitivity of estimates for treatment effectiveness. (Left panel) Treatment effectiveness with respect to the hypothesis on the number of doses administered and the duration of immunity, assuming that the peak of HBER-RSV reaches 90% of the peak of HBER. **(Right panel)** Treatment effectiveness with respect to the hypothesis on the number of doses administered and the duration of immunity, assuming that the peak of HBER-RSV reaches 100% of the peak of HBER. The scenarios of short, medium and long immunity correspond respectively to an immunity post-infection of 6, 9, 12 months combined with a maternal immunity of 1, 2 and 4 months.

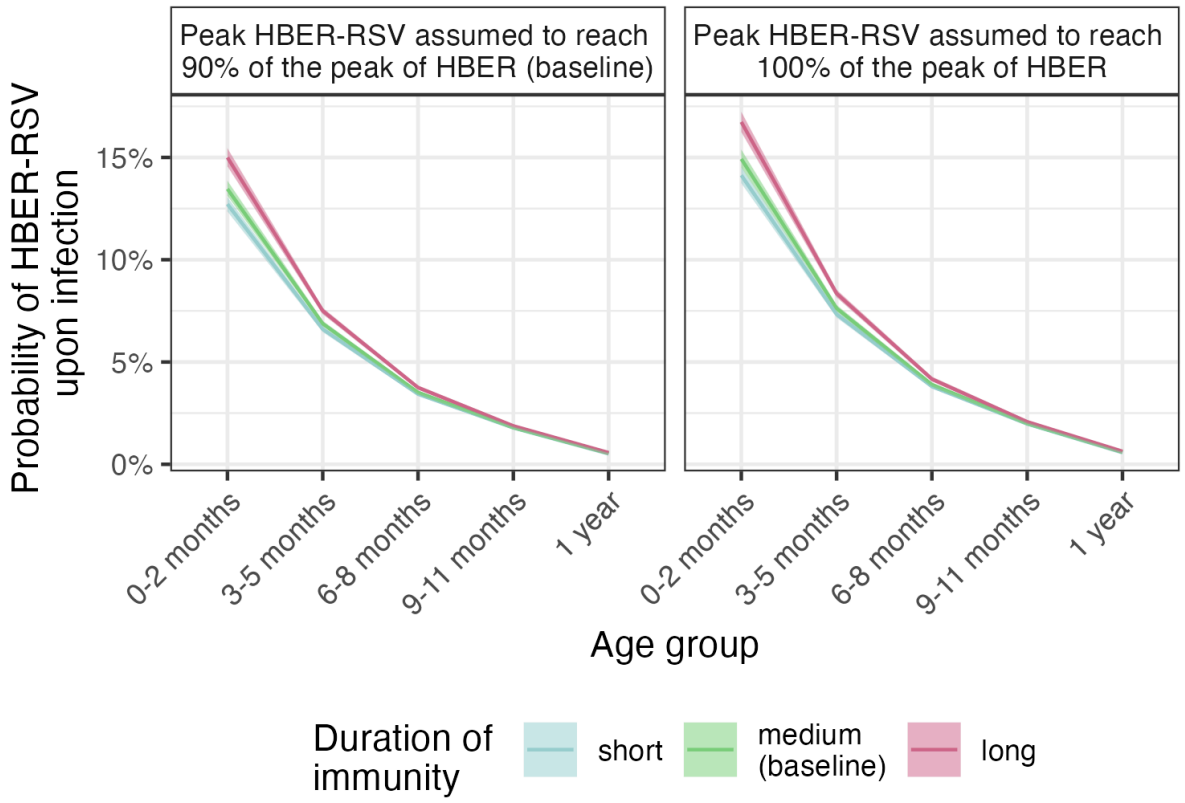

Figure S5: Sensitivity of estimates for RSV severity by age. (Left panel) Probability of HBER-RSV upon infection by age group with respect to the duration of immunity, assuming that the peak of HBER-RSV reaches 90% of the peak of HBER. **(Right panel)** Probability of HBER-RSV upon infection by age group with respect to the duration of immunity, assuming that the peak of HBER-RSV reaches 100% of the peak of HBER. The scenarios of short, medium and long immunity correspond respectively to an immunity post-infection of 6, 9, 12 months combined with a maternal immunity of 1, 2 and 4 months.

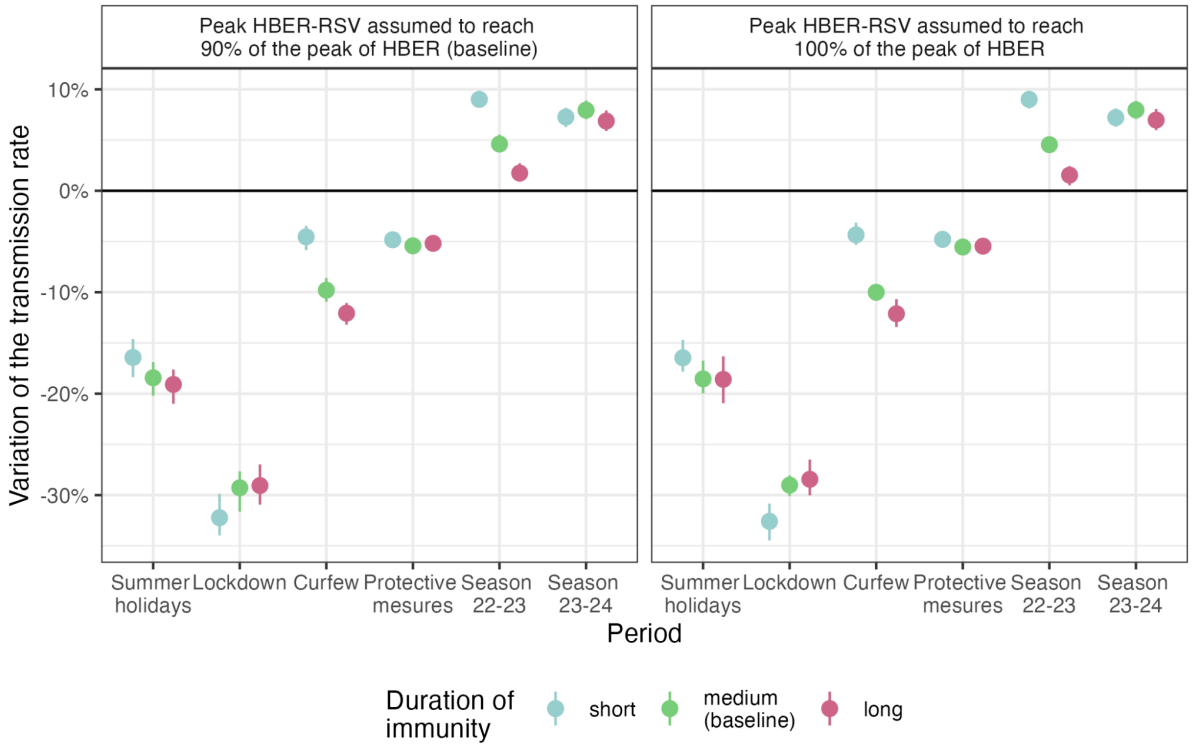

Figure S6: Sensitivity of estimates of variations in the transmission rate. (Left panel) Variations in the transmission rate during summer holidays, lockdown, curfew, season 2022-2023 and 2023-2024 with respect to the duration of immunity, assuming that the peak of HBER-RSV reaches 90% of the peak of HBER. **(Right panel)** Variations in the transmission rate during summer holidays, lockdown, curfew, season 2022-2023 and 2023-2024 with respect to the duration of immunity, assuming that the peak of HBER-RSV reaches 100% of the peak of HBER. The scenarios of short, medium and long immunity correspond respectively to an immunity post-infection of 6, 9, 12 months combined with a maternal immunity of 1, 2 and 4 months.

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