Effectiveness of nirsevimab immunoprophylaxis against respiratory syncytial virus-related outcomes in hospital and primary care settings: a retrospective cohort study in infants in Catalonia (Spain)

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Abstract:

Background: Respiratory syncytial virus (RSV) is a major cause of bronchiolitis and hospitalisations in children under two years. In Catalonia, infants under six months old were eligible to receive nirsevimab, a novel monoclonal antibody against RSV. Our aim here is to analyse nirsevimab's effectiveness across primary- and hospital care outcomes.

Methods:
Retrospective cohort study from October 1, 2023, to January 31, 2024, including all infants born between April and September 2023, were eligible for nirsevimab immunisation. We established two cohorts based on nirsevimab administration (immunised and non-immunised). We followed individuals until the earliest moment of an outcome - RSV infection, primary care attended bronchiolitis and pneumonia, hospital emergency visits due to bronchiolitis, hospital admission or intensive care unit (ICU) admission due to RSV bronchiolitis - or the end of the study. We used the Kaplan-Meier estimator and fitted Cox regression models using a calendar time-scale to estimate hazard ratios (HR) and their 95% confidence intervals, adjusting by confounders. Effectiveness of nirsevimab was calculated as (1-HR)*100.

Findings:

Among 26,525 infants, a dose of nirsevimab led to an adjusted HR for hospital admission due to RSV bronchiolitis of 0·124 (0·086 to 0·179) and an adjusted HR for ICU admission of 0·099 (0·041 to 0·237). Additionally, the adjusted HR observed for emergency visits was 0·446 (95% CI: 0·385 to 0·516), 0·393 (95% CI: 0·203 to 0·758) for viral pneumonia, 0·519 (95% CI: 0·467 to 0·576) for bronchiolitis attended in primary care, and 0·311 (95% CI: 0·200 to 0·483) for RSV infection. Sensitivity and negative control outcome analyses supported these findings.

Interpretation:

Our analysis demonstrated nirsevimab's effectiveness, with reductions of 87·6% and 90·1% in hospital and ICU admissions for bronchiolitis due to RSV, respectively. Moreover, we observed substantial decreases in less severe outcomes, including primary care attended bronchiolitis (48·1%), RSV infections (68·9%), viral pneumonia (60·7%), and hospital emergency visits for bronchiolitis (55·4%). These findings offer crucial guidance for public health authorities in implementing RSV immunisation campaigns for infants under six months old.

Funding:
None.

Background:

Respiratory syncytial virus (RSV) infection is a worldwide public health concern due to its high contagiousness and potential to cause severe illness in the paediatric population.[1] In infants under one year old, especially preterm infants, it can manifest itself as severe lower respiratory tract infections (LRTI). It is estimated that RSV is responsible for 70% of all bronchiolitis cases and 25% of pneumonia cases in infants under one year of age.[2] RSV infection typically exhibits a seasonal pattern, with peak incidence in Spain usually observed between October and March.[3]

In March 2023, nirsevimab was commercialised in Spain. This recombinant human IgG1 Kappa monoclonal antibody has demonstrated its efficacy and safety in preventing RSV infections in infants during their first epidemic season.[4–9] Prior to nirsevimab, preventive options against RSV were limited and primarily targeted for high-risk infants.

In Spain, health policies are transferred to the autonomous communities. Catalonia is an eight-million-inhabitants autonomous community in the north-east of Spain. Considering the availability of the monoclonal antibody as a preventive measure for healthy infants and the incidence of RSV infections in Catalonia, especially in infants under six months of age, as well as the impact on the healthcare system due to associated hospitalisations, the recommendation and financing for nirsevimab immunisation was introduced in October 2023 as part of the infant immunisation program.[10] The main objective of this measure was to reduce complications from RSV infection in all newborns and infants during their first epidemic season. All babies born between April and September 2023 were offered a dose of nirsevimab in primary care practices during October, in addition to all newborns born between October 2023 and March 2024, preferably in public and private hospitals, or in primary care practices during the first days of life. At the time of writing, the RSV epidemic wave has already ended and the nirsevimab vaccination campaign is still underway for children born after October; since the number of children is large and the observation period is adequate, it is a good time to analyse the data, focusing on the first group of children and providing useful information to plan the next season.

Evaluating the effectiveness of population-based public health measures is crucial and, therefore, the primary objective of the study is to assess the effectiveness of nirsevimab immunisation in infants born during the months of April and September 2023 during the epidemic season from October 2023 to January 2024.

Methods

Study design and settings

We conducted a retrospective cohort study using routinely collected data from various Catalan health databases. Nirsevimab exposure was obtained from the Catalan Shared Clinical Records, a comprehensive clinical database of electronic medical records that integrates data from the entire Catalan health system. We further linked data to the primary care electronic health records (EHR) to analyse primary care related outcomes (pneumonia, bronchiolitis, results of rapid antigen tests and negative control outcome). Data on hospital and intensive care unit (ICU) admissions were obtained from the Minimum Basic Data Set

(CMBD in Catalan) and hospital emergency department visits from the CMBD-UR. Covariables and the eligible population were sourced from the central population register (RCA) of the Catalan health service.[11]

As of 2024, all public primary care practices in Catalonia use the same EHR system, known as ECAP (Primary health-care clinical station), which has been previously validated and used for epidemiological research.[12] The CMBD furnishes information on hospital discharges from all hospitals in Catalonia, encompassing both public and private hospitals.[13]

Participants and follow-up

All infants born between April and September 2023 in Catalonia and deemed eligible for immunisation with nirsevimab were included. Due to delayed data registration for newborns during the campaign, our analysis could not be performed yet for infants born since October 2023. We excluded those without a valid health identifier number and those who died or moved outside Catalonia before the start of the immunisation campaign. For the analysis of the primary care related outcomes, we also excluded those infants who were not assigned to one of the public primary care practices in Catalonia contributing to our database.

The study was conducted from October 1, 2023, to January 31, 2024. Two cohorts were established based on the nirsevimab administration date:

- Exposed cohort (immunised with nirsevimab): infants who received a single dose of nirsevimab during the study period.
- Control cohort (non-immunised): infants who did not receive any dose of nirsevimab during the study period.

Exposure was dynamically defined. This means that infants who received one dose of nirsevimab may have previously contributed to the control cohort until the date of administration, at which point they became part of the exposed cohort.

We followed non-immunised participants from the beginning of the immunisation campaign in Catalonia (October 1, 2023) until the earliest of receiving a dose of nirsevimab (at which point they switched to the nirsevimab arm), an outcome, death or the end of the study (January 31, 2024). Immunised participants were followed from the day they received nirsevimab immunoprophylaxis until the earliest of an outcome, death or the end of the study.

Study outcomes

Several outcomes related to RSV infection and severity were analysed:

- Primary care attended bronchiolitis: Defined as a clinical diagnosis of bronchiolitis based on International Classification of Diseases 10th version (ICD-10) codes recorded in the primary care EHR (**Supplementary Table 1**).
- RSV infection: measured as a positive rapid antigen test performed in primary care settings. Since the beginning of 2021, rapid antigen tests have been available in paediatric primary care practices for testing for influenza (A and B), adenovirus, SARS-CoV-2, and RSV.

- Viral pneumonia diagnosed in primary care: Viral pneumonia diagnoses recorded in the primary care EHR were defined according to the ICD-10 classification, including all relevant codes used in the Information System for Surveillance of Infections in Catalonia (SIVIC) webpage (**Supplementary Table 1**).[14]
- Hospital emergency department visits due to bronchiolitis: Any hospital emergency visit for all-cause bronchiolitis.
- Hospital admission for RSV-related disease: Hospital admission with a discharge diagnosis of bronchiolitis due to RSV.
- Admission to ICU for RSV-related disease: Any admission to the ICU during the hospital stay due to bronchiolitis caused by RSV.

In our analysis, hospital emergency department visits and primary care diagnoses outcomes encompassed all-cause bronchiolitis, as comprehensive testing is not always conducted in these settings. Consequently, the majority of cases are reported as nonspecific bronchiolitis by medical practicioners.

Furthermore, we analysed the occurrence of a negative control outcome, selecting another infectious disease with high incidence in infants (impetigo diagnoses registered in the primary care EHR), to identify potential unmeasured confounding. Negative control outcomes are events that are known not to be causally affected by the exposure of interest, here nirsevimab immunisation.[15]

Finally, we conducted a sensitivity analysis including hospital admissions for bronchiolitis caused by other pathogens as an outcome, for which no association with nirsevimab was expected.

Additional covariables

Covariables used for confounding assessment included socio-demographics: age (in days), sex, area of residence, nationality (Spanish or immigrant), rurality and socio-economic status. We assessed socio-economic status using the validated socioeconomic index (ISC) from the Catalan Agency for Healthcare Quality and Assessment (Agència de Qualitat i Avaluació Sanitàries de Catalunya, AQuAS), calculated at the health basic area level.[16] Rurality of residence was measured, with rural areas defined by a population <10,000 inhabitants and a density <150 inhabitants/km^2, as per regional guidance.

Statistical analysis

For descriptive analyses, we expressed continuous variables as mean (standard deviation) and summarised categorical variables as a number (percentages). We assessed confounding by indication by using the standardised mean difference (SMD) of all covariables to compare both cohorts. We considered SMD>0·1 to be imbalanced and adjusted it in multivariable analysis.[17]

For each cohort, we calculated the rate of outcomes per 100,000 person-days by dividing the number of observed events within a follow-up period by the number of person-days of exposure, multiplied by 100,000.

We computed the cumulative incidence (risk) curves of each outcome using the Kaplan-Meier estimator. Cox regression models using a calendar time scale[18] were then fitted to calculate hazard ratios (HR) and

95% confidence intervals (95% CI) for each of the study outcomes according to immunisation status. All Cox models were also adjusted for any confounders with a SMD>0·1. Six models were conducted separately for each of the outcomes. Visual inspection of Schoenfeld residuals against the transformed time was used to evaluate the proportionality of hazards. We estimated effectiveness as the percent reduction in risk (1 minus adjusted HR expressed as percentage).

All analyses were conducted using the R version 4.0.0.

Ethical considerations

The study was approved by the Clinical Research Ethics Committee of the IDIAP Jordi Gol with reference number 24/015-EOm.

Role of the funding source

There was no funding received for this study.

Results

Population and immunisation campaign

Before exclusions, 27,121 infants born between April and September 2023 were eligible for nirsevimab immunisation. We excluded 596 infants due to exclusion criteria (**Figure 1**). We therefore analysed data from 26,525 infants (97·8%). For the analysis of the primary care outcomes we have excluded 1,570 infants (5·9%) not assigned to a public primary care practice.

By the end of the study period, 23,127 infants (87·2%) had been immunised against RSV. **Figure 2** shows the rapid uptake of the nirsevimab coverage, with 76·3% of infants having received nirsevimab within the first month of the immunisation campaign.

The control and nirsevimab groups were balanced without adjustment (SMD<0·1) in terms of sex, rurality and socio-economic status, but differed in age (100 vs 89·2 days) and nationality (82·2% vs 87·1% of Spanish nationality), all with SMD>0·1 (**Table 1**).

Outcomes and effectiveness

Among infants immunised with nirsevimab, 1,560 primary care attended bronchiolitis, 604 hospital emergency visits for bronchiolitis, and 52 hospital admissions and eight ICU admissions due to RSV bronchiolitis occurred. Conversely, in the control group we observed 617 primary care bronchiolitis, 354 hospital emergency visits, 76 hospital admissions and 17 ICU admissions. **Figures 3** and **4** depict the cumulative incidence of each outcome in both groups. Notably, the control group showed higher incidence rates for all outcomes, particularly for severe cases. For instance, the incidence rates of hospital admission due to RSV bronchiolitis were 9·55 per 100,000 person-days for non-immunised infants, as

compared to 2·16 for immunised infants. Similarly, incidence rates of ICU admissions were 2·13 and 0·33, and incidence rates of primary care attended bronchiolitis were 93·9 and 69·7, respectively (**Table 2**).

A dose of nirsevimab led to an adjusted hazard ratio (HR) for hospital admission of 0·124 (0·086 to 0·179) and an adjusted HR for ICU admission of 0·099 (0·041 to 0·237). In addition, the adjusted HR observed for emergency visits was 0·446 (95% CI: 0·385 to 0·516), 0·393 (95% CI: 0·203 to 0·758) for viral pneumonia, 0·519 (95% CI: 0·467 to 0·576) for primary care bronchiolitis, and 0·311 (95% CI: 0·200 to 0·483) for RSV infection (**Table 2**). **Table 2** also presents the effectiveness of nirsevimab estimated for each outcome, showcasing an effectiveness of 90·1% (95% CI: 76·3% to 95·9%) against admission to the ICU and 87·6% (95% CI: 82·1% to 91·4%) against hospital admission.

Impetigo diagnoses were used as a negative control outcome. They were recorded at similar frequencies in the two groups leading to an adjusted HR of 1·09 (95% CI: 0·80 to 1·48) (**Supplementary Figure 1**). In addition, in a sensitivity analysis we estimated the effectiveness of nirsevimab to prevent hospital admissions due to bronchiolitis caused by other pathogens, with an adjusted HR of 0·936 (95% CI: 0·420 to 2·087), indicating no association.

Finally, two deaths were observed in our study population (both not immunised). These deaths were not related to RSV infection but were premature infants with multiple pathologies who were admitted to the hospital immediately after birth and remained hospitalised until the date of their death. Therefore, we do not consider death as an outcome.

Discussion

This study offers a valuable estimation of nirsevimab effectiveness against various outcomes in infants aged < 6 months old prior to the onset of their first RSV epidemic season. Using a comprehensive linked database that integrates primary and hospital care data, we investigated the impact of the Catalan immunisation program on reducing RSV-related outcomes.[10] Our analysis found that nirsevimab effectiveness against hospital and ICU admissions was 87·6% and 90·1%, respectively. Furthermore, we observed significant and clinically relevant reductions in less severe outcomes, including all-cause bronchiolitis attended in primary care (48·1%), RSV infections (68·9%), viral pneumonia (60·7%), and hospital emergency visits due to nonspecific bronchiolitis (55·4%). To our knowledge, this study represents the first report to include outcomes of different severity in a real-world setting, providing a comprehensive assessment of the impact of nirsevimab across all levels of care.

The absence of association between nirsevimab immunisation and our negative control outcome of impetigo underscore the robustness of our findings. These results rule out residual confounding in our cohorts.[15] Additionally, sensitivity analysis showing lack of protection in hospital admissions due to bronchiolitis caused by other pathogens also strengthens our findings.

Our work reveals a notable trend: the greater the severity of the outcome analysed, the higher the effectiveness of nirsevimab. However, we also observed significant reductions ranging between 48% and 69% in other, less severe outcomes, such as bronchiolitis attended in primary care and RSV infections. It

is noteworthy that the observed differences in effectiveness between RSV infections and bronchiolitis diagnosed in primary care, viral pneumonias, or hospital emergency visits for bronchiolitis may be attributed to the fact that within these diagnoses of bronchiolitis and pneumonia, some are nonspecific and not caused by RSV. The lack of comprehensive testing for all patients in these settings may lead to an underestimation of the effectiveness for these outcomes, which are likely to resemble that of RSV infections. The results of our sensitivity analysis, showing no association between nirsevimab and hospital admission due to bronchiolitis caused by other pathogens, support this statement. However, it is worth noting that RSV is the most common pathogen identified in infants with acute LRTI, such as pneumonia and bronchiolitis,[1] so it is expected that the overall acute LRTI burden of disease is reduced by nirsevimab, even when medical attention is not required.[19] Nevertheless, further research is needed to fully and precisely quantify the effectiveness of nirsevimab against these less specific outcomes.

Our results are in line with the 77·3% (95% CI: 50·3% to 89·7%) efficacy against hospitalisation for RSV shown in randomised clinical trials.[8] Considering that only a few countries have introduced immunisation with nirsevimab this season, studies on its effectiveness are scarce but very valuable. Our finding on nirsevimab effectiveness on preventing hospital admissions due to RSV is consistent with other works. A study conducted in other regions of Spain demonstrates effectiveness against RSV hospital admissions similar to ours, ranging between 70% and 84%.[20] Similarly, reports from Galicia show great reductions in 2023-2024 season compared to previous seasons in RSV hospital admissions in infants born between April and September.[21] Additionally, in Luxembourg, researchers observed reductions in hospitalisations of approximately 69% in children under 6 months, slightly lower than our findings.[22] Nevertheless, our study adds value by complementing previous research also with a primary care perspective, offering insights about a wide variety of outcomes of different severity. This comprehensive approach enables us to obtain a complete view of the beneficial impact of a nirsevimab immunisation campaign across all levels of care.

Our study has some limitations. The observational nature of our data may have led to some type of confounding. Nevertheless, our analysis of a negative control outcome (impetigo) suggested comparability of the cohorts, including unobserved covariables. Due to administrative and data registration issues, we were unable to include infants born after September 30, 2023 in our analysis. These infants would be the youngest during the RSV epidemic and therefore the ones most likely to benefit from immunisation with nirsevimab, potentially increasing even more the high effectiveness observed in our study. We anticipate that data on these children will become available a few months after the designated immunisation campaign ends (up to March 31, 2024), allowing us to complement our work in future research. Despite this limitation, our study provides valuable and timely insights into the effectiveness of nirsevimab across multiple primary and hospital care outcomes for infants who were less than six months old before the onset of the RSV epidemic. Given that the epidemic wave has already ended in January, the large number of infants and outcomes studied, considering that Catalonia is a large autonomous community and the entire population is included, along with the need for data to plan upcoming season, we think that it is relevant to communicate our findings now. Finally, changes in the community transmission of RSV during the study period could have a differential effect on the number of outcomes recorded in each cohort. However, our Cox regression model using a calendar time-scale approach has been identified as an unbiased method for analysing outcomes with time-varying incidence and rapid uptake of immunisations.[18]

This study also boasts several strengths. The comprehensive linkage and coverage within our database, incorporating outcomes from both primary and hospital care, is unprecedented. This enables a robust analysis of the effectiveness of nirsevimab. Such insights will empower public health authorities across different regions of the world to decide the most effective strategies for preventing RSV infections and severity in infants in future seasons. Additionally, Catalonia's universal healthcare system, supported by centralised health databases, previously utilised in numerous vaccine research studies,[23,24] maximises the completeness of outcome ascertainment. Furthermore, our study period encompasses the entirety of the 2023-2024 RSV epidemic wave, providing a comprehensive understanding of the impact of nirsevimab in reducing the negative effects of RSV infection.

In conclusion, nirsevimab has demonstrated significant effectiveness in protecting infants against a wide range of outcomes associated with RSV infection. Our findings reveal substantial reductions in severe outcomes, including hospital and ICU admissions due to bronchiolitis caused by RSV, alongside notable protection against primary care outcomes. These early real-world data provide valuable insights into the effects of nirsevimab in mitigating the burden of RSV-associated disease in infants. Moreover, they offer essential evidence to inform public health authorities and guide decision-making processes regarding the implementation and prioritisation of RSV immunisation campaigns, both in countries where such programs are already underway and in those where they have yet to commence.

Figure legends

Figure 1. Population flowchart.

Figure 2. Nirsevimab immunisation uptake expressed as percentage (coverage) from October 1, 2023, to January 31, 2024, in infants born between April and September 2023 in Catalonia.

Figure 3. Estimated risk of hospital and intensive care unit admissions due to bronchiolitis caused by RSV according to immunisation status.

Figure 4. Estimated risk of RSV infections, primary care attended bronchiolitis, viral pneumonia and hospital emergency visits according to immunisation status.

Author contributions

EC, MM-M, CC and JM conceived and designed the study. EC and FF conducted data extraction, collection, curation and verified the underlying data reported in the manuscript. EH performed the statistical analysis. EC and MM-M wrote the first draft of the manuscript. All authors were involved in interpretation of the study results, critically reviewed the content of the manuscript, and edited subsequent versions. All authors had full access to the study data, read and approved the final manuscript for submission.

Data sharing

Reasonable requests for data should be submitted to the corresponding author for consideration.

Declaration of interest

ASA has received an honorarium for attending scientific meetings from Sanofi, MSD and Pfizer. VP has received an honorarium for attending scientific meetings from Sanofi andf Pfizer. AA has received sponsorship from Sanofi to attend scientific meetings.

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Research in context

Evidence before this study

Respiratory syncytial virus (RSV) is a main cause of lower respiratory tract infections (LRTI), such as pneumonia and bronchiolitis, in infants. Nirsevimab, a new monoclonal antibody, has demonstrated high efficacy in preventing RSV-associated disease, particularly in reducing hospitalisations, as shown in previous clinical trials.

Added value of this study

Catalonia initiated a RSV immunisation campaign, presenting a unique opportunity to assess the effectiveness of nirsevimab against various outcomes. Our study reveals substantial effectiveness, with a 87·6% reduction in hospital admissions and a 90·1% reduction in ICU admissions due to RSV bronchiolitis. Additionally, we observed notable reductions in less severe outcomes, including primary care-diagnosed bronchiolitis (48·1%), RSV infections (68·9%), viral pneumonia (60·7%), and hospital emergency visits for bronchiolitis (55·4%).

Implications of all the available evidence

These findings offer timely and crucial insights for healthcare authorities, informing strategies for RSV prevention and the planning of immunisation campaigns.

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Table 1. Baseline characteristic stratified by immunisation status

Variable	Control group (N= 3,398)	Nirsevimab group (N=23,127)	SMD
Mean (SD) age, days	100 (55·3)	89·2 (52·6)	0·200*
Male sex	1,739 (51·2%)	11,916 (51·5%)	0·007
Nationality (Spanish)	2,793 (82·2%)	20,154 (87·1%)	0·138*
Rural	875 (25·8%)	5,420 (23·4%)	0·054
Mean (SD) socioeconomic status (ISC index)	42·4 (21·8)	41·1 (20·9)	0·061

*A standardised mean difference (SMD) > 0·1 is considered to indicate imbalance between cohorts

Table 2. Number of different outcomes, incidence rates (per 100,000 person days), adjusted hazard ratios, and effectiveness according to nirsevimab immunisation status

Outcome	Control group		Nirsevimab group		Adjusted hazard ratio (95% CI)	Effectiveness (95% CI)
	N	Rate per 100,000 person days	N	Rate per 100,000 person days		
RSV infection	31	4·57	71	3·04	0·311 (0·200 to 0·483)	68·9% (51·7% to 80%)
Primary care attended bronchiolitis	617	93·9	1,560	69·7	0·519 (0·467 to 0·576)	48·1% (42·4% to 53·3%)
Viral pneumonia	14	2·06	42	1·79	0·393 (0·203 to 0·758)	60·7% (24·2% to 79·7%
Hospital emergency visits	354	45·1	604	25·5	0·446 (0·385 to 0·516)	55·4% (48·4% to 61·5%)
Hospital admission	76	9·55	52	2·16	0·124 (0·086 to 0·179)	87·6% (82·1% to 91·4%)
ICU admission	17	2·13	8	0·33	0·099 (0·041 to 0·237)	90·1% (76·3% to 95·9%)

Figure 1. Population flowchart