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Multicentre study on nirsevimab: Bayesian analysis reveals persisting risk for preterm infants

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ABSTRACT

Objective To evaluate whether the timing and effectiveness of nirsevimab prophylaxis vary by gestational age.

Design Retrospective cohort study conducted during two identical epidemic seasons: 2023–2024 (before nirsevimab introduction) and 2024–2025 (after nirsevimab introduction).

Setting Multicentre study involving five hospitals in Italy.

Patients All infants under 1 year of age hospitalised for acute lower respiratory tract infection across two consecutive respiratory syncytial virus (RSV) seasons. We compared the number of RSV-positive hospitalisations (283 cases) and, among those admissions, clinical severity between the pre-nirsevimab and post-nirsevimab seasons, given live birth denominators at participating hospitals were stable. RSV-negative hospitalisations (79 cases) were analysed in parallel as a sensitivity analysis.

Intervention The study compared hospitalised infants eligible for RSV immunoprophylaxis during the 2024–2025 season who received nirsevimab, with those from the 2023–2024 season who did not receive nirsevimab (or received palivizumab, if indicated).

Main outcome measures The primary outcome was the count of RSV-associated hospitalisation, with nirsevimab prophylaxis as the primary exposure, considering live birth denominators at participating hospitals were stable. Particular attention was given to whether gestational age modified the effectiveness of the prophylaxis. Secondary outcomes included measures of disease severity (eg, high-flow nasal cannula use, neonatal intensive care unit admission), adjusted for the effect of gestational age and other relevant covariates. Bayesian hierarchical regression models were used, with sensitivity analyses performed both in negative cases and using frequentist bootstrapped hierarchical models.

Results Median gestational age at birth was 39.7 (38.7–40.7) weeks in the no-prophylaxis group versus 37.3 (35.3–39.0) weeks in the nirsevimab group. Despite prophylaxis, lower gestational age was associated with an increased risk of hospitalisation (Bayesian posterior probability, 98.68%; maximum a posteriori HR 0.63; 95% highest density interval: 0.41–0.95). No RSV hospitalisations occurred between 40 and 90 days post-prophylaxis, suggesting a window of maximal effectiveness. Nirsevimab significantly reduced RSV-related hospitalisations and the need for non-invasive respiratory support.

Conclusions Nirsevimab prophylaxis was associated with reduced hospitalisation and severity. However, protection waned in preterm infants, highlighting the need to investigate modified dosing strategies for this high-risk population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Nirsevimab is a long-acting monoclonal antibody that effectively reduces respiratory syncytial virus-related hospitalisations. However, the durability of protection and its consistency across gestational ages remains unclear.

WHAT THIS STUDY ADDS

⇒ This multicentre real-world study demonstrates that while nirsevimab significantly reduces respiratory syncytial virus-related hospitalisations and disease severity, its protective effect appears to wane in preterm infants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that current immunisation strategies may not offer sufficient protection for preterm infants, highlighting the need for modified dosing schedules or earlier prophylaxis in this population.

INTRODUCTION

Acute bronchiolitis is a viral lower respiratory tract infection that primarily affects infants under 12 months of age.[1] The leading cause of lower respiratory tract infection is respiratory syncytial virus (RSV),[2] which remains the most frequent cause of hospital admission in this age group, contributing to a significant seasonal healthcare burden.[3 4] Additionally, RSV infection is associated with long-term respiratory sequelae, including recurrent wheezing and asthma, reinforcing the urgent need for effective preventive strategies.[5]

Currently, no specific antiviral therapies have been proven effective, and management remains supportive, primarily focusing on respiratory support.[6]

Given the substantial morbidity and absence of curative treatments, research has increasingly prioritised prevention as the most effective approach to mitigating RSV impact. Before September 2024, palivizumab was the only available option, but its short half-life and high cost limited its use to high-risk infants.[7] In November 2022, the European Commission approved nirsevimab, a long-acting monoclonal antibody targeting the RSV fusion protein, a critical component for viral infectivity.[8 9]

Clinical trials have demonstrated promising efficacy and safety profiles for nirsevimab. The MELODY trial[10] reported that nirsevimab reduced RSV-associated lower respiratory tract infections by nearly 75% over 150 days postadministration, along with a notable reduction in hospitalisations and severe RSV cases. The HARMONIE trial[11] further reinforced these findings, reporting even higher efficacy rates. Real-world data from France, Spain, Ireland and Luxembourg also confirmed that incorporating nirsevimab into national immunisation programmes resulted in marked reductions in RSV-related hospitalisations and intensive care admissions.[12–17]

In Italy, nirsevimab was introduced following a 17 October 2024 deliberation, with Val d'Aosta piloting its implementation during the 2023–2024 season.[18] Nirsevimab prophylaxis is administered to all infants born during the epidemic period, defined as between 1 September 2024 and 1 March 2025, as well as to children under 24 months of age with chronic conditions previously qualifying for palivizumab prophylaxis.

A unique opportunity for studying nirsevimab real-world impact arose in our setting due to the staggered timing of prophylaxis. Although all infants born since 1 September 2024, were eligible, actual nirsevimab distribution began in October 2024, leading to substantial variation in prophylaxis timing. Some newborns received nirsevimab at birth, while others received it weeks later, allowing the investigation of the relationship between timing of administration and protection against RSV hospitalisation. No previous study has examined this aspect, making this the first real-world cohort capable of evaluating the optimal timing of nirsevimab administration.

Despite compelling evidence of nirsevimab efficacy in reducing RSV incidence, its role in mitigating disease severity remains less explored, primarily due to the low number of breakthrough RSV cases post-prophylaxis. Demonstrating its effect on disease severity presents a distinct challenge, as evidenced by the scarcity of literature on this aspect compared with its well-established role in reducing RSV incidence. Paradoxically, nirsevimab's high effectiveness in preventing infections has resulted in fewer cases, introducing methodological challenges in analysing small sample sizes. Frequentist statistical approaches, which are widely used in medical research, struggle in this context due to their primary dependence on large sample sizes to ensure statistical robustness. While effective in many scenarios, this dependency makes frequentist methods poorly suited for analysing rare events.

Bayesian statistics offers a powerful alternative, as its fundamentally different mathematical framework allows for stable and robust estimates even with limited data.[19 20] Bayesian methods stabilise effect estimates when data are sparse, skewed or imbalanced, making them particularly suitable for rapidly evaluating highly effective interventions that significantly reduce disease incidence.[21 22] Moreover, Bayesian approaches allow for incorporation of prior knowledge, improved uncertainty quantification and more intuitive probabilistic interpretations, making them increasingly adopted in medical research to address challenges like those posed in this study.[23]

In this study, we aimed to investigate whether the efficacy of nirsevimab prophylaxis in preventing RSV-associated acute lower respiratory tract infections is influenced by the gestational age of recipients. In addition, we sought to confirm existing evidence on the impact of nirsevimab in reducing both RSV infection rates and disease severity among hospitalised infants despite different baseline conditions. To address challenges inherent to real-world data, we applied robust statistical approaches, including Bayesian analysis, to overcome sample size limitations and provide more precise estimates of nirsevimab effectiveness across subgroups.

METHODS

Study design and population

This multicentre retrospective cohort study analysed hospital admissions due to acute lower respiratory tract infection during two consecutive RSV seasons in Italy, where nirsevimab prophylaxis was administered to all newborns since 1 September 2024 in all participant centres (Ravenna, Faenza, Forli, Cesena and Rimini). As the highest incidence of bronchiolitis is known to peak from November to March, we analysed time-comparable cohorts of two identical periods of admissions since 1 September to 28 February in two different winters: 2023–2024 (pre-nirsevimab) versus 2024–2025 (post-nirsevimab). Live birth denominators were stable across seasons (5130 pre-nirsevimab; 4956 post-nirsevimab). Accordingly, season-level differences in hospitalisation counts approximate live birth-normalised incidence. All hospital admissions for acute lower respiratory tract infection were collected from electronic medical records for each centre, and relevant data was collected for all patients including patient demographics, clinical characteristics and RSV status, through both centralised and specific electronic medical records. All included infants underwent nasopharyngeal swab testing for RSV at the time of admission. Hospitalisations were classified as RSV-related if the swab tested positive; otherwise, they were classified as non-RSV hospitalisations. Only infants within the first year of life at hospital admission were considered. No restriction was applied on gestational age, comorbidities or perinatal issues. Infants who received

Table 1 Summary of characteristics of the cohort under analysis

	RSV (n: 283)		P value	non-RSV (n: 79)		P value
Nirsevimab	no (n: 274, 96.8)	yes (n: 9, 3.18)	<0.05	no (n: 70, 88.6)	yes (n: 9, 11.3)	<0.05
Winter 2023–2024	229 (80.9)	0 (0.0)	/	48 (60.1)	0 (0.0)	/
Winter 2024–2025	45 (15.9)	9 (3.2)	0.27	22 (27.8)	9 (11.4)	0.27
HFNC	162 (59.1)	3 (33.3)	0.13	39 (55.7)	4 (44.4)	0.77
CPAP	38 (13.9)	0 (0.0)	0.99	0 (0.0)	0 (0.0)	/
Mechanical ventilation	4 (1.5)	0 (0.0)	0.99	0 (0.0)	0 (0.0)	/
Length of hospital stay	4.00 (2.00–6.00)	3.00 (2.00–7.00)	0.61	3.00 (2.00–7.00)	4.00 (4.00–7.00)	0.33
Oxygen saturation at hospital admission	96.00 (93.75–97.00)	97.00 (96.75–98.00)	<0.05	96.00 (93.00–98.00)	96.00 (94.00–98.00)	0.70
Sex male	165 (60.2)	5 (55.6)	0.99	37 (52.9)	5 (55.6)	0.99
Gestational age at birth (weeks)	39.67 (38.67–40.67)	37.33 (35.33–39.00)	<0.001	39.00 (37.21–40.00)	39.33 (38.17–39.67)	0.72
Birth weight	3351.00 (2964.00–3643.75)	2678.00 (2178.00–3315.00)	<0.01	3070.00 (2566.50–3475.25)	2980.00 (2512.00–3040.00)	0.95
Perinatal problems	31 (11.3)	2 (22.2)	0.33	19 (24.1)	1 (11.1)	0.35
Comorbidities	30 (10.9)	2 (22.2)	0.31	13 (16.5)	0 (0.0)	0.99
Age at hospitalisation (months)	2.76 (1.61–5.19)	3.48 (1.38–3.52)	0.90	3.99 (2.31–6.25)	2.99 (1.81–3.25)	0.09

This table presents the demographic, clinical and hospitalisation characteristics of infants hospitalised with RSV and non-RSV bronchiolitis during the study period, stratified by nirsevimab prophylaxis status. Data are expressed as median and IQR for continuous variables and counts with percentages for categorical variables.
CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; RSV, respiratory syncytial virus.

palivizumab prophylaxis were included in the pre-nirsevimab cohort to ensure a consistent comparison between standard-of-care strategies across seasons and to avoid excluding preterm infants who were eligible for prophylaxis prior to the introduction of nirsevimab. Baseline variables, summarised in table 1, were measured at hospital admission.

Exposure and outcomes

Primary exposure: nirsevimab prophylaxis versus no prophylaxis or pavilizumab.

Primary outcome: RSV hospitalisation by gestational age.

Secondary outcomes:

- Need for respiratory support: high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), mechanical ventilation. The need for respiratory support was defined as the use of the support at any time during hospitalisation.
- Length of hospital stay.
- Oxygen saturation at admission.

In order to account for all relevant variables influencing either exposure or treatment status, all models were stratified for gestational age and possible relevant covariates taking into account centre variability through hierarchical regression models.

Statistical analysis

All baseline characteristics variables possibly influencing either exposure or treatment status were checked through an initial univariate association. When present, missing data for both outcomes and predictors were addressed using multiple imputation by chained equations. Five imputed data sets were generated, employing predictive mean matching for continuous variables, logistic regression for binary variables, polytomous regression for unordered categorical variables and proportional odds models for ordered categorical variables. The resulting data sets were then pooled and used for all subsequent analyses, following established procedures described in previous studies.[24 25] The extent of missing data was below 1.5% for all variables with at least one missing value. Baseline clinical characteristics which are clinically known to potentially influence exposure-outcome relationship and their associations were calculated using non-imputed data. Variables significantly associated were then tested for collinearity and association prior to inclusion in the regression model. Continuous variables that showed a significant correlation were merged through principal component analysis and considered as model covariates. Categorical associated variables were selected based on their strength of association with other covariates and discarded in case of significant association being detected. The final pool of covariates was included in the regression models, including healthcare centre as a random variable.

Bayesian regression models

Bayesian hierarchical regression models were employed to account for potential variability across the different

healthcare centres participating in the study. Consistent with prior studies,[24] models were fitted using Markov chain Monte Carlo with eight chains, 2000 warm-up iterations and 4000 sampling iterations per chain. A Cox proportional hazards model was used to assess the effect of protection timing—defined as the interval between nirsevimab administration and hospital admission—on the primary outcome, limited to infants who received prophylaxis. An unadjusted Kaplan-Meier survival curve was generated stratifying infants as preterm or term using a 37-week gestational age threshold, in order to graphically illustrate such effect. To evaluate the impact of nirsevimab on respiratory support, Bayesian logistic regression models were applied to the entire cohort. A regression model was also elaborated to assess whether the interval between birth and nirsevimab administration was associated with the risk of subsequent RSV hospitalisation among prophylaxed infants. Based on outcome distribution and graphical assessment, Poisson regression was used to model length of hospital stay, on the whole cohort. A beta regression model, appropriate for continuous outcomes bounded between 0 and 1, was used to model oxygen saturation at admission based on its distributional characteristics and also applied to the whole cohort. All models were stratified by gestational age, which was included as a continuous variable, and adjusted for relevant covariates selected based on clinical relevance and supported by univariate association analyses. These covariates included birth weight, comorbidities and age at hospitalisation. Uninformative priors were used to reflect limited prior knowledge and uncertainty: fixed effects followed a Gaussian distribution with mean 0 and SD 10, and random effects used an exponential prior with lambda 1. Posterior probabilities were visualised as log-risk ratios for the main variable (gestational age or nirsevimab) and reported as the proportion of posterior draws favouring superiority. A probability near 50% indicates no effect; higher values reflect increasing association with the outcome. Effect estimates are presented as HRs for Cox models and ORs for logistic, Poisson and beta models, using the maximum a posteriori (MAP) estimation, which regularises the maximum likelihood estimation for the point estimate effect in the model. A 95% high-density interval (HDI) is provided as a credible interval for the estimation, indicating the credible region of the posterior draws and reflecting the strength and precision of the MAP point estimate. Bayes factors (BFs) were calculated to compare each model against a null model excluding the primary variable, providing quantitative support for inclusion. To promote transparency and reproducibility, the full Bayesian framework has been made available through the R package bayer (https://github.com/cccnrc/bayer). All analyses were performed using R V.4.4.2.

Sensitivity analysis

In order to prove the robustness of the identified results overcoming the cohort imbalance, multiple sensitivity analyses were applied. First, non-RSV cases were tested using the same exact models served for the primary cohort in order to confirm absence of identified effects. Secondarily, we performed a frequentist confirmation analysis deploying hierarchical frequentist regression models using 10 000 bootstrapped permutations in order to overcome limitations associated with unbalanced groups, treating centre and season as random variables, as a robustness check. Frequentist results are presented as 95% confidence interval (CI) and relative p-value (p).

RESULTS

We collected 362 acute bronchiolitis hospitalisation cases during the study period, of which 283 RSV and 79 non-RSV cases. In the 2024–2025 respiratory virus season, RSV-related hospitalisations decreased from 229 to 54 cases following the introduction of nirsevimab. Notably, 83% of these hospitalisations occurred in infants who had not received prophylaxis, further highlighting the effectiveness of nirsevimab in preventing RSV-related hospitalisations. Non-RSV cases showed no significant differences, with 48 cases in the 2023–2024 winter and 31 in the 2024–2025 season. Table 1 summarises characteristics of the cohort under analysis. Only five infants in the cohort received palivizumab prophylaxis, representing a group too small to allow for meaningful subgroup analyses or inclusion as a covariate in statistical models. Consistent with previous reports, nirsevimab prophylaxis strongly reduced RSV infection rates, with a posterior probability of 99.97% (MAP OR 0.38, 95% HDI 0.22–0.65, BF 229.82). The effect was further corroborated by a bootstrapped frequentist hierarchical model, which yielded consistent results (95% CI 0.21 to 0.69, p=0.002). Nirsevimab demonstrated a robust protective effect against RSV-related hospitalisations, significantly reducing their incidence throughout the entire epidemic season, as shown in figure 1. The only period during which RSV hospital admissions between the two seasons appeared comparable was at the very beginning of the epidemic, when the prophylaxis campaign had just started and a substantial proportion of newborns had not yet received the monoclonal antibody. By early December—approximately 6 weeks after the start of prophylaxis—the effect of nirsevimab became evident, with hospitalisation rates remaining markedly lower than those observed during the previous winter season.

Primary outcome: RSV-related hospitalisation

Preterm infants accounted for only 5.2% of all births in the study region over the past 3 years, yet they represented 10.1% of RSV-related hospitalisations prior to the introduction of nirsevimab and 44.4% thereafter. The Bayesian Cox model demonstrated that lower gestational age was significantly associated with a higher risk of RSV hospitalisation following nirsevimab administration, with a posterior probability of 98.68% (MAP HR 1.58, 95% HDI 1.05–2.44, BF 12.2). To illustrate this effect,

Figure 1 Impact of nirsevimab prophylaxis on RSV and non-RSV bronchiolitis admissions. This figure illustrates the daily hospital admissions for bronchiolitis in two consecutive respiratory syncytial virus seasons: 1 September 2023–28 February 2024 (pre-nirsevimab, orange) and 1 September 2024–28 February 2025 (post-nirsevimab, green). Top panel: Overall daily bronchiolitis admissions, showing a substantial decline in hospitalisations during the post-nirsevimab season. Bottom left panel: RSV-positive bronchiolitis admissions, highlighting a marked reduction in RSV-related hospitalisations after nirsevimab introduction. Bottom right panel: RSV-negative bronchiolitis admissions, demonstrating no significant change between the two seasons, indicating that the reduction observed in overall admissions was due to decreased RSV-related cases. These findings suggest a strong protective effect of nirsevimab prophylaxis in reducing RSV-related hospitalisations without impacting non-RSV bronchiolitis trends. RSV, respiratory syncytial virus.

a Kaplan-Meier survival curve was generated (figure 2), comparing RSV-free survival rates—defined as the time from nirsevimab administration to RSV-related hospitalisation—with infants stratified as preterm or term using a 37-week gestational age threshold. Notably, no RSV hospitalisations were observed in either group between 40 and 90 days post-nirsevimab, aligning with previous literature.[26] Sensitivity analysis using a bootstrapped frequentist hierarchical Cox model confirmed this association, with consistent results (HR 1.69, 95% CI 1.07 to 2.56, p=0.02).

Time from birth to nirsevimab administration was not significantly associated with the timing of subsequent RSV infection, as indicated by a posterior probability of 52.83% (MAP HR 1.02, 95% HDI 0.98–2.73, BF <1) further confirmed by sensitivity analysis. However, it is important to consider that a longer interval between birth and prophylaxis inherently extends the period during which the infant remains unprotected, thereby prolonging the window of vulnerability to RSV infection.

Secondary outcomes: RSV severity reduction

Oxygen saturation at hospital admission

The Bayesian beta distribution model revealed an 88.38% posterior probability of higher oxygen saturation at hospital admission in the nirsevimab group (MAP OR 1.31, 95% HDI 0.84–2.16, BF 1.06). Sensitivity analysis in non-RSV cases confirmed the trend but did not reach significance. The bootstrapped frequentist hierarchical regression model supported the trend, identifying overlapping 95% CI, though significance was not reached.

Non-invasive respiratory support

Nirsevimab conferred strong protection against the need for HFNC (posterior probability: 98.25%, MAP OR 0.21, 95% HDI 0.03–0.94, BF 16.7) and CPAP (posterior probability: 99.68%, MAP OR 0.11, 95% HDI 0.01–0.64, BF 217.4), with no cases in the nirsevimab group requiring CPAP. Sensitivity analyses on non-RSV cases found no significant differences (posterior probabilities: 65.63% for HFNC and 51.67% for CPAP, both with HDIs overlapping 1 and BFs <3). Frequentist bootstrap hierarchical models on RSV case confirmed the association, with overlapping 95% CI and significant p values (0.03 for HFNC, <0.001 for CPAP).

Invasive respiratory support

For mechanical ventilation, the Bayesian model suggested a protective effect with a posterior probability of 86.64% (MAP OR 0.11, BF 15.36), though the HDI overlapped 1,

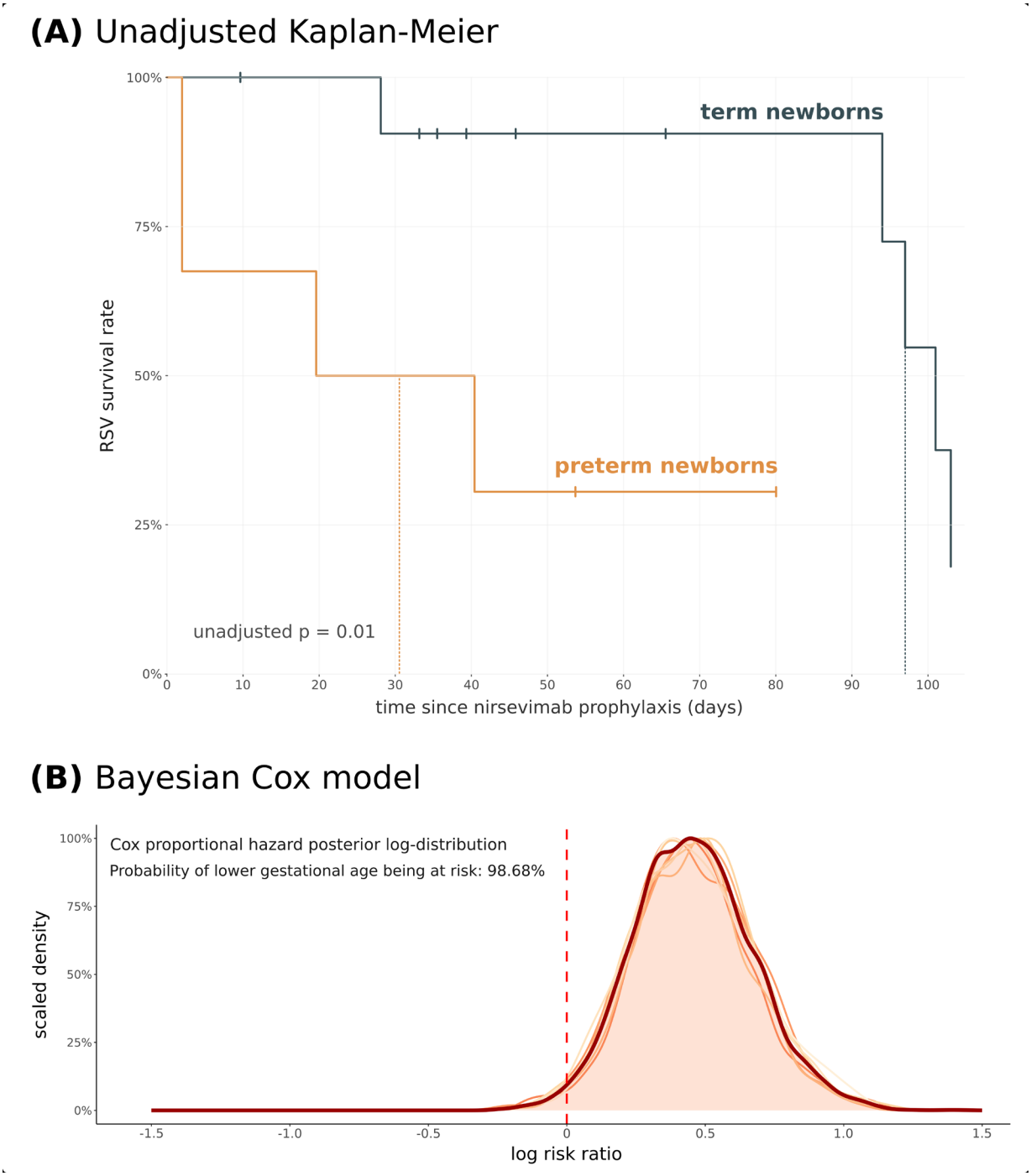

Figure 2 Gestational age and timing of RSV hospitalisation after nirsevimab prophylaxis. This figure illustrates the association between gestational age and the timing of RSV-related hospitalisation in infants receiving nirsevimab prophylaxis. *Panel A, unadjusted Kaplan-Meier survival curve*: This plot compares RSV-free survival rates—defined as the time from nirsevimab administration to RSV-related hospitalisation—between preterm (yellow) and term (blue) newborns after nirsevimab administration. Preterm infants exhibit a significantly higher risk of hospitalisation. Notably, no RSV hospitalisations were observed in either group between days 40 and 90 post-nirsevimab administration, suggesting a period of maximal protection. Dashed lines represent the median survival time for each group. Unadjusted Kaplan-Meier p value is reported. *Panel B, Bayesian Cox proportional hazard model*: To overcome the limitations associated with the low number of patients when categorising them as term or preterm, we employed a Bayesian hierarchical Cox proportional hazards model using gestational age as a continuous covariate (see Methods section). This panel displays the Bayesian posterior log-risk distributions from eight Markov chain Monte Carlo simulations (depicted in yellow and orange lines), alongside the overall averaged posterior log-risk distribution (shown as a thick red line). The dashed vertical line at the zero log-risk point indicates no difference in the risk of RSV-free survival rate between different gestational ages at birth. The distribution strongly skews to the right, suggesting a higher probability of lower gestational ages to be at higher risk, with a calculated probability of 98.68% (MAP HR 1.58, 95% HDI 1.05–2.44, BF 12.2). RSV, respiratory syncytial virus.

likely due to the limited number of cases. A similar non-significant trend was observed in non-RSV cases (posterior probability: 65.48%, MAP OR 1.12, BF 1.72, with an HDI overlapping 1), as confirmed by bootstrapped frequentist hierarchical model.

Length of hospital stay

Consistent with other findings, the Bayesian Poisson hierarchical modelling revealed a 93.71% posterior probability of a shorter length of hospital stay in the nirsevimab group (MAP OR 0.77, 95% HDI 0.55–1.09, BF 1.26). Interestingly, an inverse trend was observed in negative cases, with a posterior probability of prolonged hospitalisation of 83.66% (MAP OR 1.12, 95% HDI 0.84–1.63, BF <1). The bootstrapped frequentist hierarchical model further supported the trend, yielding a consistent 95% CI (0.79 to 1.12) without reaching significance (p=0.16).

DISCUSSION

This study provides evidence that infants with lower gestational age remain at higher risk of RSV-related hospitalisation despite nirsevimab prophylaxis. This aspect has not been previously explored in detail, highlighting the need for gestational age-specific considerations in RSV prophylaxis strategies. We also confirmed the protective role of nirsevimab in reducing RSV-related hospitalisations[11 27] and provide compelling evidence of its ability to mitigate disease severity among hospitalised infants, when adjusted for the effect of gestational age and other relevant covariates. The significant reduction in non-invasive respiratory support requirements, combined with a trend toward lower mechanical ventilation rates, suggests that prophylaxis may modify the disease course in breakthrough cases.

Gestational age and protection timing

The increased risk of RSV hospitalisation in preterm infants despite nirsevimab prophylaxis raises important clinical considerations. Several factors may contribute to this increased vulnerability, including developmental immaturity of the immune system, altered pharmacokinetics and potential differences in the persistence of nirsevimab protective effect in preterm versus term infants. Additionally, reduced transplacental antibody transfer in preterm infants may play a role, aligning with observations from the post-COVID-19 RSV resurgence, where a hypothesised loss of maternal immunity due to curfews and reduced viral circulation led to increased RSV incidence.[28 29]

These findings suggest that alternative or supplemental dosing regimens may be necessary to optimise RSV protection in this particularly high-risk population.

Reduction in disease severity

The Bayesian analysis provides compelling evidence of strong protective effects against HFNC and CPAP use, further supporting nirsevimab's role in mitigating disease burden, even when adjusted for gestational age and other relevant covariates. Consistently, a trend toward reduced mechanical ventilation and shorter hospital stay in RSV cases that underwent nirsevimab prophylaxis was detected. Interestingly, our findings suggest a longer length of stay for non-RSV cases following nirsevimab introduction. We speculate that this may be a consequence of the overall reduction in RSV hospitalisations, which have allowed clinicians to extend the duration of hospitalisation for non-RSV cases, ensuring comprehensive care and monitoring in the absence of RSV-related bed occupancy pressures. Further research is needed to validate this hypothesis and explore its potential implications for hospital resource allocation.

Methodological innovation: Bayesian approach

A key strength of our study is the use of Bayesian statistical modelling to address the methodological challenges posed by the natural reduction in RSV cases following nirsevimab prophylaxis. Unlike frequentist models, which rely on large sample sizes for statistical robustness, Bayesian methods provide stable estimates despite small sample sizes, allowing for a more precise assessment of nirsevimab impact on disease severity. Beyond this study, our findings highlight a broader shift in medical research methodology. As highly effective public health interventions reduce disease incidence, future evaluations will face similar challenges with low event rates. The growing role of Bayesian methods in clinical research[19] enables earlier and more robust conclusions, enhancing evidence-based decision-making for new preventive strategies. Their integration into future studies will be essential for optimising data interpretation and guiding public health policies in low-incidence contexts.

Clinical and public health implications

Our findings reinforce the critical role of nirsevimab prophylaxis in reducing RSV burden, both in terms of infection rates and disease severity. From a clinical perspective, the identification of gestational age-specific differences in protection timing suggests that current prophylaxis strategies may need refinement. Lower gestational age infants remain at higher risk of early RSV-related hospitalisation, raising the possibility that alternative dosing strategies (higher or more frequent doses) may be warranted in this subgroup.

Study limitations and future directions

Despite its strengths, our study has some limitations. The limited number of RSV cases requiring mechanical ventilation precluded definitive conclusions on nirsevimab impact on the most severe disease forms. While Bayesian methods improved inference, larger multicentre studies would further validate our findings. Additionally, our study lacked long-term follow-up on recurrent RSV infections or potential waning immunity over time. Furthermore, we were unable to assess circulating antibody levels at birth and after nirsevimab immunisation, which

could have provided insights into the pathophysiological mechanisms underlying the differences observed in our cohort, particularly in preterm infants.

Future research should focus on expanding sample sizes through multicentre collaborations, confirming the observed trends and evaluating long-term protection durability, especially in preterm populations. Additionally, further studies should investigate biological mechanisms underlying differential immune responses, which could be critical for refining immunisation strategies and optimising dosing regimens across gestational age groups.

CONCLUSION

This study confirms the strong protective effect of nirsevimab against RSV-related disease severity and provides novel insights into the timing of protection. For the first time, we demonstrate that gestational age significantly influences the timing of RSV-related hospitalisation despite prophylaxis, with preterm infants remaining at higher risk of infection. These findings suggest that additional or modified prophylactic strategies may be necessary to optimise protection in high-risk populations.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by Comitato Etico di IRST e di Area Vasta Romagna (C.E.ROM.), protocol number 3924/2024. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Completely anonymised data will be available to qualified academic investigators to replicate study results by reasonable request. Data transfer will be regulated by material transfer agreements.

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