180-day efficacy of nirsevimab against hospitalisation for respiratory syncytial virus lower respiratory tract infections in infants (HARMONIE): a randomised, controlled, phase 3b trial

*Alasdair P S Munro, Simon B Drysdale, Katrina Cathie, Florence Flamein, Markus Knuf, Andrea M Collins, Helen C Hill, Friedrich Kaiser, Robert Cohen, Didier Pinquier, Natalya C Vassilouthis, Mariana Carreno, Catherine Moreau, Pierre Bourron, Lydie Marcelon, Karine Mari, Michelle Roberts, Pierre Tissières, Simon Royal, Saul N Faust, for the HARMONIE Study Group**

Lancet Child Adolesc Health 2025; 9: 404–12

This online publication has been corrected. The corrected version first appeared at thelancet.com/child-adolescent on July 8, 2025

*Members are listed in the appendix pp 3–13

National Institute for Health and Care Research Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, UK (A P S Munro PhD, K Cathie MD FRCPCH, Prof S N Faust PhD FRCPCH); Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK (A P S Munro, K Cathie, Prof S N Faust); Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK (S B Drysdale PhD FRCPCH); The NIHR Oxford Biomedical Research Centre, Oxford, UK (S B Drysdale); Université de Lille, INSERM, Centre Hospitalier Universitaire (CHU) de Lille, CIC-1403 INSERM-CHU, Lille, France (F Flamein MD PhD); French Clinical Research Infrastructure Network–PEDSTART, Tours, France (F Flamein); Children's Hospital, Worms, Germany (Prof M Knuf PhD); Pediatric Infectious Diseases, University Medicine, Mainz, Germany (Prof M Knuf); Liverpool Vaccine Group, Liverpool School of Tropical Medicine, Liverpool, UK (A M Collins MD PhD, H C Hill PhD); Liverpool University Hospitals Foundation NHS Trust, Liverpool, UK (A M Collins); Gemeinschaftspraxis für Kinder und Jugendmedizin, Hamburg,

Summary

Background Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection and hospitalisations in infants worldwide. The primary analyses of HARMONIE showed that nirsevimab reduced infant hospitalisations due to RSV-associated lower respiratory tract infection through the RSV season. This analysis aims to evaluate nirsevimab's efficacy at 180 days after dosing, a period exceeding the typical 5-month RSV season.

Methods HARMONIE is an ongoing, open-label, parallel arm, randomised, controlled, phase 3b study conducted in France, Germany, and the UK. Infants aged 12 months or younger, born at a gestational age of at least 29 weeks, were randomly assigned (1:1) to receive either a single intramuscular dose of nirsevimab (50 mg for children <5 kg or 100 mg for children ≥5 kg) or standard care (without RSV prophylaxis) before or during their first RSV season. Randomisation was electronically done, stratified by country and age-group. The primary efficacy endpoint for this analysis was the incidence of hospitalisations due to RSV-associated lower respiratory tract infection up to 180 days after nirsevimab administration or randomisation in all randomised participants. Safety up to 365 days following nirsevimab administration was also assessed. This trial is ongoing and registered with ClinicalTrials.gov, number NCT05437510.

Findings Between Aug 8, 2022, and Feb 28, 2023, 8057 infants were randomly assigned to either the nirsevimab group (n=4038) or the standard care group (n=4019). The median age at randomisation was 4·00 months (IQR 1·0–7·0; range 0·0–12·0, and 4195 (52·1%) were male and 3862 (47·9%) were female. Up to 180 days, 12 (0·3%) of 4038 infants in the nirsevimab group and 68 (1·7%) of 4019 infants in the standard care group had been hospitalised for RSV-associated lower respiratory tract infection, corresponding to a nirsevimab efficacy of 82·7% (95% CI 67·8–91·5; p<0·0001). Most participants experienced grade 1 (2759 [68·7%] of 4016 in the nirsevimab group; 2696 [67·1%] of 4018 in the standard care group) or grade 2 (1447 [36·0%] of 4016 in the nirsevimab group; 1436 [35·7%] of 4018 in the standard care group) treatment-emergent adverse events, and no apparent safety concerns were raised up to 365 days after dosing.

Interpretation Nirsevimab offers consistent and sustained protection against hospitalisation due to RSV-associated lower respiratory tract infection for at least 6 months. This finding provides global health systems greater flexibility when implementing nirsevimab, providing substantial benefit in the ongoing effort to reduce the burden of infant RSV and the potential wider public health value.

Funding Sanofi and AstraZeneca.

Introduction

Lower respiratory tract infections associated with respiratory syncytial virus (RSV) are a major cause of morbidity and mortality in infants worldwide.[1] RSV-associated lower respiratory tract infection is the most common cause of hospitalisation of children in high-income countries.[1] Most hospitalisations from RSV-associated lower respiratory tract infection occur in otherwise healthy children with no comorbidities.[1] Illness associated with RSV infection results in a large burden on hospitals, public health, and primary care systems.[2,3] Until recently, no options to prevent severe RSV infection in children without comorbidities or specific risk factors have been available.

Nirsevimab is an extended half-life monoclonal antibody (mAb) that neutralises RSV.[4] Phase 2b and phase 3 clinical trials have demonstrated it to be highly effective at protecting full-term and preterm infants with or without comorbidities from severe RSV infection.[5,6] Following these findings, several countries have

Research in context

Evidence before this study

We searched PubMed for clinical trials in infants during their first respiratory syncytial virus (RSV) season published between database inception and March 4, 2025, using the terms, "(nirsevimab) AND (RSV) AND (clinical trial)", with no language restrictions. We found no clinical trials of nirsevimab that evaluated efficacy in infants up to 180 days post administration. Existing clinical trials have only evaluated nirsevimab up to 150 days in healthy late preterm and term infants, and have found it to significantly reduce RSV-associated lower respiratory tract infection in this population.

Added value of this study

This is the first clinical trial of nirsevimab demonstrating that the protection offered by nirsevimab extends beyond the typical RSV season, providing sustained efficacy for up to 180 days after administration.

Implications of all the available evidence

This analysis suggests that nirsevimab can significantly reduce the burden of hospitalisations due to RSV-associated lower respiratory tract infection in infants. This extended duration of protection offers greater flexibility for global health systems in implementing nirsevimab as part of routine immunisation schedules. This study supports the inclusion of nirsevimab in national immunisation programmes and highlights the need for further research to evaluate its long-term impact, including its effect on pre-school wheezing illnesses.

introduced nirsevimab into their routine child immunisation schedule. Real-world evidence from several countries including Spain,[7,8] Luxembourg,[9] Italy,[10] France,[11] and the USA[12] provides further evidence for nirsevimab in protecting all infants against RSV-associated lower respiratory tract infection, with effectiveness ranging from 70% to 90%. In 2023, the primary outcome results of the HARMONIE pragmatic randomised clinical trial demonstrated 83·2% (95% CI 67·8–92·0) efficacy in protecting infants against hospitalisations due to RSV-associated lower respiratory tract infection during their first RSV season.[13]

Although the primary outcome results of the HARMONIE trial showed excellent efficacy up to the end of the participants' first RSV season, the full duration of protection is still unknown. The half-life of nirsevimab is about 70 days[4] compared with the half-life of maternal IgG when passed onto term infants being about 50 days from birth.[14,15] The aim of this study was to evaluate the efficacy of nirsevimab versus standard care (no intervention) against hospitalisation due to RSV-associated lower respiratory tract infection in the HARMONIE randomised controlled trial at 6 months after administration. Safety up to 12 months is also reported.

Methods

Study design and participants

HARMONIE is a multicentre, randomised, open label, controlled, phase 3b trial assessing the protection of nirsevimab against hospitalisation due to RSV-associated lower respiratory tract infection versus standard care. The study was conducted across 235 sites in primary and secondary care settings (64 sites in Germany, 64 sites in France, 107 sites in the UK), with the primary analyses previously reported.[13] The trial protocol (provided in the appendix p 26) and any amendments were approved by the appropriate independent ethics committee or institutional review board at each participating site and by the relevant regulatory agencies in each country in accordance with local regulations (UK NHS Research Ethics Committee #22/SC/0132; France Comité de Protection Des Personnes Sud-Est Iv #22.01486.000060; Germany Ethik-Kommission der Landesärztekammer Rheinland-Pfalz, #2022-16494-AMG-ff). Consent was given by the parents or legally acceptable representatives of all the infants before any trial procedures were performed.

Infants were eligible for inclusion if they were otherwise healthy, 12 months of age or younger, born at a gestational age of 29 weeks or over, entering their first RSV season, and not eligible for palivizumab treatment. These criteria included infants born either before or during the RSV season, which started on Sept 11, 2022 (week 37) in France; on Oct 9, 2022 (week 41) in Germany; and on Sept 4, 2022 (week 36) in the UK. The RSV season concluded on Feb 28, 2023, in all three countries. A full list of inclusion and exclusion criteria is available in the appendix (p 14). This trial is ongoing and registered with ClinicalTrials.gov, number NCT05437510.

Randomisation and masking

Eligible infants were randomly assigned (in a 1:1 ratio) to receive either a single intramuscular injection of nirsevimab (50 mg for infants weighing <5 kg and 100 mg for those weighing ≥5 kg) or standard care (without RSV prophylaxis). Randomisation was performed centrally via an interactive response technology system and stratified by country and age group (≤3·0 months, >3·0 to ≤6·0 months, and >6·0 months). The study followed an open-label design (provided in the appendix p 22), so neither neither parents or guardians of participants nor study investigators nor study investigators were masked to the treatment allocation; however, treating physicians

Germany (F Kaiser MD); **Centre Hospitalier Intercommunal de Créteil, and Association Clinique et Thérapeutique Infantile du Val-de-Marne, Créteil, France** (R Cohen MD); **Department of Neonatal Pediatrics and Intensive Care and Neuropediatrics, Charles Nicolle University Hospital, Rouen, France** (D Pinquier MD); **Sanofi, Reading, UK** (N C Vassilouthis MD, M Carreno MD); **Sanofi Vaccines, Marcy L'Etoile, France** (C Moreau MSc, K Mari PhD); **Sanofi Vaccines, Lyon, France** (P Bourron PharmD, L Marcelon PhD); **Sanofi Vaccines, Bridgewater, NJ, USA** (M Roberts MD); **IHU-PROMETHEUS Comprehensive Sepsis Center and Pediatric Intensive Care, Neonatal Medicine, and Pediatric Emergency Department, AP-HP Paris Saclay University, Bicêtre Hospital, Le Kremlin-Bicêtre, France** (Prof P Tissières MD DSc); **Institute of Integrative Biology of the Cell, Centre National de la Recherche Scientifique, Commissariat à l'Energie Atomique, Paris–Saclay University, Gif sur Yvette, France** (Prof P Tissières MD DSc); **University of Nottingham Health Service, University of Nottingham, Nottingham, UK** (S Royal MPH MRCGP)

Correspondence to:
Prof Saul N Faust, National Institute for Health and Care Research Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO166YD, UK
s.faust@soton.ac.uk

See Online for appendix

treating participants admitted to hospital were rarely involved as study investigators.

Procedures

Infants were enrolled in the HARMONIE trial between Aug 8, 2022, and Feb 28, 2023. From day 1 (the day of randomisation and administration of the nirsevimab injection), all infants were remotely monitored for safety events, including admissions to hospital due to lower respiratory tract infections, up to 365 days after randomisation (ie, 12 months follow-up). This monitoring was based on reports submitted by parents or legally acceptable representatives through electronic diaries. During the first 6 months after randomisation, parents or legally acceptable representatives received monthly automated reminders to submit reports in the electronic diaries. Investigators at trial sites reviewed the reports and contacted parents or representatives for further details if necessary.

On day 366, all parents or legally acceptable representatives were contacted by telephone to gather information on any safety events that occurred since day 181, the last time they entered information in the electronic diary.

Infants with lower respiratory tract infections who were admitted to hospital by their treating physicians underwent routine diagnostic testing for RSV according to hospital protocols. Parents and legally acceptable representatives were also provided with a card to give to the treating physician, to encourage RSV testing if it had not yet been done and to facilitate data transfer to the trial sites.

Centralised data review was performed to ensure completeness and consistency of the collected data. Every effort was made to retrieve missing data by means of data-management queries, onsite monitoring visits, and remote follow-up.

Outcomes

The trial endpoints were aligned with the European Medicines Agency guidelines for the clinical evaluation of medicinal products intended for RSV prophylaxis. The efficacy endpoints for this analysis were the incidence of hospitalisation due to RSV-associated lower respiratory tract infection up to 180 days after randomisation. Lower respiratory tract infection was diagnosed by the treating physician, and RSV was confirmed in diagnostic tests according to routine practice in France, Germany, and the UK.

Secondary endpoints were incidence of very severe RSV-associated lower respiratory tract infection up to 180 days defined as hospitalisation due to RSV-associated lower respiratory tract infection with oxygen saturation below 90% and requiring oxygen supplementation at any time during treatment in hospital (according to WHO case definition); incidence of hospitalisation due to RSV-associated lower respiratory tract infection in each country up to 180 days; and incidence of hospitalisations due to all-cause lower respiratory tract infection up to 180 days.

Adverse events were monitored throughout the trial and coded according to MedDRA version 25.0. Non-serious adverse events were assessed up to day 31, whereas adverse events of special interest, medically attended adverse events, and serious adverse events were evaluated for up to day 365 after randomisation. Adverse events of special interest included hypersensitivity reactions such as anaphylaxis, immune complex disease, and thrombocytopenia. Medically attended adverse events were those that prompted the infant's parents or legally acceptable representatives to seek unplanned, in-person medical advice in any clinical setting.

Previously, outcomes as of the end of the RSV season (Feb 28, 2023) have been reported.[5] This study reports the outcomes up to 180 days of follow-up, extending it past the end of the RSV season for most participants. In the UK, participant follow-up was extended to 24 months after enrolment, whereas the study ended after 12-month follow-up in France and Germany.

Statistical analysis

This report is based on the first-year analysis, which was concluded when participants had completed the scheduled 12-month safety follow-up phone call or terminated the study earlier. All randomised participants were included in the efficacy analyses (all randomised set). For participants with multiple occurrences of an efficacy endpoint, only the first occurrence was used in the analysis. Safety was assessed in all participants who received nirsevimab and all participants randomised to the standard care group (safety analysis set). There was no data monitoring committee for this study.

The incidence rate expressed as person-month was calculated as the number of participants who had an efficacy endpoint of interest divided by the total person-time (in months) contributed by participants randomised in the corresponding group. The efficacy of nirsevimab in preventing hospitalisation due to RSV-associated lower respiratory tract infection up to 180 days after randomisation was defined as (1 minus the incidence rate ratio) × 100%. The efficacy up to 180 days after randomisation was calculated by the exact method using binomial distribution accounting for the follow-up time. No multiplicity adjustments were conducted. The efficacy outcome was analysed by intention to treat, and efficacy estimates are presented as a percentage with 95% CI.

We compared treatment group differences in time to first hospitalisation RSV-associated lower respiratory tract infection using the log-rank test stratified by country and age group at randomisation and presented in a Kaplan-Meier plot.

Efficacy analysis of nirsevimab in preventing RSV-associated lower respiratory tract infection up to 180 days after randomisation were conducted in subgroups according to age group at randomisation (≤3·0 months,

>3·0 to ≤6·0 months, and >6·0 months), weight at randomisation and timing of dosing (before or during the season). 2-sided 95% CIs for the efficacy were presented in a forest plot and calculated by an exact method assuming a binomial distribution of the number of hospitalisations due to RSV-associated lower respiratory tract infection up to 180 days after randomisation in the nirsevimab group conditional on the total number in both groups (described by Breslow and Day) accounting for the follow-up time after randomisation. All data processing, summarization and analyses were performed using SAS environment version 9.4.

Role of the funding source

The trial was funded by AstraZeneca and Sanofi. This trial was designed by SNF with input from other authors and from Sanofi, the trial sponsor. The sponsor led the collection and statistical analysis of the data and jointly interpreted the data with academic authors.

Results

Of 8119 infants screened, 8057 were included in the study from 235 sites in the three participating countries (2177 [27·0%] in France, 1789 [22·2%] in Germany, and 4091 [50·8%] in the UK). Between Aug 8, 2022, and Feb 28, 2023, these 8057 infants were randomly assigned to receive either nirsevimab (4038 infants) or standard care (4019 infants). Among the 4038 infants assigned to the nirsevimab group, 23 (0·6%) did not receive passive immunisation with nirsevimab. One infant assigned to the standard care group wrongly received the study intervention (due to an error in reading the randomisation notification).

At the time of the data cutoff for the first-year analysis, follow-up data were available for 4038 infants assigned to the nirsevimab group and 4019 assigned to the standard care group (figure 1). In the safety analysis, the nirsevimab group included 4016 immunised infants (including the infant from the standard care group immunised by error) and the standard care group included 4018 not immunised infants.

The study population included 4195 (52·1%) males and 3862 (47·9%) females, and the median age at randomisation was 4·00 months (IQR 1·0–7·0; range 0·0–12·0; table 1). 6868 (85·2%) infants had a gestational age at birth of 37 weeks or longer. 946 (23·4%) infants in the nirsevimab group and 963 (24·0%) infants in the standard care group were neonates (aged 0–28 days) at the time of randomisation. Overall, 2175 (27·0%) infants had at least one medical condition reported (1086 [26·9%] in the nirsevimab group and 1089 [27·1%] in the standard care group; table 1). Prevalence of medical conditions at baseline was similar between the treatment groups. The most frequently reported medical conditions were a past diagnosis of bronchiolitis (3·2%), gastroesophageal reflux disease (2·7%), and preterm birth (2·5%). A table of the representativeness of study participants is available in supplementary appendix (p 17).

Hospitalisations due to RSV-associated lower respiratory tract infection occurred in 12 (0·3%) of 4038 infants in the nirsevimab group (incidence rate 0·001 person-months) and in 68 (1·7%) of 4019 infants in the standard care group (incidence rate 0·003 person-months) up to 180 days after randomisation, corresponding to an efficacy of 82·7% (95% CI 67·8–91·5; p<0·0001) for nirsevimab (appendix p 19). At country level, the efficacy against hospitalisations due to RSV-associated lower respiratory tract infection was 86·1% (95% CI 60·3–96·5) in France, 85·9% (52·9–97·3) in the UK, and 74·4% (29·1–92·5) in Germany. The corresponding incidences for country-level efficacy were 0·001 person-months in the nirsevimab group and 0·005 in the standard care group for France; <0·001 in the nirsevimab group and 0·002 in the standard care group for the UK; and 0·001 in the nirsevimab group and 0·004 in the standard care group for Germany. A Kaplan-Meier plot of the incidence of hospitalisations due to RSV-associated lower respiratory tract infection is presented in figure 2. 12 events occurred within 7 days of randomisation (four in the nirsevimab group and eight in the standard of care group). The median time for occurrence of events was 28·5 days (IQR 5·5–52·0) in infants receiving nirsevimab and 27 days (IQR 13·5–55·5)

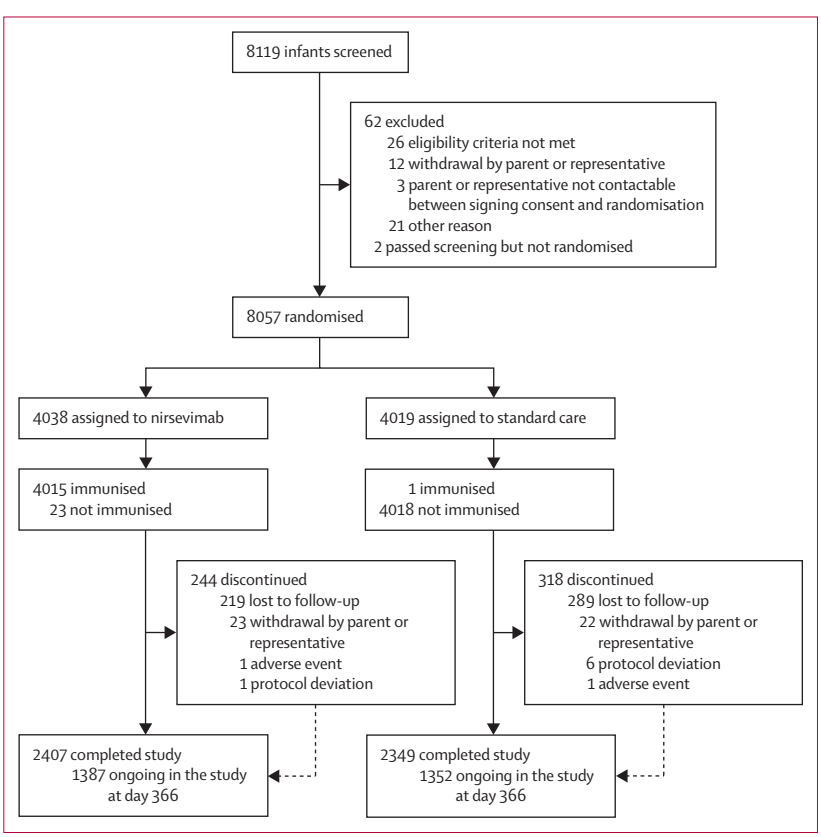

Figure 1: **Trial profile of participants through the study at the time of the cutoff date for the first-year analysis**

	Nirsevimab (n=4038)	No intervention (n=4019)	Total (n=8057)
Age at randomisation, months			
Median (IQR)	4·00 (2·0–7·0)	4·00 (1·0–7·0)	4·00 (1·0–7·0)
Age group			
≤3·0 months	1962 (48·6%)	1953 (48·6%)	3915 (48·6%)
>3·0 to ≤6·0 months	959 (23·7%)	954 (23·7%)	1913 (23·7%)
>6·0 months	1117 (27·7%)	1112 (27·7%)	2229 (27·7%)
Sex			
Male	2088 (51·7%)	2107 (52·4%)	4195 (52·1%)
Female	1950 (48·3%)	1912 (47·6%)	3862 (47·9%)
Gestational age at birth, weeks			
Number of participants with data available	4005	3973	7978
Median (IQR)	39·29 (38·0–40·3)	39·29 (38·0–40·3)	39·29 (38·0–40·3)
Gestational age at birth			
<37 weeks	567 (14·0%)	543 (13·5%)	1110 (13·8%)
≥37 weeks	3438 (85·1%)	3430 (85·3%)	6868 (85·2%)
Missing	33 (0·8%)	46 (1·1%)	79 (1·0%)
Weight at baseline, kg			
Number of participants with data available	4038	4019	8057
Median (IQR)	5·80 (4·0–7·8)	5·80 (4·0–7·7)	5·80 (4·0–7·7)
Weight at baseline			
<2·5 kg	146 (3·6%)	164 (4·1%)	310 (3·8%)
≥2·5 kg	3892 (96·4%)	3855 (95·9%)	7747 (96·2%)
Weight at baseline			
<5 kg	1537 (38·1%)	1521 (37·8%)	3058 (38·0%)
≥5 kg	2501 (61·9%)	2498 (62·2%)	4999 (62·0%)
Neonates aged 0–28 days			
Yes	946 (23·4%)	963 (24·0%)	1909 (23·7%)
No	3092 (76·6%)	3056 (76·0%)	6148 (76·3%)
Country			
France	1090 (27·0%)	1087 (27·0%)	2177 (27·0%)
Germany	896 (22·2%)	893 (22·2%)	1789 (22·2%)
UK	2052 (50·8%)	2039 (50·7%)	4091 (50·8%)
Birth categories			
Born in RSV season*	2001 (49·6%)	2026 (50·4%)	4027 (50·0%)
Born out of RSV season*	2037 (50·4%)	1993 (49·6%)	4030 (50·0%)
Number of participants with at least one medical history record	1086 (26·9%)	1089 (27·1%)	2175 (27·0%)

Data are n (%), unless otherwise indicated. Compared with the primary analysis reported by Drysdale and colleagues,[5] two participants in the standard care group were excluded from this first-year analysis: for one participant the informed consent form was not signed by both parents, the other participant was a duplicate due to a site error. One participant was randomly assigned to the nirsevimab group but withdrew consent before immunisation. This participant was excluded from the primary analysis because the withdrawal was not recorded at the time of database lock for the primary analysis but was included in the first-year analysis. RSV=respiratory syncytial virus. *The following start dates were defined for the RSV season: week 36, 2022, for the UK, week 37, 2022, for France, and week 41, 2022, for Germany. The end date was defined as the data cutoff date for the primary analysis, ie, Feb 28, 2023, for the three participating countries.

Table 1: **Summary of demographic characteristics (all randomised set)**

in infants in the standard care group. Analyses of subgroups according to age group at randomisation (≤3·0 months, >3·0 to ≤6·0 months, and >6·0 months), weight at randomisation, and timing of dosing (before and during RSV season) showed efficacy estimates similar to that of the overall efficacy estimate (figure 3). Hospitalisations due to all-cause lower respiratory tract infection occurred in 82 (2·0%) of 4038 infants in the nirsevimab group (incidence rate 0·004 person-months) and in 138 (3·4%) of 4019 infants in the standard care group (incidence rate 0·006 person-months) through 180 days after randomisation, corresponding to an efficacy of 41·9% (95% CI 23·1–56·3; p<0·0001) for nirsevimab (appendix p 19). The efficacy in preventing hospitalisation due to all-cause lower respiratory tract infection was 32·2% (95% CI –7·2 to 57·5) in France, 39·8% (8·4 to 60·9) in the UK, and 64·1% (23·4 to 84·5) in Germany.

Very severe RSV-associated lower respiratory tract infections occurred in six (0·1%) of 4038 infants in the nirsevimab group (incidence rate <0·001 person-months) and in 24 (0·6%) of 4019 infants in the standard care group (incidence rate 0·001 person-months) up to 180 days post-randomisation, corresponding to an efficacy of 75·3% (95% CI 38·1–91·8; p=0·0013) for nirsevimab (appendix p 19).

Nirsevimab was well tolerated, and no apparent safety concerns were generated during the 12 months following randomisation. Table 2 shows a summary of medically attended treatment-emergent adverse events. A summary table of treatment-emergent adverse events by category and severity is presented in the appendix (p 19). Most participants experienced grade 1 (2759 [68·7%] in the nirsevimab group; 2696 [67·1%] in the standard care group) or grade 2 (1447 [36·0%] in the nirsevimab group; 1436 [35·7%] in the standard care group) treatment-emergent adverse events.

Discussion

The primary endpoint of hospitalisation due to RSV-associated lower respiratory tract infection through the RSV season previously reported in the primary report of HARMONIE included participants who had a median follow-up time of 2·3 months (range 0–7·0) in the nirsevimab group and 2·0 months (range 0–6·8) in the standard care group.[13] The analysis presented here demonstrates that protection against hospitalisation due to RSV-associated lower respiratory tract infection by nirsevimab remains robust beyond the end of the infant's first RSV season and up to 180 days after randomisation, with efficacy remaining over 80% (82·7%, 95% CI 67·8–91·5, at the end of the 180 days *vs* 83·2%, 67·8–92, at the end of the first RSV season).[13] Efficacy results also remain similar at 180 days when compared with the end of the first RSV season for outcomes of very severe lower respiratory tract infection (75·3%, 95% CI 38·1–91·8, at 180 days *vs* 75·7%, 32·8–92·9, at the end of the first RSV season)[13] and hospitalisations due to all-cause lower respiratory tract infection (41·9%, 23·1–56·3, at 180 days *vs* 58·0%, 39·7–71·2, at the end of the first RSV season). The subgroup efficacy results were also similar to those previously reported.[13] No new safety concerns were

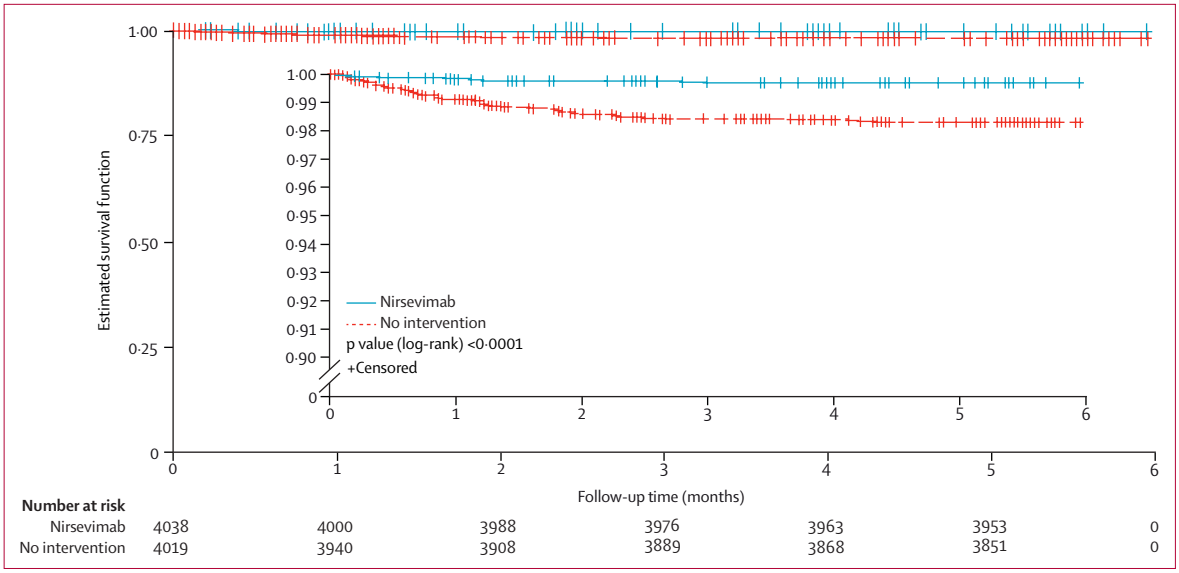

***Figure 2*: Kaplan-Meier plot for overall incidence of hospitalisation due to RSV-associated lower respiratory tract infection up to 180 days after randomisation (all randomised set)**

Efficacy of nirsevimab in preventing hospitalisation due to RSV-associated lower respiratory tract infection up to 180 days after randomisation was calculated as (1 minus the incidence rate ratio) × 100%. The 2-sided 95% CI for the efficacy was calculated by an exact method assuming a binomial distribution of the number of hospitalisations due to RSV-associated lower respiratory tract infection up to 180 days after randomisation in the nirsevimab group conditional on the total number in both groups (described by Breslow and Day) accounting for the follow-up time after randomisation. The inset shows the same data on an enlarged axis. RSV=respiratory syncytial virus.

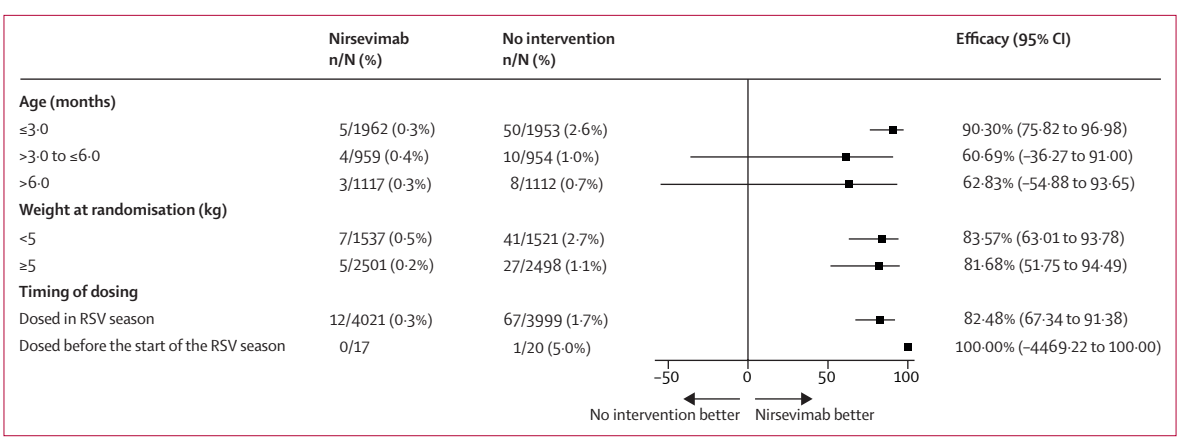

***Figure 3*: Forest plot of incidence of hospitalisation due to RSV-associated lower respiratory tract infection up to 180 days after randomisation, by subgroup at randomisation (all randomised set)**

Confidence intervals are not graphically represented if lower bound is lower than −100·0% and upper bound is greater than 0. RSV=respiratory syncytial virus.

established.[13] Prevention of RSV-associated lower respiratory tract infections has several positive implications, including reduction in post-infectious sequelae of RSV, reduction in the burden on health services during peak periods, and reduction of socioeconomic burden on caregivers of unwell infants.[16,17]

The consistent results observed after 6 months of follow-up in this study provide reassurance about the duration of protection, which is crucial for flexible national deployment strategies. The extended duration of protection allows for flexibility in dosing schedules, helping to avoid nirsevimab-specific visits and enabling its administration during regularly scheduled well-baby visits alongside routine vaccinations. Real-world implementation has shown a substantial uptake of nirsevimab, with preliminary data from Luxembourg indicating an 84% uptake among eligible neonates in 2023.[9] Data from three different autonomous regions in Spain indicated population uptake of between 78·7% and 98·6%, depending on the immunising hospital,[7] and in Catalonia, 87% of eligible neonates were given nirsevimab in a mix of primary care provider settings and hospitals during the 2023–24 RSV season.[8] In the Valle d'Aosta region of Italy, uptake was 65% during the 2023–24 RSV season.[10] Encouragingly, uptake remains high across these studies despite different models of nirsevimab

	Nirsevimab (n=4016)		No intervention (n=4018)		Total (n=8034)	
	n (%; 95% CI)	Number of events	n (%; 95% CI)	Number of events	n (%; 95% CI)	Number of events
Number of participants with medically attended treatment-emergent adverse events	3106 (77·3%; 76·0–78·6)	10546	3100 (77·2%; 75·8–78·4)	10598	6206 (77·2%; 76·3–78·2)	21144
Infections and infestations	2658 (66·2%; 64·7–67·6)	6885	2676 (66·6%; 65·1–68·1)	7019	5334 (66·4%; 65·3–67·4)	13904
Nasopharyngitis	605 (15·1%; 14·0–16·2)	777	565 (14·1%; 13·0–15·2)	735	1170 (14·6%; 13·8–15·4)	1512
Ear infection	475 (11·8%; 10·8–12·9)	691	464 (11·5%; 10·6–12·6)	737	939 (11·7%; 11·0–12·4)	1428
Viral infection	455 (11·3%; 10·4–12·4)	534	417 (10·4%; 9·5–11·4)	475	872 (10·9%; 10·2–11·6)	1009
Conjunctivitis	446 (11·1%; 10·1–12·1)	515	418 (10·4%; 9·5–11·4)	490	864 (10·8%; 10·1–11·5)	1005
Bronchiolitis	387 (9·6%; 8·7–10·6)	505	458 (11·4%; 10·4–12·4)	626	845 (10·5%; 9·9–11·2)	1131
Upper respiratory tract infection	304 (7·6%; 6·8–8·4)	413	337 (8·4%; 7·5–9·3)	470	641 (8·0%; 7·4–8·6)	883
Gastroenteritis	214 (5·3%; 4·7–6·1)	239	231 (5·7%; 5·0–6·5)	257	445 (5·5%; 5·0–6·1)	496
Bronchitis	189 (4·7%; 4·1–5·4)	261	201 (5·0%; 4·3–5·7)	288	390 (4·9%; 4·4–5·3)	549
Otitis media	192 (4·8%; 4·1–5·5)	242	197 (4·9%; 4·3–5·6)	244	389 (4·8%; 4·4–5·3)	486
Lower respiratory tract infection	162 (4·0%; 3·4–4·7)	191	179 (4·5%; 3·8–5·1)	220	341 (4·2%; 3·8–4·7)	411
Respiratory, thoracic and mediastinal disorders	662 (16·5%; 15·3–17·7)	969	665 (16·6%; 15·4–17·7)	996	1327 (16·5%; 15·7–17·3)	1965
Cough	358 (8·9%; 8·1–9·8)	422	373 (9·3%; 8·4–10·2)	421	731 (9·1%; 8·5–9·7)	843
Gastrointestinal disorders	567 (14·1%; 13·1–15·2)	716	548 (13·6%; 12·6–14·7)	708	1115 (13·9%; 13·1–14·7)	1424
Diarrhoea	173 (4·3%; 3·7–5·0)	183	172 (4·3%; 3·7–5·0)	177	345 (4·3%; 3·9–4·8)	360
Skin and subcutaneous tissue disorders	485 (12·1%; 11·1–13·1)	578	480 (11·9%; 11·0–13·0)	575	965 (12·0%; 11·3–12·7)	1153
Eczema	180 (4·5%; 3·9–5·2)	189	172 (4·3%; 3·7–5·0)	191	352 (4·4%; 3·9–4·9)	380
General disorders and administration site conditions	395 (9·8%; 8·9–10·8)	442	356 (8·9%; 8·0–9·8)	414	751 (9·3%; 8·7–10·0)	856
Pyrexia	338 (8·4%; 7·6–9·3)	375	321 (8·0%; 7·2–8·9)	366	659 (8·2%; 7·6–8·8)	741

95% CIs are based on Clopper-Pearson method. All percentages are calculated based on n as the denominator. MedDRA version 25·0. *Within a system organ class, participants may have reported more than one preferred term. Participants are counted once for each preferred term and each system organ class.

Table 2: **Medically attended treatment-emergent adverse events by system organ class and preferred term* in at least 4% of participants (safety analysis set)**

delivery across primary, outpatient, and secondary hospital care settings.

This study has several strengths. It was a large, randomised controlled trial conducted across primary and secondary inpatient and outpatient settings in several countries in Europe, with consistent efficacy findings. The timing of follow-up in this study provides new data regarding the duration of protection of nirsevimab beyond the RSV season, with no evidence of significant waning over the extended follow-up period to 180 days. Among the limitations of the study is the fact that the follow-up does not include a second RSV season where most of the loss of efficacy would be expected to occur. The unblinded nature of the study also introduces the possibility of bias; however, extensive efforts have been made to reduce the risk of bias, including the use of endpoints that are robust to the open-label nature of the study.[13] Finally, the HARMONIE study was conducted in the epidemiological setting typical for European countries, with a high RSV circulation period followed by low circulation after February. While a significantly lower incidence of hospitalisation due to RSV-associated lower respiratory tract infection remains through 6-months in the nirsevimab group compared with the standard care group, the lower number of cases in the latter part of the follow-up due to low viral circulation makes it more difficult to definitely assess sustained protection. Conducting studies in different epidemiological settings with sustained RSV circulation throughout the year would be informative to better characterise nirsevimab's duration of protection.

There are two recently approved therapies for the prevention of RSV-associated lower respiratory tract infection in infants representing different technologies: nirsevimab as a monoclonal antibody for infants and a vaccine for mothers given during pregnancy. Both therapies were shown to be highly effective in phase 3 clinical trials,[13,18] although differences in settings and outcome measures mean direct comparison is not possible at this stage. A follow-up study from the phase 3

trial of maternal immunisation reported efficacy of 55·3% (95% CI 23·8–74·6) with respect to RSV-associated hospitalisation within 180 days after birth.[19]

Further research is required to understand the impact of nirsevimab for protection against RSV-associated lower respiratory tract infection. Possible protection by nirsevimab across a second RSV season has not yet been determined. Follow-up from the HARMONIE trial has been extended beyond 12 months in UK to assess for an impact on incidence of recurrent wheeze. This study conducted in three European countries reports efficacy results likely to be generalisable to other countries (including low-income and middle-income countries) where public decision-makers implement all-infant protection campaigns.

This study demonstrates that protection with nirsevimab against RSV-associated lower respiratory tract infection extends to 6 months from administration. No safety concerns were raised during the trial, with follow-up data suggesting sustained safety up to 12 months after administration. These findings demonstrate that the duration of protection afforded by nirsevimab is longer than previously reported, providing greater flexibility for the timing of deployment of nirsevimab to protect a greater number of infants from RSV during their first RSV season.

Contributors

APSM contributed to the writing of the original draft with SNF and SBD. All other authors contributed to the writing, reviewing and editing of the manuscript. AMC, FF, KC, MK, PT, and SR contributed equally to this article, to the conceptualisation of the study and investigation. HCH contributed to the investigation. NCV contributed to the conceptualisation of the study. PB contributed to project administration. LM contributed to data validation. KM contributed to the formal analysis. All authors had access to all the data reported in the study. KM and PB verified the data. PB and SNF had final responsibility to submit for publication.

Declaration of interests

CM, KM, LM, MR, MC, NCV, and PB are employed by Sanofi and have stock and/or share options. AMC, APMS, DP, FF, FK, HCH, KC, MK, PT, SBD, SNF, and SR have declared to not receiving any funding for the present manuscript. HCH and APSM declare no competing interests. FK received a contract from Sanofi as investigator in HARMONIE, fees paid to institution. SBD received fees paid to his institution from Sanofi to run the present study; a travel grant from Sanofi (October 2022); and fees for consulting or investigator roles for Janssen, AstraZeneca, Pfizer, Moderna, Valneva, MSD, iLiAD, MundiPharma, and Sanofi; and is a member of the UK Department of Health and Social Care Joint Committee on Vaccination and Immunisation and Medicines and Healthcare products Regulatory Agency PMEAG. MK declares being the treasurer of the Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI) e.V. SNF received funding for HARMONIE from Sanofi, paid to the institution; grants or contracts from Pfizer, Sanofi, GlaxoSmithKline, Johnson & Johnson, Merck, AstraZeneca, Valneva, Moderna, BioNTech as clinical trial investigator on behalf of institution; honoraria for symposium participation paid to institution from Moderna, Pfizer, and Novavax; and honoraria for ad-boards participation paid to institution from AstraZeneca, MedImmune, Sanofi, Pfizer, Seqirus, Merck, Johnson & Johnson and MSD; and was the chair of UK National Institute for Health and Care Excellence (NICE) Sepsis (2014–16) and Lyme Disease (2016–18) Guidelines. RC has received consulting fees from Pfizer, Sanofi, MSD, GlaxoSmithKline, Viatris; symposia honoraria from Pfizer, MSD, GlaxoSmithKline, Sanofi; payment for expert testimony from Pfizer and MSD; travel grants from Pfizer, MSD, Sanofi, GlaxoSmithKline; and honoraria for participation to ad-board from Pfizer, Sanofi, MSD, and GlaxoSmithKline. DP received consulting fees from Sanofi, GlaxoSmithKline, MSD, Pfizer; symposia honoraria from AstraZeneca, GlaxoSmithKline, MSD, Pfizer and Sanofi; travel grant from Sanofi, Pfizer, MSD; and honoraria for ad-board presence from Sanofi, Pfizer, and GlaxoSmithKline. SR received a grant to the National Institute for Health Research Clinical Research Network East Midlands (where he is employed as the primary care specialty lead for the organisation); and honoraria for ad-board presence from Sanofi; for involvement in HARMONIE from Sanofi. FF was invited by Sanofi to the European Society For Paediatric Infectious Diseases 2023. AMC received grants or contracts from Pfizer, MSD, Moderna, Infex, Sanofi; consulting fees from Sanofi; travel grants from Sanofi (ESPID); payment or honoraria for lectures and presentations from Sanofi and Pfizer; and honoraria for ad-board participation from Oxford Vaccine Group; and has leadership in the Forum on Respiratory Tract Infections conference committee, the Pandemic Institute (Liverpool) scientific committee, and Liverpool Clinical Research Facility committee. KC received grants or contracts from Pfizer, Sanofi, GlaxoSmithKline, Janssen, Merck, Iliad, MedImmune, AstraZeneca, and Valneva as clinical trial investigator on behalf of institution; and consulting fees on behalf of institution from Sanofi. PT received grants and consulting contract from Baxter; consulting fees from Sedana, Sanofi, Thermo Fisher, and Viatris; and honoraria for symposium presentation from Thermo Fisher, Baxter, and BioMerieux.

Data sharing

The datasets generated or analysed during the current study, including the raw data, are not publicly available in order to safeguard the privacy of participants and the confidentiality and protection of their data, as well as protect commercially sensitive information. Qualified researchers (researchers demonstrating a strong rationale for accessing the data and experience of past work related to the topic of our article) may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of our trial participants.

Acknowledgments

We extend our heartfelt gratitude to the infants who participated in the trial and their families, as well as the dedicated personnel at the trial sites, the NIHR Clinical Research Network (UK), the Association Française de Pédiatrie Ambulatoire (AFPA), the PEDSTART network of pediatric clinical investigation centers and the ACTIV pediatric ambulatory and hospital surveillance network (in France); and the NETSTAP network of pediatricians for clinical studies in ambulatory pediatrics (in Germany).

References

1 Munro APS, Martinón-Torres F, Drysdale SB, Faust SN. The disease burden of respiratory syncytial virus in Infants. *Curr Opin Infect Dis* 2023; **36:** 379–84.
2 Ares-Gomez S, Mallah N, Pardo-Seco J, et al. Short- and mid-term morbidity and primary-care burden due to infant respiratory syncytial virus infection: a Spanish 6-year population-based longitudinal study. *Pediatr Allergy Immunol* 2024; **35:** e14131.
3 Global Burden of Disease Lower Respiratory Infections, Antimicrobial Resistance Collaborators. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Infect Dis* 2024; **24:** 974–1002.
4 Domachowske JB, Khan AA, Esser MT, et al. Safety, tolerability and pharmacokinetics of MEDI8897, an extended half-life single-dose respiratory syncytial virus prefusion f-targeting monoclonal antibody administered as a single dose to healthy preterm infants. *Pediatr Infect Dis J* 2018; **37:** 886–92.
5 Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. *N Engl J Med* 2020; **383:** 415–25.
6 Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med* 2022; **386:** 837–46.

7 López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. *Euro Surveill* 2024; **29:** 2400046.

8 Coma E, Martinez-Marcos M, Hermosilla E, et al. 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). *Arch Dis Child* 2024; **109:** 736–741.

9 Ernst C, Bejkoi D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. *Euro Surveill* 2024; **29:** 2400033.

10 Consolati A, Farinelli M, Serravalle P, et al. Safety and efficacy of nirsevimab in a universal prevention program of respiratory syncytial virus bronchiolitis in newborns and infants in the first year of life in the Valle d'Aosta region, Italy, in the 2023–2024 epidemic season. *Vaccines* 2024; **12:** 549.

11 Assad Z, Romain AS, Aupiais C, et al. Nirsevimab and hospitalization for RSV bronchiolitis. *N Engl J Med* 2024; **391:** 144–54.

12 Moline HL, Tannis A, Toepfer AP, et al. Early estimate of nirsevimab effectiveness for prevention of respiratory syncytial virus–associated hospitalization among infants entering their first respiratory syncytial virus season — New Vaccine Surveillance Network, October 2023–February 2024. *MMWR Morb Mortal Wkly Rep* 2024; **73:** 209–14.

13 Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for prevention of hospitalizations due to RSV in infants. *N Engl J Med* 2023; **389:** 2425–35.

14 Chu HY, Steinhoff MC, Magaret A, et al. Respiratory syncytial virus transplacental antibody transfer and kinetics in mother-infant pairs in Bangladesh. *J Infect Dis* 2014; **210:** 1582–89.

15 Nyiro JU, Sande C, Mutunga M, al. Quantifying maternally derived respiratory syncytial virus specific neutralising antibodies in a birth cohort from coastal Kenya. *Vaccine* 2015; **33:** 1797–801.

16 Ma KS, Tsai SY, El Saleeby CM, Kotton CN, Mansbach JM. Nirsevimab decreased the subsequent risk of respiratory syncytial virus infection and wheezing in the 2023-2024 RSV season. *Pediatr Res* 2025; published online Jan 9.

17 Mallah N, Pardo-Seco J, Pérez-Martínez O, et al. Full 2023–24 season results of universal prophylaxis with nirsevimab in Galicia, Spain: the NIRSE-GAL study. *Lancet Infect Dis* 2024; 25: e62–63.

18 Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med* 2023; **388:** 1451–64.

19 Simoes EAF, Pahud BA, Madhi SA, et al. Efficacy, safety, and immunogenicity of the MATISSE (maternal immunization study for safety and efficacy) maternal respiratory syncytial virus prefusion F protein vaccine trial. *Obstet Gynecol* 2025; **145:** 157–67.