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Review Article

Nirsevimab For Infant Respiratory Syncytial Virus Infection Prevention: Clinical Data, Practical Efficacy, Safety, And Prospects

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ABSTRACT

The most common cause of hospitalisation and lower respiratory tract infections (LRTI) in newborns worldwide is still respiratory syncytial virus (RSV). Regardless of underlying risk status, nirsevimab, a long-acting monoclonal antibody that targets the RSV fusion (F) protein, was approved in 2023 as the first passive immunoprophylaxis medication advised for all infants starting their first RSV season. Pivotal trials (MELODY and HARMONIE) showed an efficacy of around 74–83% against hospitalisation linked to RSV and medically attended RSV LRTI [1,2]. Since its launch, a fast-growing corpus of empirical research from Europe, North America, and Asia has demonstrated efficacy against hospitalisation, typically in the 70–90% range, with comforting post-marketing safety data [4-8]. The mechanism of action, pivotal trial evidence, accumulated real-world effectiveness data, safety profile, and the changing role of nirsevimab in conjunction with maternal RSV vaccination and more recent monoclonal antibodies like clesrovimab are all summarised in this review, which also outlines current recommendations from professional societies.

INTRODUCTION

Respiratory syncytial virus (RSV) is one of the most common respiratory pathogens affecting children, with almost all children experiencing at least one infection by two years of age. Although RSV infection is generally mild in many children, young infants, particularly those below six months

of age, are more vulnerable to severe lower respiratory tract disease, including bronchiolitis and pneumonia. Globally, RSV contributes substantially to acute lower respiratory tract infections and hospital admissions among infants.

Before the introduction of long-acting preventive antibodies, prophylactic options were limited

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mainly to palivizumab. Because palivizumab has a relatively short duration of action, it requires repeated intramuscular administration at monthly intervals throughout the RSV season. Its use was therefore primarily restricted to infants considered at high risk of severe RSV disease, such as those born extremely prematurely or those with chronic lung disease or significant congenital heart disease.

Nirsevimab (Beyfortus) was developed to address several of these limitations. Through modification of its antibody structure, nirsevimab has an extended half-life and can provide passive protection for approximately five months, corresponding to the duration of a typical RSV season. Unlike palivizumab, its use is not limited to selected high-risk infants and can be administered as a single intramuscular dose. Nirsevimab received approval from the European Medicines Agency in late 2022 and from the U.S. Food and Drug Administration in mid-2023, after which it was incorporated into national RSV prevention programs [9].

2. MECHANISM OF ACTION OF NIRSEVIMAB

Nirsevimab is a recombinant human IgG1κ monoclonal antibody that specifically targets the prefusion form of the RSV fusion (F) glycoprotein. This protein is highly conserved between RSV subtype A and subtype B, making it an important target for viral neutralization.

Following administration, nirsevimab binds to a specific epitope on the prefusion F protein and neutralizes the virus. This interaction prevents the membrane fusion process that RSV requires to enter host cells, thereby interfering with viral entry and subsequent infection.

Nirsevimab contains a YTE modification consisting of three amino-acid substitutions within the Fc region of the antibody. This modification increases the antibody's serum half-life to approximately 70 days. Consequently, a single weight-based intramuscular dose can provide protection throughout an RSV season of approximately five months. Infants weighing less than 5 kg receive 50 mg, whereas those weighing 5 kg or more receive 100 mg.

Unlike active vaccination, nirsevimab provides passive immunity by directly supplying protective antibodies rather than stimulating the infant's immature immune system to produce its own immune response. Therefore, protection is available soon after administration and does not depend on the development of an infant's adaptive immune response.

3. PIVOTAL CLINICAL TRIAL EVIDENCE FOR NIRSEVIMAB

The clinical development of nirsevimab was supported by several major clinical trials evaluating its efficacy and safety across different infant populations. The key studies included the MELODY, HARMONIE and MEDLEY trials.

Table 1. Summary of pivotal nirsevimab clinical trials.

Trial	Population	Design	Primary Endpoint	Key Result
MELODY (Phase 3)	1,490 healthy late-preterm and term infants (≥ 35 wGA)	Randomized 2:1, nirsevimab vs. placebo	Medically attended RSV lower respiratory tract infection (LRTI) through day 150	1.2% vs. 5.0% incidence; efficacy 74.5% (pooled Phase 2b/3 analysis: ~79%)

HARMONIE (Phase 3b)	8,058 infants ≥29 wGA, palivizumab- ineligible	Open-label, randomized, nirsevimab vs. no intervention, real- world setting	Hospitalization for RSV-confirmed LRTI	0.27% vs. 1.49% incidence; efficacy 83.2%
MEDLEY (Phase 2/3)	Preterm infants and those with congenital heart or chronic lung disease	Randomized, nirsevimab vs. palivizumab (active comparator)	Safety and tolerability through two RSV seasons	Comparable safety profile to palivizumab; no new safety signals

The MELODY trial, a Phase 3 randomized study, evaluated nirsevimab in healthy late-preterm and term infants born at or after 35 weeks of gestational age. Participants were randomly assigned in a 2:1 ratio to receive either nirsevimab or placebo. Medically attended RSV lower respiratory tract infection through day 150 was assessed as the primary endpoint. RSV LRTI occurred in 1.2% of infants receiving nirsevimab compared with 5.0% of those receiving placebo, corresponding to an efficacy of 74.5%. When combined with data from the earlier Phase 2b study, the estimated efficacy was approximately 79% [1].

The HARMONIE trial, a Phase 3b randomized study, enrolled 8,058 infants born at or after 29 weeks of gestational age who were not eligible for palivizumab. The study compared nirsevimab with no preventive intervention under routine clinical conditions. RSV-confirmed lower respiratory tract infection requiring hospitalization occurred in 0.27% of infants receiving nirsevimab compared with 1.49% of controls. The resulting efficacy against the primary endpoint was 83.2% [2].

The MEDLEY trial evaluated nirsevimab in higher-risk infant populations, including preterm infants and those with congenital heart disease or chronic lung disease. Nirsevimab was compared

with palivizumab, with safety and tolerability assessed through two RSV seasons. The findings demonstrated a safety profile generally comparable to palivizumab, with no new safety concerns attributable to nirsevimab [3].

Collectively, these pivotal studies provided clinical evidence supporting the efficacy and safety of nirsevimab across both healthy infants and infants with selected underlying risk factors.

4. REAL-WORLD EFFECTIVENESS

Although randomized clinical trials provide strong evidence regarding the efficacy and safety of nirsevimab, their findings may not fully reflect the diversity encountered in routine clinical practice. Differences in circulating RSV strains, timing of administration, coadministration with other vaccines, patient characteristics, and healthcare systems can influence treatment outcomes. Consequently, post-marketing observational studies have become an important source of evidence for evaluating the effectiveness of nirsevimab under real-world conditions. Since its introduction during the 2023–2024 RSV season, data from several countries have provided additional evidence regarding its effectiveness in preventing severe RSV disease in infants.



4.1 EARLY POST-MARKETING EVIDENCE: 2023–2024 SEASON

The first RSV season following the introduction of nirsevimab generated important real-world evidence. One population-based cohort study conducted using data from the French National Health Data System compared infants who received nirsevimab with matched infants who had not received immunization. The findings demonstrated a substantial reduction in RSV-associated lower respiratory tract infection (LRTI) requiring hospitalization and were broadly consistent with the results observed in randomized clinical trials [4].

Similar observations were reported during the same season in several European countries, including France and Spain, as well as in the United States. Across these early post-marketing studies, effectiveness against RSV-associated hospitalization generally ranged from approximately 70% to 90%. These findings were comparable to the protection observed in the HARMONIE trial and provided early evidence that the clinical benefits of nirsevimab could be reproduced outside controlled trial settings [4].

4.2 EVIDENCE FROM THE 2024–2025 SEASON AND SUBSEQUENT STUDIES

Evidence from the 2024–2025 RSV season has further expanded the understanding of nirsevimab effectiveness across different populations and healthcare settings. A surveillance study conducted in southern Italy used three complementary analytical approaches: a screening method, a test-negative case-control design, and a cohort analysis. The estimated effectiveness against RSV-associated hospitalization was 84.4%, 72.5%, and 81.6%, respectively. The differences between these estimates highlight the influence that study methodology can have on

measured vaccine effectiveness while demonstrating an overall consistent protective effect [5].

Large-scale evidence from the United States has also supported these findings. Analysis of a dataset involving more than 400,000 infants during the 2024–2025 RSV season found that infants who received nirsevimab experienced approximately a 71–77% reduction in the risk of RSV-associated hospitalization compared with unimmunized infants [6].

Evidence from regions outside Europe and North America has provided further support for the effectiveness of nirsevimab. A population-based retrospective cohort study conducted in Beijing, China, during a season characterized by relatively low nirsevimab coverage and delayed RSV circulation also demonstrated a meaningful reduction in hospitalization among immunized infants. These findings complement evidence previously reported from countries such as Spain, France, the United States, and Chile, suggesting that the protective effect of nirsevimab is not restricted to a particular healthcare setting or geographic region [7].

A systematic review and meta-analysis of observational studies evaluating nirsevimab immunization programs, including evidence available through early 2025, also reported a generally consistent protective effect against RSV-related disease in infants. However, the magnitude of effectiveness varied between studies because of differences in population characteristics, timing of administration, implementation strategies, and study methodology. Variation was also observed between programs using birth-dose administration and those implementing catch-up strategies [8].

Overall, real-world evidence accumulated since the introduction of nirsevimab has demonstrated a



consistent reduction in RSV-associated hospitalization among infants. Across observational studies, effectiveness estimates have generally been within the range of approximately 70–90%, although estimates from test-negative case-control studies have sometimes been lower. Such differences may partly reflect the more conservative nature of the test-negative methodology compared with screening and conventional cohort approaches.

4.3 BROADER PUBLIC HEALTH IMPACT

The potential benefits of nirsevimab extend beyond protection at the individual level. Population-based studies evaluating large-scale immunization programs have reported reductions in RSV-related emergency department visits and hospitalizations for bronchiolitis among young children. These findings suggest that widespread use of nirsevimab may contribute to reducing the healthcare burden associated with seasonal RSV outbreaks and may help alleviate pressure on pediatric emergency and inpatient services during periods of intense RSV circulation.

Nevertheless, population-level studies should be interpreted with caution because observed reductions may be influenced by factors other than nirsevimab administration, including changes in RSV circulation, healthcare-seeking behavior, diagnostic practices, and other preventive interventions. Despite these limitations, the broader population-level findings are generally compatible with individual-level observational studies and clinical trials, collectively supporting the effectiveness of nirsevimab in reducing severe RSV disease in infants.

5. SAFETY PROFILE

Nirsevimab has shown a safety profile that is generally equivalent to either palivizumab (in the

higher-risk MEDLEY comparison) or placebo throughout the pivotal study program. In MELODY, the previous Phase 2b trial, and MEDLEY, the rates of serious adverse events and adverse events of Grade 3 severity or higher were generally similar between the nirsevimab and control arms. Adverse events of special interest, primarily hypersensitivity reactions with cutaneous manifestations, were rare and occurred at low, generally comparable rates in both study arms. Serious adverse event rates were low and comparable between nirsevimab patients and controls (about 1.7–2.2%) in HARMONIE, the biggest and most practical trial; no deaths in either arm were thought to be connected to study medication [1-3].

The 30-day safety profiles reported by post-marketing real-world safety monitoring, such as a real-world monocentric investigation of nirsevimab use in a mixed preterm and term neonatal population, are consistent with the pivotal trial experience and have not revealed any new safety signals. The cumulative dataset, which now spans multiple RSV seasons and sizable multinational populations, indicates a positive overall safety profile, but pharmacovigilance is still ongoing as with any biologic.

6. NIRSEVIMAB IN THE BROADER RSV PREVENTION LANDSCAPE

6.1 Comparison with Palivizumab

Due to its high cost and administration burden, palivizumab, the previous standard of therapy, is only used for a small group of high-risk newborns and needs monthly intramuscular injections during the RSV season. The season-long, single-dose protection of nirsevimab and its applicability to all infants—not just high-risk subgroups—represent a significant practical and public health advancement. Due to the availability of long-



acting substitutes, a number of professional and national organizations, such as the American Academy of Pediatrics, have shifted away from routine palivizumab use, and at least one manufacturer has declared that palivizumab will no longer be used.

6.2 Comparison with Maternal RSV Vaccination

By giving the fetus protection maternal antibodies, Abrysvo (RSVpreF), a maternal RSV vaccination given during weeks 32–36 of pregnancy, provides an alternate method of prevention. Maternal vaccination decreased the risk of severe LRTD by almost 70% and the likelihood of a medically attended RSV lower respiratory tract visit by about half in the first six months of life, according to clinical trials [11]. The U.S. Advisory Committee on Immunization Practices (ACIP) currently recommends either maternal vaccination or infant nirsevimab, but not usually both, for a given infant. Dual use is reserved for certain situations where vaccine-derived protection is deemed insufficient (e.g., vaccination too close to delivery to allow adequate antibody transfer). Children who received either maternal immunization or nirsevimab had reduced rates of RSV infection than children who got neither intervention, according to 2026 comparative cohort research that assessed infants during a season with concurrent RSV, influenza, and COVID-19 circulation [12].

6.3 Emergence of Clesrovimab

The field has expanded beyond nirsevimab alone with the recent regulatory approval and ACIP recommendation of clesrovimab (Enflonsia), a second long-acting anti-RSV monoclonal antibody, as an additional single-dose choice for infants starting their first RSV season. There is currently little data comparing the two treatments'

real-world efficacy, and both products are considered suitable for newborns who qualify.

7. CURRENT RECOMMENDATIONS

As of the most recent ACIP guidance [9,10], key recommendations include:

- It is advised that all infants under 8 months old who are born during or entering their first RSV season receive a single dose of nirsevimab (or clesrovimab).
- Except in some situations where vaccine-derived protection is deemed insufficient, it is typically not advised for infants whose mothers got an appropriately timed dose of Abrysvo during pregnancy to additionally get an RSV preventive antibody [9,11].
- Only a certain fraction of infants between the ages of 8 and 19 months who are still at high risk of developing severe RSV disease (for instance, because of immunocompromise, substantial congenital heart disease, or chronic lung disease of prematurity) should receive a second-season dose.
- In most of the continental United States, the routine administration window runs from October to March. However, some jurisdictions with unusual RSV seasonality, like parts of Alaska and the U.S. Gulf Coast/Southeast, have adopted locally extended or shifted windows based on regional circulation patterns.

8. LIMITATIONS OF THE CURRENT EVIDENCE BASE

When understanding the nirsevimab literature, it is important to take into account a few constraints. First, even when screening-method, test-negative, or matched-cohort designs are employed to reduce bias, the majority of real-world efficacy studies are observational and susceptible to residual



confounding. Second, test-negative case-control studies typically produce more conservative (lower) estimates than screening-method or simple cohort analyses carried out in the same population and season, making direct comparison across studies challenging. Third, real-world coverage has been inconsistent and insufficient across health systems, which could have an impact on impact estimates at the population level (though not necessarily at the individual level). Lastly, the best combined-strategy approaches at the health-system level are still being determined, and there is still a lack of head-to-head comparative effectiveness evidence for nirsevimab, maternal immunization, and clesrovimab.

9. FUTURE PERSPECTIVES

Long-term results: Program cohorts are well-positioned to address the open, clinically significant topic of whether preventing severe early RSV infection lowers subsequent recurrent wheezing and asthma.

- Extended follow-up and evidence in high-risk children after the first season of protection and second-season use.
- Efficiency in year-round transmission environments in low- and middle-income nations, when trial evidence is hard to come by.
- Viral surveillance: ongoing genomic surveillance for binding-site variations and their therapeutic implications.
- Combined and comparative strategies: the effectiveness of layered techniques, maternal vaccination and other monoclonal antibodies, and head-to-head comparisons of nirsevimab.
- Indirect impacts include effects on antibiotic use, healthcare capability, community RSV circulation, and transmission.
- Pricing and access: procurement methods, technology transfer, and tiered pricing to

facilitate utilization in high-burden environments.

10. DISCUSSION

The real-world numbers for nirsevimab have held up remarkably close to what MELODY and HARMONIE predicted. Those trials put efficacy at 74–83% against RSV LRTI and hospitalization [1,2], and now, several seasons later, cohort studies from France, Spain, Italy, the US, and China are landing in the same 70–90% range [4,5,6,7]. That kind of agreement across such different healthcare systems and populations is hard to dismiss — it suggests the protective effect is real rather than a quirk of the original trial conditions.

Where studies do disagree, the gap seems to come down to methodology more than anything else. Test-negative designs consistently produce lower, more conservative numbers than cohort or screening-method studies looking at the same population — the Italy surveillance data made this especially clear, with three methods on the same infants yielding estimates from 72% to 84%. Safety-wise, nothing alarming has turned up either; serious adverse events have stayed rare and balanced against controls through MEDLEY and beyond, which is a big part of why palivizumab has largely fallen out of use.

What's less settled is how nirsevimab should sit alongside the other tools now available — maternal vaccination with Abrysvo, and the newer antibody clesrovimab. Right now guidance leans toward picking one rather than layering them, but there isn't much direct comparison data yet to say whether that's the right call for every infant.

The evidence isn't without gaps. Most of it is observational, so confounding can't be fully ruled out; coverage varies a lot by region, which



muddies population-level comparisons; and nirsevimab hasn't really been tested head-to-head against the newer alternatives. More of that comparative work, plus continued tracking as RSV strains shift, would help fill in the picture.

11.CONCLUSION

By providing season-long, single-dose passive immunoprophylaxis to the total infant population for the first time, nirsevimab offers a major advancement in RSV prevention. A growing, geographically diverse body of real-world evidence spanning multiple RSV seasons has supported pivotal trial efficacy estimates of approximately 74–83% against medically attended RSV LRTI and RSV-related hospitalization, with effectiveness against hospitalization typically in the range of 70–90% and a comforting cumulative safety profile. Ongoing real-world surveillance, comparative effectiveness research, and cost-effectiveness analysis will be crucial to optimizing RSV prevention strategy at both the individual and population level as nirsevimab, maternal RSV vaccination, and more recent agents like clesrovimab are increasingly used in combination across national immunization programs.

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