Editorial Commentary

Will nirsevimab be the holy grail for prevention of respiratory syncytial virus lower respiratory tract infections in infants?

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Comment on: Simões EAF, Madhi SA, Muller WJ, *et al.* Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health 2023;7:180-9.

Keywords: Respiratory syncytial virus (RSV); respiratory syncytial virus prophylaxis (RSV prophylaxis); monoclonal antibody; nirsevimab; infants

Submitted Oct 30, 2023. Accepted for publication Dec 29, 2023. Published online Mar 08 2024.
doi: 10.21037/tp-23-534
View this article at: https://dx.doi.org/10.21037/tp-23-534

Globally acute lower respiratory infections (ALRIs) including bronchiolitis and pneumonia remain the leading causes of morbidity and mortality in children aged <5 years (1). Respiratory viruses including respiratory syncytial virus (RSV), influenza, rhinovirus, human parainfluenza virus and human metapneumovirus are well recognized causes of lower respiratory tract infections (LRTIs) in children (2). RSV alone is associated with almost 40% of all respiratory hospitalisation in under five children making it the leading cause of paediatric respiratory hospitalisation specifically in children <1 year of age (3). In 2019 it was estimated that, among children under 5 years, there were 33 million RSV-associated LRTI episodes, 3.6 million RSV-associated hospital admissions and 26,300 RSV-associated in-hospital deaths across the world (4).

Symptoms of RSV LRTI may vary in intensity from mild-severe and can even be life-threatening in infants (5). More than 70% of infants who require hospitalisation due to severe RSV LRTI will develop at least one complication including respiratory (e.g., respiratory failure, apnoeic episode, stridor), infectious (e.g., otitis media, bacteria pneumonia) and cardiovascular (e.g., cardiac arrythmias, cardiopulmonary resuscitation) with respiratory complications being most common (6). In very severe RSV LRTI, children may also develop rare respiratory complications such as pneumothorax, pleural effusion and sepsis (5). Severe RSV LRTI in infancy also predisposes abnormalities in lung function, which may persist into adulthood; this unique property of RSV increases the risk of recurrent wheezing and asthma at a later stage of life (7).

Up until 2022, palivizumab, a humanized anti-RSV monoclonal antibody, was the only available preventative therapeutic against severe RSV disease. Despite the fact that the vast majority of very young children who develop severe RSV disease are otherwise healthy full term infants, use of palivizumab is only recommended in high-risk children including those born prematurely, with chronic lung disease or with hemodynamically significant congenital heart disease, with pulmonary abnormality or neuromuscular disease and those who are profoundly

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immunocompromised (8). The cost of a single 50 mg vial of palivizumab is US$ 1,820.66 (9) and is most effective if administered to eligible infants each month during the RSV season for up to 5 months (8). The high cost limits its use in preterm infants born ≥29 weeks' gestational age (GA) without chronic lung disease and hemodynamically significant congenital heart disease due to cost-effectiveness concerns (8). Highlighting the need for a universal prevention strategy that is accessible, affordable and easily administered to all infants.

Nirsevimab, a recently approved anti-RSV monoclonal antibody with an extended half-life, was evaluated in a phase 2b trial for its efficacy against the prevention of RSV-associated LRTI in otherwise healthy infants who had been born preterm (29 weeks 0 days to 34 weeks 6 days of gestation) (10). Infants were randomly assigned (2:1 ratio) to receive a single 50 mg dose of nirsevimab in an intramuscular injection, or placebo at the start of an RSV season. The incidence of medically attended RSV-associated LRTI was 70.1% lower [95% confidence interval (CI): 52.3–81.2%] in nirsevimab group compared to placebo group [2.6% (25 infants) *vs.* 9.5% (46 infants); P<0.001]. However, pharmacokinetic and drug exposure-response analyses of phase 2b trial data suggested that a dose of 50 mg was suboptimal in infants weighing 5 kg or more. Subsequently a weight-banded regimen of 50 mg for infants <5 kg and 100 mg for infants ≥5 kg was developed and tested in phase 3 MELODY trial for efficacy against infants born at GA ≥35 weeks (11). In the MELODY trial, using this weight-banded dosing regimen there was a 74.5% (95% CI: 49.6–87.1%) relative risk reduction in medically attended RSV LRTI. However, none of these two trials included high-risk infants including those with existing heart and lung conditions who are otherwise eligible for palivizumab. The phase 2–3 MEDLEY trial used a palivizumab-controlled study design to assess the safety and pharmacokinetics of nirsevimab in high-risk infants and demonstrated a similar safety profile to that of palivizumab (12). While these three studies independently investigated the safety, pharmacokinetics and efficacy of nirsevimab in different sub-groups of children using different dosing regimen, uncertainty remined around the efficacy of nirsevimab using a weight-banded optimal dosing schedule for all infants born at a GA of ≥29 weeks. Simões *et al.* in the study "Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials" published recently in *Lancet Child and Adolescent Health* (13) aimed to address this specific gap in our understanding of efficacy of nirsevimab in preventing RSV disease in all infants (GA ≥29 weeks) and conducted a pooled analysis of the efficacy of weight-banded dose schedule for all infants. This analysis determined the efficacy in infants who were born at GA ≥29 weeks with a weight <5 kg and received a 50 mg dose of nirsevimab (who were either part of phase 2b or MELODY trials) and the efficacy of a 100 mg dose of nirsevimab for all infants with a weight ≥5 kg born at GA ≥35 weeks (who were part of MELODY trial as the infants in phase 2b trial only received 50 mg dose). The authors also extrapolated the results for high-risk infants including those with existing heart and lung conditions.

The data from this pooled analysis comprised of 2,350 infants: 860 infants born preterm (≥29 to <35 weeks GA) who weighed less than 5 kg in the phase 2b trial, and 1,490 infants born at term or late preterm (≥35 weeks' GA) in the MELODY trial of which 786 infants were allocated to receive placebo and 1,564 to receive nirsevimab. Overall compared to placebo group, a single weight-banded dose of nirsevimab led to 79.5% (95% CI: 65.9–87.7%) relative risk reduction of medically attended RSV LRTI which was the primary efficacy endpoint for the pooled analysis. Efficacy of nirsevimab was measured over 150 days and the protective effect persisted over the follow-up period suggesting that infants receiving nirsevimab will have a significant extended protection over the first 5 months of their life when they are most vulnerable (14). A recent study published by Rosas-Salazar and colleagues demonstrated that in a birth cohort of more than 1,700 children, avoiding RSV infection during infancy could lead to 15% of childhood asthma being prevented (15). Also, it will be crucial to measure incidence of RSV LRTI in children older than 5 months to understand whether protection in first 5 months of life rendered by nirsevimab results in higher disease burden in children older than 5 months of age. RSV is generally transmitted within the household through school-aged children (16) and as nirsevimab will not result in sterilizing immunity, there may be buildup of susceptible children beyond the age of 5 months who will still be at risk of acquiring their first severe RSV infection from older siblings. However, a modeling study suggested that if nirsevimab led to a 50% (arbitrary cut-off) reduction in viral shedding there should be a potential impact on reducing burden of severe RSV disease in children who are beyond 6 months of age (17). As use of nirsevimab has started in

some clinical settings and its impact is being monitored though routinely collected data (18), real world effectiveness data from these settings will help determine the long and short term benefits of nirsevimab.

In this pooled analysis (13), nirsevimab met its primary endpoint with a single dose. Currently eligible infants are required to receive five monthly doses of palivizumab to be protected against severe RSV disease during the first RSV season. The multiple dosing required, and the high cost makes the use of palivizumab restricted. The demonstrated efficacy of nirsevimab with a single dose will contribute to its uptake. However, the market price of a single dose of nirsevimab and its cost-effectiveness in different settings will play a critical role. The private sector cost of one single dose of nirsevimab is set at US$ 490 for the American market (19). A recently published study from the Canada (20) based on economic modeling suggested that a price per dose of 290 Canadian dollars (approximately US$ 214) would be cost-effective from a societal perspective if nirsevimab was used for all infants but would have a significant impact on the national budget. On the other hand, the same study reported that a combined strategy of year-round maternal vaccination against RSV for all pregnant women and use of nirsevimab for high-risk infants would be as effective as nirsevimab alone but would result in a lower budget impact. As different countries have different health care financing structure, more context specific data are needed to determine the cost-effectiveness in different settings. Nevertheless, including nirsevimab in the World Health Organization's Essential Medication List (EML) and substantially curtailing the cost of nirsevimab may help in achieving equitable access for the vast majority of children residing in low-middle-income settings.

Another strength of this study is that, as this was a pooled analysis of two randomised controlled trials, it allowed investigators to measure efficacy of nirsevimab across multiple endpoints. In addition to the primary efficacy endpoint, the study also investigated secondary efficacy around hospital admissions for medically attended RSV LRTI and other prespecified exploratory endpoints including very severe RSV LRTI, medically attended LRTI of any cause, and admissions to hospital. There were significant risk reductions across all endpoints. As post hoc analysis, the study also investigated other important exploratory endpoints including health resource use, outpatient visits, and antibiotic use. There was a 23.6% reduction in relative risk of antibiotic use in children who received nirsevimab compared to placebo group which may have been due to reduction in severe RSV disease that could have led to reduced incidence of secondary bacterial infection. Even in the absence of bacterial infection, antibiotics are often inappropriately prescribed to children with acute respiratory illness with almost 80% children being prescribed antibiotics in low middle income countries (21). Even in high income countries antibiotics are inappropriately prescribed to 14% of children with LRTIs (22). If indeed nirsevimab plays a role in reducing use of antibiotic by 20% in all infants with RSV LRTIs, at a population level this will have a significant impact on curtailing emergence of antibiotic resistance.

More importantly extrapolation of data from MEDLEY trial suggested that more than 80% (predefined exposure target) of infants including those with existing heart and lung conditions reached serum concertation level of nirsevimab at or above the predicted efficacy level with a single dose. While the vast majority of children with severe RSV disease are otherwise healthy infants, the risk of severe RSV disease is highest in children with existing underlying chronic conditions (23).

The study has some important limitations. While the results presented are based on geographical regions from where the infants were recruited for the trials, efficacy data specific to high-, middle- and low-income settings would have added value to the findings given the highest burden of severe disease and death associated with RSV is in low middle-income countries (4). In addition, although American Indian or Alaska Native infants were included in the study, the efficacy of nirsevimab for these children was not analysed separately. Globally Indigenous and First Nations children comprise an important priority population who are at 2–4 times increased risk of severe RSV disease compared to non-Indigenous children (24,25). The social and structural inequities that disproportionately burden Indigenous communities (26) expose many children to high levels of maternal smoking during pregnancy, overcrowded living conditions and a high prevalence of underlying chronic comorbidities which in turn place them at higher risk of severe RSV disease (27). It is likely that the small numbers of American Indian or Alaska Native infants or infants from low middle income countries recruited in the trials, precluded specific population-based analysis highlighting the need for future studies evaluating effectiveness of emerging RSV preventative therapeutics specifically in priority or underserved populations.

Nirsevimab has already been approved for clinical use in mulitiple countries including US, Australia and Europe (28)

and will potentially be approved in other high income countries over the next 1 or 2 years. Although randomised controlled trials provide high level evidence, as different countries start to administer nirsevimab to all infants, it will be important to conduct post-licensure observational studies which will provide real-world data around effectiveness of nirsevimab in less controlled environments. In conclusion, we must recognise that for an RSV preventative therapeutic to have any meaningful impact on reducing the exceptionally high burden of LRTI associated with RSV in infants, it will have to be made available for all infants, not only to those in high income settings but also in low middle-income settings. Unless we can ensure equitable access of nirsevimab for all infants, the true effectiveness of this promising therapeutic will not be achieved.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Pediatrics*. The article has undergone external peer review.

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-534/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-534/coif). The author reports that she has received payment from Pfizer to write an educational piece on RSV for Australian College of Midwives, taken part as invited speaker for Sanofi, received support from Sanofi for meeting registration, accommodation and/or travel expenses, taken part in an Advisory board for MSD, and is a Chief investigator on an investigator-initiated grant investigating RSV complications in children funded by MSD, all outside of the present manuscript. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Homaira N. Will nirsevimab be the holy grail for prevention of respiratory syncytial virus lower respiratory tract infections in infants? Transl Pediatr 2024;13(3):525-529. doi: 10.21037/tp-23-534