Peer Review File

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Reviewer A

In the last quarter of 2022, the monoclonal antibody nirsevimab, in accordance with the EMA and FDA recommendation, was approved for marketing in the European Union. Nirsevimab is Recombinant Human Monoclonal Antibody IgG1k of Long-lasting action directed against RSV preF. This product was modified to extend the serum half-life. The approval of the drug was based on the results of three studies that demonstrated the protective effect of a single dose of the antibody within 150 days of administration

Editorial Commentary presented by Nusrat Homaira School of Clinical Medicine, Faculty of Medicine, UNSW Sydney, New South Wales, Australia Respiratory Department, Sydney Children's Hospital Randwick, New South Wales, Australia and James P. Grant School of Public Health, BRAC University, Dhaka, Bangladesh is based on data from the two trials MELODY and MEDLEY. The Melody study included newborns <35 weeks of gestation. This study met its expected endpoint of reducing RSV LRTI by 75% compared to placebo. The Medley study analyzed children <35 weeks of age with BDP and hemodynamic heart defect and showed the effectiveness and safety of Nirsevimab.

I agree with the authors that unless we can ensure equitable access of nirsevimab for all infants, the true effectiveness of this promising therapeutic will not be achieved. Nirsevimab should therefore be available as soon as possible in all countries in where preventive programs financed by government institutions responsible for health care should be implemented.

Below the detailed reviewer comments on Editorial Commentary

Line 28-29 "Symptoms of RSV LRTI may vary in intensity from moderate to severe and can even be life-threatening in infants" Instead of severe should be "mild-severe and can ……"

Response: corrected

Line 40 "Up until 2023…." should be change to Up until 2022

Response: Corrected

Line 41-44 Despite the fact that the vast majority of very young children who develop severe RSV disease are otherwise healthy infants, use of palivizumab....." should be change to healthy full-term infants……."

Response: changed

Line 74 “safety profile to that of palivizumab [14]. 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 gestational age of >29 weeks”

This is an inaccurate statement at there is an exploratory were was locked at the incidence of an LRTI in the phase 2b Study in those participants who received Nirsevimab at recommemded dose

Response: I am not sure I understand the point the reviewer is trying to make. In Phase 2B trial it was demonstrated that for healthy preterm infants (29-<35 weeks gestation) who weighed ≥5kg a dose of 50 mg was not optimal which led to weight-band dosing in MELODY trial for late preterm and term babies (gestational age ≥35 weeks). Neither of these trials investigated the overall efficacy of the different doses in infants born after 29 weeks of gestation with different body weights irrespective of gestational age. So, in this pooled analysis, Simoes et al. pooled the data from the two trials to investigate the efficacy of a 50 mg dose of nirsevimab for all infants with a weight <5kg born at gestational age ≥29 weeks who were part of either phase 2b or MELODY trials (irrespective of gestational age) and the efficacy of a 100 mg dose of nirsevimab for all infants with a weight ≥5kg born at gestational age ≥35 weeks who were part of MELODY trial. I have now added the following liens to make this clearer (Lines 79-84) “ This analysis determined the efficacy in infants who were born at gestational age ≥29 weeks with a weight <5kg and received a born at gestational age >29 weeks 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 ≥5kg born at gestational age ≥35 weeks (who were part of MELODY trial as the infants in phase 2b trial only received 50mg dose).”

Line 97-99 “protective effect persisted over the follow-up period suggesting that infants receiving nirsevimab will have a significant extended protection over the first five months of their life when they are most vulnerable [16].”

Reviewer's comment: also, the kaplan maier curve from South Africa participants in the Melody 1 st cohort and the Wilkins on his paper on microneutralization strongly suggest that nAb levels remain high beyond 5 months again suggesting protection for at least 5 months.

Wilkins D et al.Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants Nat Med 2023-29:1172-1179

Response: Yes, I agree with the reviewer

Line 113-115 “once it becomes available for clinical use. However, the market price of a single dose of nirsevimab and cost-effectiveness data will play a critical role”.

Reviewer's comment: I fully agree but there are currently available data of Cost Effectiveness

Response: Thank you for making this important point. I have now added these lines (lines 120-133) 'The private sector cost of one single dose of nirsevimab is set at 490US$ for the American market [18]. A recently published study from the Canada [19] based on economic modeling suggested that a price per dose of 290 Canadian dollars (approximately 214 US$) 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."

Line 142 conditions reached serum concertation Should be change to concentration
Response: I think this should remain as serum concentration.

The literature contains well-selected titles from recent years, but requires a complete correction of the bibliographic edition. The fixes are listed below

1.The Lancet please change to Lancet

2. The Pediatric Infectious Disease Journal- J. Pediatr. Infect. Dis.

3. Lancet. 2017 Sep 193 2;390(10098):946-958. Lancet. 2017;390(10098):946-958

4. Epidemiol Infect. 2016 Jun;144(8):1612-21

7. Children (Basel). 2022 Dec 17;9(12)

8. The Journal of pediatrics. 207 2003;143(5):142-149 J Pediatr 2003;143(5):142-149

9. BMJ Open. 2017 Nov 8;7(11):e017936

12. New England Journal of Medicine. 2020;383(5):415-425 NEJM 2020;383(5):415-425

13. New England Journal of Medicine. 2022;386(9):837-846. NEJM. 2022;386(9):837-846.

14. New England Journal of Medicine 2022;386(9):892-894. NEJM 2022;386(9):892-894.

15. The Lancet Child & Adolescent Health. 2023;7(3):180-189 Lancet Child Adolesc 2023;7(3):180-189

16. Med J Aust. 2019 Jun;210(10):447-453

17. The Lancet. 2023;401(10389):1669-1680. The Lancet. 2023;401(10389):1669-1680.

18. The Lancet infectious diseases. 2020;20(2):179-187 Lancet Infect Dis. 2020;20(2):179-187

19. BMJ Qual Saf. 2019 Oct;28(10):817-825. BMJ Qual Saf. 2019 Oct;28(10):817-825.

21. J Med Virol. 2010 Jul;82(7):1282-90.J Med Virol. 2010 Jul;82(7):1282-90.

22. The Pediatric infectious disease journal. 2009;28(8):697-701. J. Pediatr. Infect. Dis 2009;28(8):697-701.

23. The lancet. 2006;367(9527):2019-2028 Lancet. 2006;367(9527):2019-2028
24. Pediatrics. 2002 Feb;109
Response: I have made the enecessary changes to the references as suggested by the reviewer however as I chose the standard NLM version for referencing in Endnote, some of the journals names are auto-configured in the output.

Reviewer B

From lines 40-46, you utilized the US AAP COID guidelines for palivizumab, yet, when talking about Nirsevimab, you call it an emerging therapy (line 55), when it is approved for use in the US and EU, and the same boy (AAP COID) has issued guidance for widespread use in infants younger than 6 months. I am not quite sure why this is.
Response: I have changed the text to (Line 50) "Nirsevimab, a recently approved anti-RSV monoclonal antibody…"

Line 101: add "to" after the word lead
Response: Added

In lines 102-106, you discuss needing to monitor childhood asthma rates and burden of disease on infants and children older than 6 months of age- explain or offer some suggestions on who should be doing this and how it should be done. This is an editorial piece, so state those opinions.
Response: I have now added the following text (Line 99-101) "which can be done by linking different administrative health data sets to monitor disease trend over time in countries where there is access to good quality routinely collected health data"

Line 151: Strike out the "an" in the starting sentence of "In an addition, "
Response: Corrected

Line 151-152: THis statement is biased: in the Simoes study, there is data from American Indian and Native Alaskan subjects, making up 3% of the placebo group and 4% of the study group. This study also included subjects native to Hawaii and the pacific islands and the demographic data is described nicely in Table 1 and also described in the text of the article. While there isn't a secondary analysis of the racial demographics and response rates specifically, these populations were included in the study and your statement leads the reader to believe otherwise.
Response: Yes, I agree that these populations were included but we do not see a sub-analysis of these populations which is the point I have tried to make. These are key populations and sub-group data from these high-risk populations are important. I have now rephrased the line as follows (Line 165-167) "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"

Line 169: change word to world.
Response: Corrected

Line 170: change environment to environments.
Response: Corrected

Lines 171-176: reword this section- it implies that nirsevimab will not be availalbe in low resource countries and/or communities. Unless you have information to back this up, it is quite inflammatory to insinuate such.
Response: I have now rephrased the sentence (Line 185) "In conclusion, we must recognise that for a RSV preventive therapeutic to have any meaningful impact on reducing the exceptionally high burden of LRTI associated with RSV in infants, any RSV preventive therapeutic will have to be made available for all infants not only to those in high income settings but also in low middle-income settings.
The attached pdf file shows the highlighted sentences that need to be reworded mentioned above.

Reviewer C

Homaira summarized key trial results about nirsevimab and raised interesting points to look out for in future studies. Minor comments:

1. In line 47, the author mentioned that palivizumab costs up to $5,117. The reference is published in 2004, so the number is likely to be outdated. In addition, the author may want to clarify if the cost is per administration or per RSV season, since it's 5 doses per season according to the label. If using a US price, the author should also clarify if reporting a wholesale acquisition cost (WAC, can be obtained from Red Book), Federal Supply Schedule (FSS) cost, or some patient out-of-pocket cost.
Response: Thank you for raising this issue, I have now modified the sentence as follows (Lines 41-49) "The cost of a single 50mg vial of palivizumab is US$ 1,820.66[11] and is most effective if administered to eligible infants each month during the RSV season for up to five months [10]. 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 [10] highlighting the need for a universal prevention strategy that is accessible, affordable and easily administered to all infants.

2. The author should consider elaborate on the point raised in line 104-106. It isn't clear to me why "protection in first five months of life rendered by nirsevimab results in higher disease burden in children older than five months of age." I don't see the link here but think that, if anything, protecting the younger infants would slow down virus from spreading in the community and, to some extent, help the older infants.

Response: Thank you for your comment. I have made the following changes clarifying this issue (Lines 104-113) "RSV is generally transmitted within the household through school-aged children [18] and as nirsevimab will not result in sterilizing immunity, there may be buildup of susceptible children beyond the age of five months who will still at risk of acquiring their first severe RSV infection from older siblings. However, a modeling study suggests that if nirsevimab led to a 50% (arbitrary cut-off) reduction in viral shedding there should a potential impact on reducing burden of severe RSV disease in children who are beyond six months of age [19]. As use of nirsevimab has started in some clinical settings and its impact is being monitored though routinely collected data [20], real world effectiveness data from these settings will help determine the long- and short-term benefits of nirsevimab."

3. In line 113-114, the author briefly mentioned the market price and the cost-effectiveness. I think it may be worth it to expand it a bit more, since, as the author noted, they will "play a critical role". The market price in the US and EU should be available, since the product is approved in those two places. Additionally, several cost-effectiveness studies have been published regarding nirsevimab. E.g., studies compared nirsevimab and palivizumab (Yu et al), different strategies of nirsevimab immunization (Kieffer et al), or nirsevimab vs maternal vaccine (Shoukat et al). The cost-effectiveness is an important piece if nirsevimab is to be the "holy grail". This also tied to the equitable access the author mentioned in the end.

Response: Thanks for raising this issue, please refer to my response to reviewer A's comment above