Potential Adverse Effects of Passive Immunization Against Respiratory Syncytial Virus (RSV) in Low-Risk Infants in the United States

Ali T. Farid, BPharm
Email: alitfarid@brandeis.edu
The Heller School for Social Policy and Management, Brandeis University
415 South Street, Waltham, MA 02453 USA

Ali T. Farid, BPharm[1] ;Dhwani Hariharan, MS[1]; Donald S. Shepard, PhD[1]

[1]The Heller School for Social Policy and Management, Brandeis University, 415 South Street, Waltham, MA 02453 USA

Background

- Most medical products generate both benefits and risks.
- Nirsevimab, a recombinant monoclonal antibody (mAb), provides passive prophylaxis against respiratory syncytial virus (RSV), and would be administered at the start of a typical RSV season.
- The limited duration of protection from this mAb and the sharply defined RSV season may require an additional visit to immunize infants born before the RSV season.
- This literature-based model estimates the adverse effects that could result from nirsevimab that requires an additional visit in a hypothetical cohort of 100,000 low-risk infants.

Methods

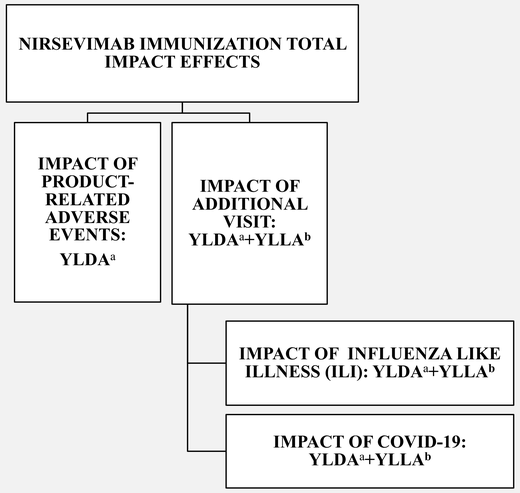
Population

- We applied the adverse effects to 100,000 infants who we assumed would be immunized in-season after birth without the need for an additional visit and those that would need an additional visit.

Total Impact Effects

- The impact effects of immunization are the sum of: (1) the impact of the product-related adverse events (respiratory and non-respiratory related adverse events) and (2) the impact that arises from a potential additional visits for immunization including influenza and COVID-19

Fig 1. Nirsevimab immunization total impact effects breakdown



[a]**YLDA**=Years lost to disability averted

[b]**YLLA** =Years of life lost averted

Product-related adverse events (PRAEs)

- Product-related adverse events were obtained from the safety information of the phase 3 clinical trial[1]. The disability burden per adverse event was calculated from information in the Global Burden of Disease study by the Institute for Health Metrics and Evaluation (IHME).
- Actual values were used and proxies were applied for conditions not listed in IHME. For instance, the product adverse event (gastroenteritis) was assigned the proxy "GIT Disorders." The impact per adverse events was calculated as the aggregate non-fatal DALYs averted for the years lost to disability averted (YLDA) divided by the incidence.
- Discounted years of life lost averted (YLLA) were not included in the base case measurements because the investigators reported that they did not consider any of them product related.
- **A sensitivity analysis** incorporated the added burden from deaths. It used the breakeven value (0.52% probability that the product might have been a contributing factor to the 3 reported deaths) that negated the products benefits.[2]

Additional Visits

- Our scenario assumes that infants are born in April and the RSV season begins in November, when the infant is 7 months old. The American Academy of Pediatrics recommends well-child visits at 6 and 9 months of age, but not at 7 months.
- We assumed that all the cohort of 100,000 April-born infants would require an additional visit.
- In-season infants would be immunized in hospital and would not require an additional visit.
- **Influenza Like Illness (ILI):** The influenza like illness (ILI) transmission rate was obtained from a study which calculated a 3.17% percentage-point increase for any household member in ILI office visits following a well child visit, this was calculated by using the Medical Expenditure Panel Survey (MEPS) through 1996-2008.[3]
- **COVID-19:** After adjusting for underreporting, symptomatic adjusted COVID-19 cases were 3.64 times the rate of adjusted influenza cases.
- The **underreporting adjustment** for influenza weekly symptomatic cases was computed using an average of the expansion factor (204.5) as the average of two studies [4,5] and CDC 's factor of 3.4 for COVID-19.
- The **impact for ILI and COVID-19** symptomatic cases expected to result from the additional visits was calculated as the sum of the discounted years lost to disability averted (YLDA) and the discounted years of life lost averted (YLLA) from the fatalities.
- **ILI and COVID-19** (YLDA) impact per case was calculated from (IHME) as YLD averted for the aggregate years lost to disability from lower respiratory infection divided by the aggregate incidence.
- The **case fatality** rate for ILI was calculated from the CDC estimated symptomatic flu cases and deaths (including adjustments for under reporting) from the 2010-2020 influenza seasons.
- **The case fatality rate** for COVID-19 was calculated as a ratio of adjusted deaths to the adjusted cases.
- Adjusted **COVID-19 deaths** came from National Center for Health Statistics (NCHS) reported deaths from 1/30/22 through 2/12/22 from and the CDC death expansion factor of 1.32.
- Adjusted **COVID-19 cases** came from reported cases from 1/16/22 through 1/29/22 for CDC daily COVID-19 surveillance.
- The case fatality rate for COVID-19 was calculated from the **latest data** to represent the most recent strains.

Results

Key: RESP=PRAE for respiratory disease, NON-R=PRAE for non-respiratory disease, ILI=burden from visit-associated exposure to influenza-like illness, COVID=burden from visit-associated COVID-19 exposure, DEATHS=Product related deaths.

Fig 2. Immunization impact per 100,000 infants with additional visits.

- The DALYs averted from **respiratory** and **non-respiratory** PRAEs were **18.20** and **-0.16,** respectively, indicating a positive (favorable) **spillover effect** from nirsevimab on respiratory adverse events.
- **ILI** and **COVID-19** infections from additional visits resulted fewer DALYs averted (**-58.43** and **-237.39,** respectively).

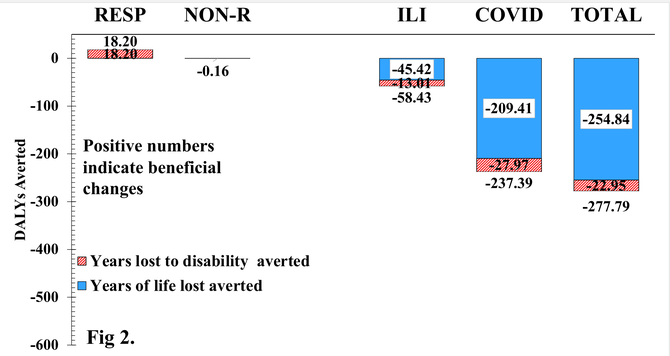


Fig 2.

Fig 3. % Change in product-related effects excluding deaths.

- The respiratory product effects contributed to a YLDA increase of **22.16%** of the placebo respiratory burden.
- The non-respiratory adverse effects caused a decrease of YLDA by **0.03%** of the placebo non-respiratory burden.
- The combined adverse events had an overall benefit where the YLDAs increased by **2.58%** over the placebo group**.**

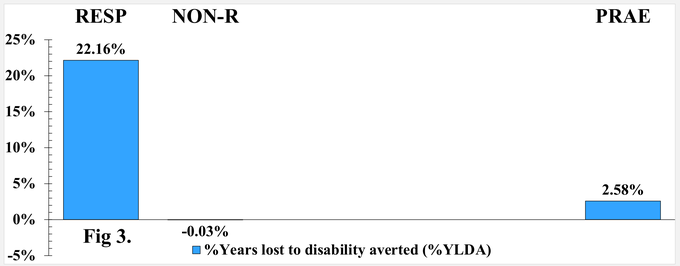


Fig 3.

Fig 4. Sensitivity analysis for the immunization impact per 100,000 infants with additional visits.

- The deaths resulting from the product related adverse events had a YLLA of **-46.99** resulting in a combined DALYs averted **-324.78**
- This negative DALYs averted is unfavorable because it indicates an increased burden.

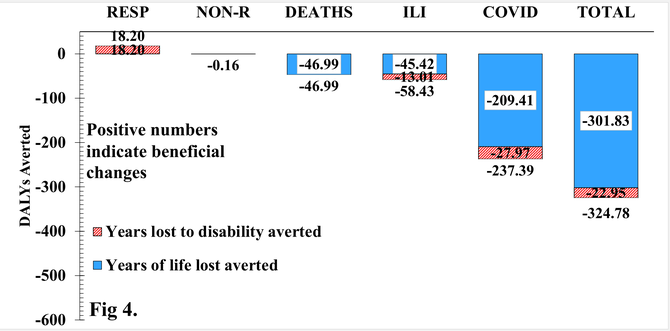


Fig 4.

Conclusion

- Synchronizing nirvebimab's 5-month window of protection with the 5-month RSV season could lead to an additional visit just for immunization, risking possible infant and family exposure to influenza and COVID-19.
- Providing nirsevimab immunization during the birth hospitalization for infants born during the RSV season and shifting this immunization to an existing well-child visit for infants born out-of-season would avoid these added exposures and their potentially fatal consequences.
- If nirsevimab made even a small contribution to the deaths observed in its phase 3 trial, the adverse effect burden would increase, indicating the need for further research on product safety.

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Potential conflict of interest - *We have no conflicts of interest to disclose*