National Advisory Group
on Immunisations (NAGI)
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23 April 2025

The Ministry of Health, Republic of South Africa
Office of the Minister

SUBJECT: Use of the Bivalent Respiratory Syncytial Virus (RSV) Vaccine (Abrysvo™, Pfizer) During Pregnancy for the Prevention of RSV–Associated Lower Respiratory Tract Disease in Infants.

Dear Honorable Dr PA Motsoaledi

PROBLEM STATEMENT

Several epidemiological studies in South Africa (SA) corroborate RSV as a leading cause of lower respiratory tract infection (LRTI) hospitalization in children[1]. Out of all severe acute respiratory illness (SARI) hospitalization episodes in children under-5 years in SA, 48% are in infants aged ≤ 3 months and 62% are ≤ 6 months age, with peak incidence at 1 month of age[1]. Furthermore, 73% of all RSV-associated deaths occur in the first 6 months of life[1]. Also, studies from SA report that HIV-exposed-uninfected infants have a 1.4 times higher incidence of RSV LRTI hospitalization compared with HIV-unexposed infants[2]. Preterm-born infants and those with underlying cardio-respiratory conditions are at higher risk for hospitalization for RSV-LRTI[3].

BACKGROUND

Two new interventions to protect young infants against severe RSV-LRTI have recently been licensed, including a single-dose long-acting monoclonal antibody (Nirsevimab; Bevfortus™) from Sanofi and AstraZeneca, for infants; and a bivalent RSV pre-fusion F protein (RSV preF vaccine; Abrysvo™) from Pfizer targeted at pregnant women. Abrysvo™ has just been licensed by the South African Health Products Regulatory Authority (SAHPRA) for use in SA while licensure for Nirsevimab is currently under consideration. A decision by SAHPRA on licensure of Nirsevimab is anticipated by mid-2025. The cost of Abrysvo™ in SA is expected to be $10 to $20 per dose, whereas the cost of Nirsevimab has not yet been established for SA. Currently Nirsevimab is priced at $520 in the United States of America. Although tiered pricing by country income is expected for Nirsevimab, the pricing which will be available through the public sector in SA remains to be established.

Based on the uncertainty around timing of registration of Nirsevimab and pricing in SA, two separate recommendations for Abrysvo™ and Nirsevimab, will be presented.

Based on this, the key decisions required are:

1. Whether RSV preF vaccine (Abrysvo™) should be introduced into the public immunization program as a single dose vaccination for all pregnant women?
2. At what gestational age should the vaccine be administered?
3. Should the vaccine be administered seasonally or all year round?
4. Can the vaccine be co-administered with other vaccines in the maternal immunization programme?
5. Should women be revaccinated with Abrysvo™ in subsequent pregnancies?

CLINICAL TRIAL –PFIZER

Maternal Immunization Study for Safety and Efficacy (MATISSE Study)[4]

The pivotal phase III trial on RSV preF vaccine (Abrysvo™), was undertaken in 7358 pregnant women in a multi-country, multi-centred trial, which included 964 (13.0%) and

196 (2.6%) pregnant women enrolled from SA and The Gambia respectively, the only two African countries which participated in the trial.

Efficacy

Vaccine efficacy was observed in the infants of vaccinated women through to six months of age for RSV preF vaccine against RSV-confirmed medically attended LRTI (51.3%; 97.58%CI: 29.4 to 66.8); as well as RSV-confirmed severe-LRTI (69.4%; 97.58%CI: 44.3 to 84.1).[4]

Although there was waning of efficacy against severe RSV LRTI in the MATISSE study, with the point estimate of vaccine efficacy declining from 82.4% at day 90 to 40.2% at day 360, vaccine efficacy was still noted between day 90 and day 180 (estimated at 67%). Furthermore, vaccine efficacy against RSV-confirmed and all-cause LRTI endpoints was similar in the overall group of women vaccinated between 24-36 weeks of gestational age, compared with women vaccinated at 32-34 weeks of gestational age.

Safety

Among maternal participants, the incidences of serious adverse events through six months after vaccination were similar in the two groups; the most frequent were preeclampsia (among 1.8% of participants in the vaccine group and 1.4% of those in the placebo group).

Overall, there was a non-significant (1.2 times) higher rate of preterm birth in RSV preF vaccine compared with placebo recipients. While there was a statistically significant (2 times) higher rate of preterm birth in vaccine compared with placebo recipients in SA women who participated in the MATISSE study, most preterm births were of late gestational age (~35 weeks). Furthermore, there was no clear temporal association of preterm birth and vaccination, the excess of preterm births coincided with the surge of COVID-19 cases during the Delta and Omicron dominant waves and was notably not evident in other high-income countries or low-income countries involved in the trial. Consequently, the pathogenesis of RSV preF vaccine-associated preterm births is unclear but could be due to an interaction with SARS-CoV-2 infection at a time when there was incomplete population immunity against SARS-CoV-2.

There was no difference in death rates in infants born of RSV preF vaccine recipients compared with placebo recipients in the MATISSE study, irrespective of whether born at term or preterm (0.03% in RSV preF vaccine vs. 0.05% in placebo). There was a statistically non-significant lower death rate through to 24 months of age in infants born to RSV preF vaccine recipients (0.2%) compared with placebo recipients (0.4%).

SYSTEMATIC REVIEWS

A recent systematic review of RSV vaccine studies in pregnant women[5] did not identify an increased risk of premature births in women who received RSV vaccine during pregnancy.

SEASONALITY

Based on the circulation pattern of RSV in SA, including variability in onset and peak of the epidemics and perennial circulation of RSV, it is recommended that the RSV preF vaccine be offered year-round.[6]

COST EFFECTIVENESS

A recent analysis in SA suggests that at vaccine prices of up to US$20 per dose, an RSV maternal vaccine is likely to be cost-effective, even when conservative cost-effectiveness thresholds are assumed[7]. At lower vaccine prices of US$5-10 per dose, RSV maternal vaccines could potentially be cost saving[7] suggesting that costs incurred by the health system in providing RSV maternal vaccines may be fully offset by clinical management costs averted due to a reduction in RSV-related ARI and SARI in infants. Programmatic vaccine delivery costs were not included in the analysis.

SAFETY and EFFICACY in PREGNANT WOMEN LIVING with HIV (PWWH)

Investigation of the safety and immunogenicity of RSV preF vaccine in pregnant women living with HIV (PWWH), which may be benchmarked against yet to be established correlates of protection, are currently underway in SA, with the results expected in mid-2025.

Nevertheless, findings from other vaccines indicate that Tetanus, diphtheria and acellular pertussis (Tdap)[8] is safe and immunogenic in PWWH on antiretroviral treatment or who are not immunocompromised, even though compared with HIV-uninfected pregnant women, immune responses are less robust. Also, although PWWH have slightly lower immune responses to inactivated influenza vaccine compared with HIV-uninfected women, immune responses were similar with alternate dosing schedules of a double-strength dose or two doses[9].

Furthermore, based on the higher rates of RSV LRTI hospitalization and poorer outcomes in the offspring of PWWH[2], who constitute approximately 25% of all pregnant women in SA, it is recommended that PWWH be vaccinated with RSV preF vaccine.

CO-ADMINISTRATION of VACCINES

No safety concerns were identified with concomitant administration of Abrysvo™ and Tdap[10] in non-pregnant women. Although co-administration resulted in lower immune responses to pertussis toxoid, there was no difference in immune response to Abrysvo™.[10]

Co-administration of Tdap, Hepatitis B or Influenza vaccines and Abrysvo™ in pregnant women have not been studied.

SOUTH AFRICAN CONTEXT

Maternal RSV preF vaccination is required to take place at least 14 days before the birth of the child, for there to be adequate transplacental transfer of protective antibody to the foetus. Limiting vaccination to a narrower window period in SA, i.e., only between 32 to 36 weeks gestational age, could inadvertently result in lack of protection in children born

at or before 34 weeks gestational age who are at higher risk of severe RSV-LRTI[3]. In addition, considering that ultrasound is not done routinely in public antenatal facilities in SA, especially before 24 weeks gestational age, a very restrictive recommendation of the gestational age when vaccination should be provided would be challenging to implement.

WHO STRATEGIC ADVISORY GROUP of EXPERTS on IMMUNISATION (SAGE)

The London School of Hygiene and Tropical Medicine (LSHTM) was commissioned to undertake risk-benefit modelling (see Figure 1 below). The analysis was presented to WHO SAGE, at their meeting in September 2024[11], during their deliberations on the use of Abrysvo™ in pregnant women. The risk-benefit modelling for death due to potential increased risk of preterm birth in women vaccinated with Abrysvo™ relative to deaths which would be preventable by RSV preF vaccine, indicated a favorable benefit of maternal RSV preF vaccination if the single preterm event which occurred in a vaccine recipient at 27 weeks gestational age was excluded from the analysis.

Figure 1: Risk-benefit analysis for use of RSV preF in South Africa.

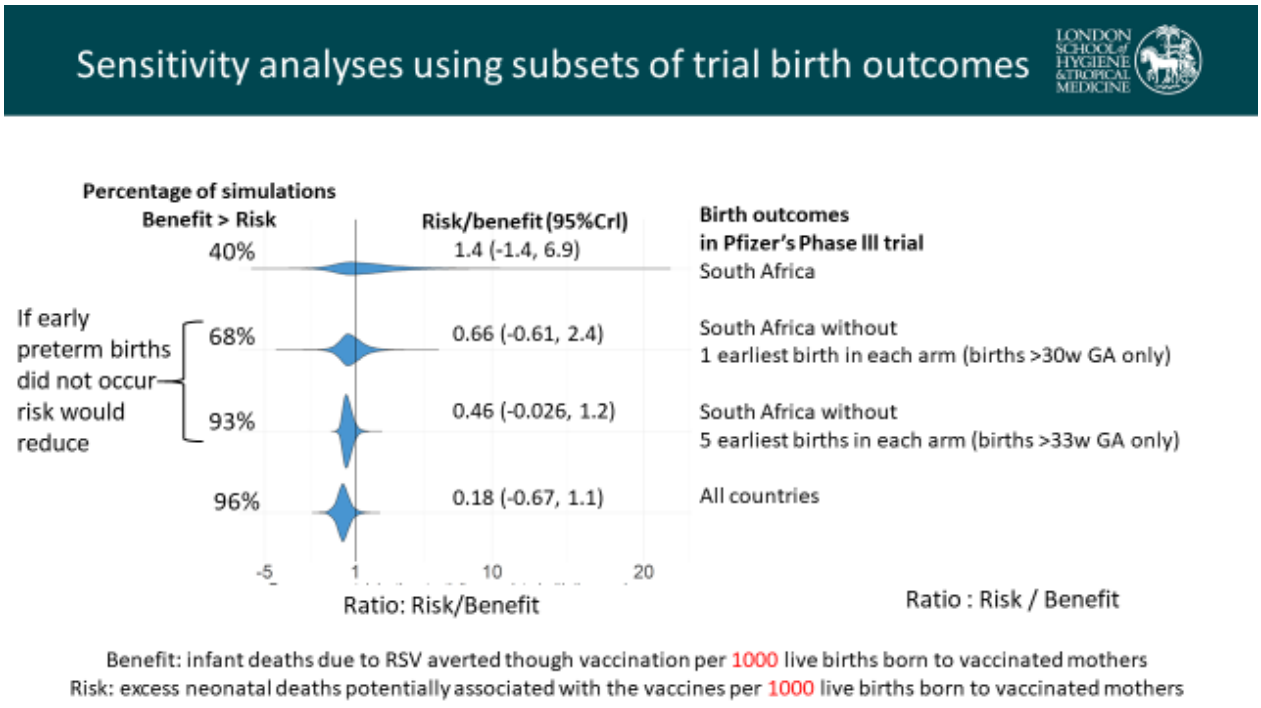


Figure 1 note: Analysis from LSHTM presented at WHO SAGE meeting, September 2024

Draft GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tables and Evidence to Recommendation Framework documentation[12] were presented at the WHO SAGE meeting and have been shared with NAGI.

The WHO SAGE recommended vaccination of pregnant women with RSV preF vaccine in the 3rd trimester[11](i.e., 28 weeks gestational age or more).

RECOMMENDATIONS

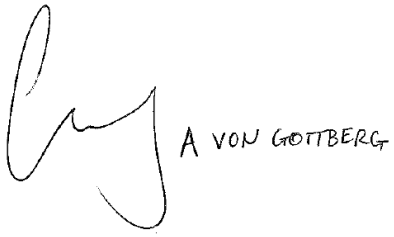
Considering the epidemiology of RSV in SA, the safety and efficacy results from the MATISSE study, as well as uncertainties regarding the near-term availability and affordability of Nirsevimab as an alternate or adjunct intervention to maternal RSV preF vaccine, the recommendation for SA is:

1. To introduce RSV preF vaccine into the public immunization program for a single dose vaccination for all pregnant women. At this stage, it is recommended for every pregnancy as there is a waning of antibody - i.e., there may not be protection at the next pregnancy.
2. To vaccinate women from the onset of the third trimester (28 weeks gestational age or more).
3. To offer the vaccine year-round.
4. To allow co-administration of RSV preF vaccine with other vaccines in the maternal immunization program, including influenza (which is given seasonally). It is suggested that the Tdap and RSV vaccines are preferably spaced two weeks apart but can be co-administered if patient presents late in pregnancy. Where possible, administer vaccines in different arms or at different injection sites.
5. To ensure that implementation of vaccination with RSV preF vaccine should be done in conjunction with monitoring of the safety and effectiveness of the vaccine, including in women living with HIV. Vaccine safety surveillance should include increased awareness of and training on reporting of adverse events following immunization amongst vaccinators and pregnant women.

Thank you for your consideration.

Yours sincerely,

PROFESSOR ANNE VON GOTTBERG (CHAIRPERSON: NAGI)



CC: Dr S Buthelezi (Director-General)

CC: Mr Morewane (Acting Deputy Director-General: HIV, TB and MCWH

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