Respiratory Syncytial Virus (RSV) long-acting human recombinant monoclonal antibody, nirsevimab: Evidence to recommendation table

And

Respiratory Syncytial Virus (RSV) pre-F maternal vaccine: Evidence to recommendation table

for consideration by the Strategic Advisory Group of Experts (SAGE) on Immunization

SAGE Evidence to Recommendation Framework

Policy question: Should a single dose (50 mg for infants <5 kg and 100 mg for infants ≥5 kg) of the RSV long-acting human recombinant monoclonal antibody (mAb) (nirsevimab) be recommended for infants aged <12 months born during or entering their first RSV season to prevent RSV-associated morbidity and mortality?

Background: Respiratory Syncytial Virus (RSV) causes significant morbidity and health system utilisation in all geographies and across all income settings. It contributes to about a third of all lower respiratory tract illness (LRTI) in children. It is estimated that close to 33 million RSV-associated LRTI cases occur each year, of which about 7 million occur in infants < 6 months of age. The annual estimated number of RSV-associated hospitalizations is 3.6 million, of which 0.9 million occur in infants < 6 months of age.

Secondary bacterial infections can follow a primary infection with RSV, contributing to morbidity and mortality. Early RSV infection is also known to be associated with an increase in wheezing disorders in children. Hence, the impact of immunization against RSV infections might extend beyond RSV-associated LRTI and potentially lead to a reduction in all-cause LRTI and wheezing disorders, including asthma in children.

Globally, it is estimated that 101,400 RSV-attributable deaths occur in children under five years of age annually. Approximately 45% of these deaths occur in infants < 6 months of age. Most RSV-associated deaths (>97%) occur in low- and middle-income countries (LMICs) because of low care-seeking and limited access to quality care in health facilities. Hence, the impact on RSV-associated mortality will be highest in these settings.

In most settings, RSV infection is seasonal, though the timing and duration of the RSV season may vary across and within countries.

Currently, two effective approaches to RSV passive immunization are available to prevent RSV-associated severe disease in young infants: giving a vaccine to pregnant persons in the latter part of pregnancy to protect infants through transplacental transfer of maternal antibodies; and use of a long-acting monoclonal antibody administered directly to the infant. Since a high proportion of RSV morbidity and an even higher proportion of RSV-associated deaths occur in young infants, passive immunization can have a substantial impact on reducing RSV-associated morbidity and mortality.

Nirsevimab is a recombinant human IgG1 kappa monoclonal antibody that targets the highly conserved epitope (site Ø) on the pre-fusion protein of RSV and has a prolonged serum half-life. It is recommended as a single dose administered at birth or just prior to the RSV season in a dose of 50 mg (for infants < 5kg) or 100 mg (infants ≥ 5 kg). It is licensed in over 40 countries globally.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	RSV is one of the leading causes of LRTI in all geographies and income settings. Annually, it is estimated to cause close to 33 million cases of LRTI, 3.6 million of which require hospitalization. An estimated 101,400 RSV-attributable deaths occur in children under five years of age annually, 45% of which occur in infants <6 months of age. 97% of RSV-associated deaths occur in LMICs.	Passive immunization with a long-acting monoclonal antibody administered before the RSV season at or close to birth will protect infants exposed to RSV during the first 6 months of life, when a high proportion of deaths and hospitalisation due to RSV occur.

BENEFITS & HARMS	**Benefits**: Are the desired anticipated effects large?	No ☐	Uncertain ☐	Yes ☒	Varies ☐	The efficacy of nirsevimab administered just before or during the RSV season against medically attended RSV lower respiratory tract infection (MA-LRTI)[1] was 79.0% (95% CI: 68.5% - 86.1%) and against MA-LRTI requiring hospitalization was 80.6% (95% CI: 62.3% - 90.1%) through 150 days after administration. The efficacy against severe RSV MA-LRTI[2] was 78.6% (95% CI: 48.8% – 91.0%).	Antibody levels wane in the months after administration. At 360 days, all infants who received the 50 mg dose had nirsevimab serum concentrations of <10 µg/ml. Statistically non-significant efficacy was observed at 360 days among participants from South Africa in the phase 3 trial (hazard ratio 0.49, 95% CI 0.16-1.52)[3]. The benefits of nirsevimab administered 6 months or more before the RSV season are uncertain if year-round administration at or soon after birth is adopted, especially in infants who receive the 50 mg dose.

[1] **Definition:** MA-RTI visit AND RSV-positive test result
AND ≥1 of the following
- Rhonchi
- Rales
- Crackles
- Wheeze

AND ≥ 1 of the following
- Increased respiratory rate (*≥60 breaths/min for <2-month-old; ≥50 breaths/min for 2–6-month-old, ≥40 breaths/min for 6–24month-old)
- Hypoxemia in room air: O2 <95% at ≤1800 m; O2 <92% at >1800 m
- Clinical signs of severe respiratory disease: New-onset apnoea; retractions; grunting, nasal flaring; acute hypoxic or ventilatory failure; dehydration due to respiratory distress requiring IV hydration; intercostal, subcostal, or supraventricular retractions

	Harms: Are the undesirable anticipated effects small?	No ☐	Uncertain ☐	Yes ☒	Varies ☐		Nirsevimab administered to infants aged < 8 months before or during the first RSV season did not demonstrate a statistically significant increase in severe adverse events during 150 days after administration.	The trial did not include participants from low-income and lower-middle income countries, and the trial was not powered to detect any rare serious adverse events. No serious safety signals have been observed in post-marketing safety surveillance. A few cases of severe hypersensitivity reactions were reported in the US FDA Adverse Events Reporting System (FAERS). However, the accuracy of the hypersensitivity diagnosis is currently not known, neither is the rate at which these reactions occur.
	Balance of benefits and harms	Favours intervention ☒	Favours comparison ☐	Favours both ☐	Favours neither ☐	Unclear ☐		
		Effectiveness of the intervention						

[2] **Definition**: any confirmed RSV MA-LRTI for which hospitalization and supplemental oxygen (any level) or intravenous fluids are warranted (defined as very severe RSV MA-LRTI in the trial protocol).
[3] Supplement to: Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med 2022;386:837-46. DOI: 10.1056/NEJMoa2110275 (Figures S5 and S3),

	What is the overall certainty of this evidence for the critical outcomes?	No included studies ☐	Very low ☐	Low ☐	Moderate ☐	High ☒	The evidence supports a high level of confidence that the true effects of efficacy against RSV MA-LRTI, RSV MA-LRTI requiring hospitalization, and severe MA-LRTI lie close to the effects on these outcomes observed during the trial.	The point estimates of vaccine effectiveness observed in post-marketing studies were close to the efficacy point estimates observed during the clinical trials.[4] In these studies, nirsevimab was administered just before or during the RSV season.
		Safety of the intervention						
		No included studies ☐	Very low ☐	Low ☐	Moderate ☒	High ☐	The evidence supports a low level of confidence that the true effect on serious adverse events in infants aged < 12 months lies close to the effect observed in the clinical trials.	No serious adverse events were observed in a post-marketing study conducted in Spain in over 9000 eligible infants. The accuracy of the hypersensitivity diagnosis reported in FAERS is currently not known, neither is the rate at which these reactions occur.
VALUES AND PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	Important uncertainty/ variability ☐	Possible important uncertainty/ variability ☐	Probably no important uncertainty/ variability ☐	No important uncertainty/ variability ☐	No known undesirable outcomes ☒		

[4] Ares-Gomez S, Mallah N, Santiago-Perez MI, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. Lancet Infect Dis 2024.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐	Probably no ☐	Uncertain ☐	Probably yes ☐	Yes ☒	Varies ☐	Available data show that nirsevimab demonstrates high efficacy and effectiveness in preventing RSV disease for up to 150 days following administration. No serious adverse events have been reported to date.	Acceptance of nirsevimab 6 months or more before the RSV season, when the benefits of the product are uncertain, is not known.
RESOURCE USE	Are resources required small?	No ☒		Uncertain ☐	Yes ☐		Varies ☐	The price per dose of nirsevimab may vary between countries and is US $ 300 in Europe and over US $ 500 in the United States of America. Prices for nirsevimab for national programmes in LMICs are currently not known because no LMIC has started using nirsevimab and there is no public commitment for tiered pricing for LMICs	

	Is the intervention cost-effective?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	The results from 3 studies conducted in Canada, England and Wales and the United States of America[5] varied considerably, and the nirsevimab programmes differed in terms of patients' eligible for immunization. In general, nirsevimab was more cost-effective and associated with lower total costs than comparator programs[6]. The results were sensitive to the modelled region, source of efficacy data, price of nirsevimab, and severity of the RSV season. At a price of US$3 and US$5 for Gavi-eligible and non-eligible LMICs, a mAb offering 60-70% protection for 6 months was estimated to be impactful and cost-effective in these countries (ICER per DALY averted 315 and 577, respectively).[7] However, given the estimated cost of goods for producing nirsevimab, it is uncertain whether these prices are attainable.	

[5] Brown R, Tiggelaar S, Tsoi B, Cromwell I. Cost-Effectiveness of Nirsevimab for the Prevention of Respiratory Syncytial Virus Infection in Infants: CADTH Health Technology Review. Ottawa (ON), 2023.
[6] Comparators used varied between the 3 studies and included a monthly palivizumab programme in high-risk infants and different strategies for using maternal pre-F vaccination and nirsevimab.
[7] Baral R, Higgins D, Regan K, Pecenka C. Impact and cost-effectiveness of potential interventions against infant respiratory syncytial virus (RSV) in 131 low-income and middle-income countries using a static cohort model. BMJ Open 2021; 11:e046563.

EQUITY	What would be the impact on health inequities?	Increased ☐	Uncertain ☐	Reduced ☐	Varies ☒		At current prices, nirsevimab is unlikely to be affordable for widespread use in LMICs, creating inequities between countries. If the product is available only in the private market on payment in LMICs, it is likely to increase health inequities within countries.	At a Gavi-acceptable price, nirsevimab is estimated to be cost-effective in Gavi-eligible countries. Nirsevimab has received market authorisation for use in India, although no commitment for its introduction in a publicly funded routine immunization programme has been made.
ACCEPTABILITY	Which option is acceptable to key stakeholders (MOH, Immunization Managers)?	Intervention ☐	Comparison ☐	Both ☐	Neither ☐	Uncertain ☒	This will depend on whether the price of the product is affordable in the country.	
	Which option is acceptable to target groups?	Intervention ☒	Comparison ☐	Both ☐	Neither ☐	Uncertain ☐	If made accessible through a publicly funded national programme, the intervention is likely to be acceptable to target groups, given the acceptability of other preventive interventions administered at birth or during early infancy.	Name recognition of RSV is low in most LMICs, but there is caretaker awareness of bronchiolitis in babies; prevention of this syndrome is preferable. Communication and advocacy about the burden of RSV will be important to stimulating demand and influencing perceptions, particularly among healthcare workers who are providing health education to parents, as well as key opinion leaders.

FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably no ☐	Uncertain ☒	Probably Yes ☐	Yes ☐	Varies ☐	In countries without a clearly defined season, seasonal administration is likely to be challenging. Administration of nirsevimab at or shortly after birth in a year-round approach to administration is likely to be more feasible in LMICs if linked to administration of a birth-dose of another vaccine, any other neonatal intervention, or the first dose of DTP-containing vaccine.	

BALANCE OF CONSEQUENCES	Undesirable consequences clearly outweigh the desirable consequences in most settings. ☐	Undesirable consequences probably outweigh the desirable consequences in most settings. ☐	The desirable and undesirable consequences are closely balanced or uncertain. ☐	The desirable consequences probably outweigh the undesirable consequences in settings with high dengue transmission. ☐	The desirable consequences clearly outweigh the undesirable consequences in most settings. ☒

TYPE OF RECOMMENDATION	We recommend the intervention (based on affordability and feasibility).[8] ☒	We suggest considering the recommendation of the intervention. ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific subpopulations.	We recommend the comparator. ☐	We recommend against the intervention and the comparator. ☐
RECOMMENDATION	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**			

[8] The recommendation for use is not conditional to every country conducting disease or safety surveillance. However, SAGE recommends monitoring for safety in multiple settings across country income groups.

IMPLEMENTATION CONSIDERATIONS	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**
MONITORING AND EVALUATION	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**
RESEARCH	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**

SAGE Evidence to Recommendation Framework

Policy question: Should the RSV pre-F vaccine (Abrysvo®, Pfizer) be recommended for use in pregnant people in a single-dose schedule at 24-36 weeks of gestation to prevent RSV disease in infants during the first 180 days of life?

Background: Respiratory Syncytial Virus (RSV) causes significant morbidity and health system utilisation in all geographies and across all income settings. It contributes to about a third of lower respiratory tract illness (LRTI) in children. It is estimated that close to 33 million cases of RSV-associated cases occur annually each year, of which about 7 million occur in infants < 6 months of age. The annual estimated number of RSV-associated LRTI hospitalisations is 3.6 million, of which 0.9 million occur in infants < 6 months of age.

Secondary bacterial infections can follow a primary infection with RSV contributing to morbidity and mortality. Early RSV infection is also known to be associated with an increase in wheezing disorders in children. Hence, the impact of immunization against RSV infections may extend beyond RSV-associated LRTI and potentially lead to a reduction in all-cause LRTI and wheezing disorders, including asthma in children.

Globally it is estimated that that 101,400 RSV-attributable deaths occur in children under five years of age annually. Approximately 45% of these deaths occur in infants < 6 months of age. Most RSV-associated deaths (>97%) occur in low- and middle-income countries (LMICs) because of low care-seeking and limited access to quality care in health facilities. Hence the impact on RSV-associated mortality will be highest in these settings.

In most settings, RSV infection is seasonal, though the timing and duration of the RSV season may vary across and within countries.

Currently, two effective approaches to RSV passive immunization are available to prevent RSV-associated severe disease in young infants: giving a vaccine to pregnant persons in the latter part of pregnancy to protect infants through transplacental transfer of maternal antibodies and use of a long-acting monoclonal antibody administered directly to the infant. Since a high proportion of RSV morbidity and an even higher proportion of RSV-associated deaths occur in young infants, passive immunization can have a substantial impact on reducing RSV-associated morbidity and mortality.

A bivalent stabilised RSV pre-fusion F protein vaccine (RSV-preF, Abrysvo®) has received market authorisation in several countries. It contains the stabilised pre-fusion protein of RSV A (Ontario) and RSV B (Buenos Aires) genotypes of the virus. The vaccine is licensed for use between 24 to 36 weeks of gestation by the European Medicines Agency, though other regulatory agencies have recommended a narrower gestational age window for vaccination.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	RSV is one of the leading causes of LRTI in all geographies and income settings. Annually, it is estimated to cause close to 33 million cases, 3.6 million of which require hospitalisation. An estimated 101,400 RSV-attributable deaths occur in children under five years of age annually, 45% of which occur in infants <6 months of age. 97% of RSV-associated deaths occur in LMICs.	Passive immunization through passive transfer will mainly protect infants during the first 6 months of life. However, a high proportion of deaths and hospitalisation due to RSV occur during this period.

BENEFITS & HARMS	**Benefits**: Are the desired anticipated effects large?	No ☐	Uncertain ☐	Yes ☒	Varies ☐	In a phase 3 randomised clinical trial, a single dose of the pre-F vaccine administered to pregnant women from 24 to 36 weeks gestation demonstrated efficacy of 70% (95% CL 50.6-82.5%) against severe medically-attended RSV LRTI (RSV MA-LRTI) up to 180 days after birth. The evidence supports a high level of confidence that the true effect lies close to the estimate of the effect.	The efficacy of the maternal pre-F vaccine against MA-LRTI was 49.2% (95% CL 31.4 - 62.8%) and was 54.8% against MA-LRTI requiring hospitalisation (95% CL 20.5-75.2%) up to 180 days after birth. The evidence supports a moderate level of confidence that the true effect lies close to the estimate of effect if the vaccine is administered during the 24-to-36-week gestational age window. The efficacy of the vaccine if the vaccine is administered after 36 weeks of gestation is unknown and may be lower if the vaccination occurs within a week of birth.

	Harms: Are the undesirable anticipated effects small?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	The RSV pre-F vaccine administered at 24-36 weeks of gestation did not demonstrate a statistically significant risk of serious adverse events or systemic reactogenicity in pregnant people or any serious adverse events in infants up to 24 months of follow-up. The vaccine demonstrated a statistically non-significant risk of pre-term births (RR 1.2, 95% CL 0.98-1.46) in the full study population. The risk of pre-term births was higher in the two upper-middle-income countries (Argentina and South Africa), which contributed the largest number of subjects among countries in this income level; the RR of pre-term births in South Africa was statistically significant (RR 2.06, 95% CL 1.21 to 3.51) The evidence supports a very low level of confidence that the true effect lies close to the estimate of this outcome.	The relative risk of pre-term very or extreme pre-term births (< 32 weeks gestation) was 1.0 (95% CL 0.35 to 2.84). The relative risk was highest for pre-term births < 34 weeks of gestation (RR 1.83, 95% CL 0.91 – 3.69). Administration of the vaccine during the third trimester (gestational age ≥ 27 weeks) is associated with lower incremental risk of extremely pre-term births. The data on pre-term births were examined by feto-maternal experts and no biological explanation was found for the excess in pre-term births observed in the trial. A clinical trial with a similar pre-F vaccine administered during pregnancy showed a similar increase in pre-term births, predominantly in LMICs. This led to the trial being halted. Both vaccines were evaluated during the COVID-19 pandemic.

<table>
<tr><td rowspan="4"></td><td>Balance of benefits and harms</td><td>Favours intervention

☒</td><td>Favours comparison

☐</td><td>Favours both

☐</td><td>Favours neither

☐</td><td>Unclear

☐</td><td>Mathematical models using clinical trial data from South Africa indicate that if vaccination is provided during the third trimester of pregnancy (27 to 36 weeks of gestation), the benefits of vaccination will exceed risks based on estimated impact on child mortality in 98% of simulations.</td><td></td></tr>
<tr><td rowspan="3">What is the overall certainty of this evidence for the critical outcomes?</td><td colspan="5">Effectiveness of the intervention</td><td></td><td></td></tr>
<tr><td>No included studies

☐</td><td>Very low

☐</td><td>Low

☐</td><td>Moderate

☒</td><td>High

☐</td><td>There is a high level of certainty on the effectiveness of the vaccine against severe RSV MA-LRTI and moderate level of certainty on the effectiveness against total RSV MA-LRTI and RSV MA-LRTI requiring hospitalization.</td><td></td></tr>
<tr><td colspan="5">Safety of the intervention</td><td></td><td></td></tr>
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		No included studies ☐	Very low ☒	Low ☐	Moderate ☐	High ☐	There is high certainty of the evidence that the vaccine does not result in severe adverse events in the vaccine recipients (pregnant people) or their infants. There is very low level of confidence in the evidence that the intervention leads to an excess of pre-term births.	Early data from post-authorization safety monitoring of the vaccine in the U.S. and Argentina have not shown increased preterm birth; however, more data from early adopting MICs will provide further clarity on this potential safety signal. A study to assess the effect of the vaccine on RSV and all-cause LRTI as well as birth outcomes including pre-term births and low birth weight is planned in LMICs.
VALUES AND PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	Important uncertainty/ variability ☐	Possible important uncertainty/ variability ☒	Probably no important uncertainty/ variability ☐	No important uncertainty/ variability ☐	No known undesirable outcomes ☐	There is an important uncertainty about the potential risk of pre-term births following maternal pre-F vaccination when administered at 24-36 weeks gestation.	A study to assess the impact of the vaccine in reducing LRTI and the risk of excess pre-term births in LMIC settings is planned to start in late 2024/ early 2025.
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐	Probably no ☐	Uncertain ☐	Probably yes ☒	Yes ☐	Varies ☐	Mathematical modelling of the trial data from South Africa, the country with the highest pre-term birth imbalance in the trial, shows that if vaccination is provided during the third trimester, the desirable effects would be larger relative to the undesirable effects.	

RESOURCE USE	Are resources required small?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	This will depend on the prices at which the vaccines are made available in LMICs, the additional programmatic costs for deploying and administering the vaccines and access to external funds to support introduction, e.g., through Gavi.	There is a commitment by the manufacturer to develop products programmatically suitable and affordable for LMIC markets.
	Is the intervention cost-effective?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	This will depend on the price of the vaccine and the country's income level. It is estimated that it would cost US $17/DALY averted in Gavi-eligible countries, assuming a vaccine cost of US $ 3.50 per dose of the vaccine. If there is a proven link to pre-term births following maternal pre-F vaccination, the vaccine may not be cost-effective.	The vaccine is estimated to be cost-saving in South Africa (at US $7 per dose) and cost-effective in Kenya (US $179 /DALY at a vaccine cost of US $3.50 per dose).
EQUITY	What would be the impact on health inequities?	Increased ☐	Uncertain ☐	Reduced ☒	Varies ☐	If equal access to vaccination is provided through the national immunization programme, vaccination would reduce health inequities, since poor health outcomes are associated with poor access to quality health care.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (MOH, Immunization Managers)?	Intervention ☒	Comparison ☐	Both ☐	Neither ☐	Uncertain ☐	Currently, there are no preventive measures against RSV in most countries. RSV bronchiolitis is recognized by mothers in LMICs when they are shown videos of the condition. If key stakeholders are provided with reliable evidence to demonstrate the benefits of the pre-F vaccine, it is likely to be acceptable. However, the cost of RSV vaccination is likely to influence how countries will prioritize its introduction relative to other vaccines or public health interventions.	

	Which option is acceptable to target groups?	Intervention ☒	Comparison ☐	Both ☐	Neither ☐	Uncertain ☐	In general, available evidence suggests that acceptance of vaccination during pregnancy is acceptable if there is clear communication from trusted sources that it will benefit the infants. Recent evidence suggests a lack of understanding of the benefits of maternal immunisation.	The primary concern around maternal immunization is safety in pregnant women. Name recognition of RSV is low in most LMICs, but there is caretaker awareness of the bronchiolitis syndrome in babies; prevention of this syndrome is preferable. Communication and advocacy about the burden of RSV will be important to stimulating demand and influencing perceptions, particularly among healthcare workers who are providing health education to parents, as well as key opinion leaders. However, communication on the potential of the vaccine to cause pre-term births would need to be carefully managed to optimise acceptability.

FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably no ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐	Available data on antenatal care (ANC) visits during the third trimester of pregnancy indicate that vaccination is feasible in most countries, including LMICs, if vaccination is provided during ANC visits. The lack of precise estimates of the gestational age may raise some challenges but these could be overcome if a flexible approach is used and health workers are appropriately trained.	

BALANCE OF CONSEQUENCES	Undesirable consequences clearly outweigh the desirable consequences in most settings. ☐	Undesirable consequences probably outweigh the desirable consequences in most settings. ☐	The desirable and undesirable consequences are closely balanced or uncertain. ☐	The desirable consequences probably outweigh the undesirable consequences. ☒	The desirable consequences clearly outweigh the undesirable consequences in most settings. ☐

TYPE OF RECOMMENDATION	We recommend the intervention.[9] ☒	We suggest considering the recommendation of the intervention. ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific subpopulations.	We recommend the comparator. ☐	We recommend against the intervention and the comparator. ☐
RECOMMENDATION	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**			

[9] The recommendation for use is not conditional to every country conducting disease or safety surveillance for pregnancy outcomes. However, SAGE recommends monitoring for safety in pregnancy in multiple settings across country income groups. This should include using standardized case definitions for important birth outcomes, such as preterm birth and low birthweight (i.e., Brighton Collaboration Global Alignment of Immunization Safety in Pregnancy (GAIA) project).

IMPLEMENTATION CONSIDERATIONS	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**
MONITORING AND EVALUATION	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**
RESEARCH	**REFER TO THE BACKGROUND DOCUMENT FOR THE DRAFT RECOMMENDATIONS**