



WHO Preferred Product Characteristics for Group B Streptococcus Vaccines

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A. INTRODUCTION

I. Background and purpose

Vaccine preferred product characteristics (PPCs) published by the World Health Organisation (WHO) describe preferred parameters pertaining to vaccine indications, target population, data collected for safety and efficacy evaluation, research and development (R&D) and immunization strategies. Selected disease areas are identified as WHO priorities based on the unmet public health need for vaccines, technical feasibility assessment and suitability for use in low- and middle-income countries.

The PPCs are intended to encourage innovation and the development of vaccines for use in settings most relevant to the global unmet public health need. They do not include minimally acceptable characteristics and it is important to note that if a vaccine does not meet the PPC criteria, it could still be assessed by WHO for policy recommendation. Any GBS vaccine that becomes licensed and potentially available will undergo evidence-based assessment for policy recommendations by the Strategic Advisory Group of Experts (SAGE) on Immunization.

The primary target audience for WHO PPCs is any entity intending to eventually seek WHO policy recommendation and prequalification for their products. WHO preferences can be useful to all those involved in vaccine development activities, including academic groups, funders and manufacturers.

WHO PPCs intend to provide early guidance on vaccine development strategies and targets, and are to be updated regularly to account for innovations or any other change in the identified need and R&D landscape. WHO PPCs do not override existing WHO guidance on vaccine development. Useful links to existing documents are provided in Appendix 1.

II. GBS vaccines, a strategic priority for WHO

Group B streptococcus (GBS) is a leading cause of sepsis and meningitis in neonates and young infants. It is also an important cause of stillbirth. GBS can be transmitted from the maternal ano-genital tract through mucosal surfaces to cause invasive disease in the foetus, newborn and young infant, potentially leading to stillbirth, early onset disease (<7 first days of life) and late onset disease (day 7 to first 3 months of life). Case fatality is high, particularly in early onset disease and resource poor settings. Maternal colonization in pregnancy has been found in a proportion of women (about 10–40%) in all geographical settings evaluated. Reported incidence of neonatal and infant invasive GBS disease varies geographically. The vast majority of the disease burden lies in low-and-middle-income



countries, with estimates as high as 3 cases per 1000 live births in some areas, excluding stillbirth. GBS is also a cause of invasive disease in women during and after pregnancy, and in the elderly, but precise disease burden estimates are lacking. Intra-partum antibiotic prophylaxis (IAP), based on pregnancy screening for GBS colonization or on the presence of other risk factors, has been only partially effective in reducing the risk of disease in high income countries, and is neither available nor practical in most resource-limited countries (1–4). IAP also raises concerns about emerging antimicrobial resistance and neonatal microbiome development.

Ten GBS envelope polysaccharide-based serotypes have been described, five of which (Ia, Ib, II, III, V) are estimated to account for the vast majority of the disease burden, although regional differences have been reported and more data are needed. Currently, no vaccine exists for prevention of GBS disease, but evidence suggests maternal immunization with protein-conjugated GBS capsular polysaccharides may reduce the disease risk in neonates and young infants in a serotype-specific manner through trans-placental passage of protective immunoglobulins (1, 5, 6). Protein-based vaccine candidates aiming to provide protection across the serotype spectrum are also under evaluation (7).

In its 2015 and 2016 meetings, the Product Development for Vaccines Advisory Committee (PDVAC), which informs SAGE on vaccine R&D matters and contributes to prioritize topics for WHO Initiative for Vaccine Research involvement, identified the development of GBS vaccines suitable for maternal immunization in pregnancy and use in low and middle income countries as a priority.

III. WHO strategic goal for GBS vaccines

To develop and license safe, effective and affordable GBS vaccines for maternal immunization during pregnancy to prevent GBS-related stillbirth and invasive GBS disease in neonates and young infants, appropriate for use in high-, middle- and low-income countries.

IV. Clinical research and development considerations

1. Early clinical development pathway

GBS vaccine candidate testing in pre-clinical animal models must demonstrate favourable safety and immunogenicity before human testing. Valuable data can also be derived from animal GBS disease models. Favourable outcomes in relevant animal reproductive toxicology studies must have been demonstrated before studies in pregnant women proceed.

Phase 1 and 2 studies would initially be conducted in non-pregnant women of childbearing age, for initial characterization of safety, immunogenicity, schedule, optimal vaccine dose and potential requirement for an adjuvant. Studies in pregnant women would be expected to start after favourable safety and immunogenicity has been documented in non-pregnant women of childbearing age, for further characterization of safety and immunogenicity in both the mother and her offspring.

2. Role of correlates of protection in the vaccine development pathway, licensure and policy decision

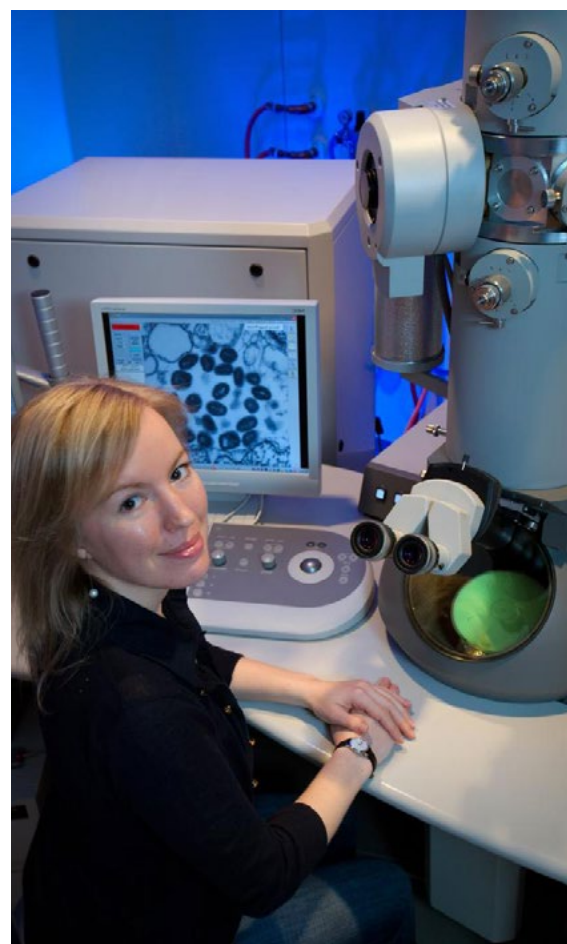
A clinical efficacy trial of a GBS candidate vaccine candidate will need to be of substantial size due to the incidence rates of outcomes of interest. Vaccine developers may therefore consider applying for licensure based on a surrogate of protection determined to be reasonably likely to predict clinical benefit. In addition, established correlates of protection can be very useful to compare results across studies, to allow bridging studies supporting the extrapolation of pivotal data from one population to another (such as, for instance, different risk groups or geographical areas) and in licensing further vaccines.

Correlates of protection can be derived from demonstration of a strong association between a validated immunological assay or other clinical biomarkers and protection against disease. In the case of neonatal and infant protection derived from passive transfer of maternal antibodies, supportive evidence to identify correlates could be derived from either an efficacy trial that incorporates an immunological assessment, or observational studies showing an association between antibody levels (acquired following natural GBS exposure) in mothers or infants at birth (or through the period at-risk) and protection against invasive GBS disease. One source of complexity relates to the serotype-specific nature of the putatively protective antibodies targeting envelope polysaccharide antigens. It will likely be difficult to establish an evidence basis for less common capsular serotypes.

As maternal GBS colonization is a critical precursor to GBS-related stillbirth and early onset invasive disease, a vaccine-induced reduction or prevention of colonization might be considered a relevant surrogate endpoint. It should be considered, however, that various factors (such as bacterial virulence factors) may influence the risk of invasive disease and the estimate of vaccine efficacy against colonization may not be reflective of vaccine efficacy against invasive GBS disease. Similarly, the lack of an effect on colonization may not necessarily translate into the lack of an effect against invasive disease, as immune effectors and protective thresholds against mucosal infection and invasive disease may be different.

These issues should be discussed in advance with regulatory authorities and decision makers. An FDA accelerated approval pathway exists for products targeting serious or life-threatening diseases leading to non-traditional licensure based on a surrogate endpoint, with a requirement for post-licensure studies to verify and describe clinical benefit (8, 9).

Beyond licensure, additional criteria will be relevant for policy decision making on vaccine implementation in national health programs, including cost-effectiveness and clinical impact.



3. Vaccine efficacy evaluation

As mentioned above, alternative licensure pathways may be considered, with a role for correlates of protection studies. The generation of clinical efficacy data and a comprehensive evaluation of the risk-benefit balance and potential public health impact of a vaccine candidate are however generally required for product licensure and policy decision. Randomized, double-blind placebo-controlled trial designs with a relevant, well-defined, specific disease entity as primary endpoint provides the strongest evidence to support proof-of-efficacy estimates.

a. Trial site considerations

Research should be conducted in a variety of settings including areas where the medical need is highest, generating results to support local decision-making. The consequences of regional differences in predominant serotypes should be evaluated. Research centres should have the ability to conduct GCP trials with appropriate regulatory and ethical oversight. Laboratory testing should be conducted under GLP with quality-assured testing tailored to the vaccine development phase. Baseline studies are usually necessary to demonstrate local feasibility of protocol-defined study procedures as well as to confirm the baseline incidence rate of relevant study safety and efficacy endpoints, informing statistical power analyses and required sample size estimation. The capacity for accurate determination of gestational age should be ensured.



b. Standards of care

In settings in which preventive measures are part of the standard of care, the baseline GBS-related disease incidence may be low and the conduct of an efficacy trial may not be feasible. In high GBS burden settings where universal screening is not the local standard of care and IAP has not been routinely implemented, the conduct of a trial without introducing screening-based IAP would be ethical (10). Arguments against implementation of screening-based IAP in the context of a phase 3 trial include the need to generate data relevant to the local population in the context of the existing health care delivery system, and lack of post-trial sustainability. Locally-approved criteria for antibiotic treatment initiation should be defined in standard operating procedures, delineating essential needs for antenatal care, delivery, and postnatal care, following national guidelines when available, considering WHO recommendations (Box) and the local context.

c. Efficacy endpoints case definitions

WHO recommends all women found to be colonized with GBS during pregnancy to be treated with antibiotics during labour. In addition, of particular relevance in settings where GBS screening is not the standard of care, evidence-based review led WHO to recommend antibiotic prophylaxis to women in labour with chorioamnionitis, and to women with pre-term (<37 weeks) pre-labour membrane rupture. It is also routine practice to start antibiotic treatment in women identified to be in labour with membrane rupture for >18 hours. Antibiotic treatment should be administered to babies with fever or suspected sepsis. Empirical antibiotic treatment at birth should be provided to neonates with high risk of infection (membranes ruptured >18 hours before delivery, maternal fever before delivery and during labour, foul-smelling or purulent amniotic fluid) (11–15).

Challenges in implementation of these guidelines in low-and-middle-income countries, related to the difficulty in determining gestational age, the frequency of home deliveries or late presentation to health facilities are acknowledged.

For the evaluation of vaccine efficacy, endpoint case definitions should be pre-specified in trial protocols. Endpoints should be clinical entities of the disease spectrum that are identified as the priority target for vaccine prevention. The case definitions should be sensitive and specific. Baseline incidence should be sufficient for vaccine efficacy estimation with the desired precision within a feasible study sample size. Case definitions should be defined in a way that is mindful of the practicalities of data collection in different settings, including in low- and middle-income countries, and practicalities of data analyses and presentation. Pre-trial baseline research is likely to be needed to demonstrate that case definitions have the required characteristics and relevant data collection is possible.

i. Primary endpoint

Confirmed GBS invasive neonatal and infant disease would constitute the most relevant primary endpoint when considering the disease burden.

The primary case definition may be inclusive of various relevant GBS laboratory-confirmed clinical syndromes (post-natal sepsis, meningitis, pneumonia). The use of a relevant composite endpoint may increase baseline trial endpoint incidence and reduce the required sample size. Still-birth due to confirmed GBS infection together with early and late onset disease, might constitute the primary endpoint. Post-natal death due to GBS invasive disease might also be included.

The optimal sampling and laboratory methodologies for diagnostic confirmation, including the role of molecular biology (PCR), should be defined.

Further research is needed to generate composite endpoint standard case definitions with high sensitivity and specificity. The role of clinical signs and symptoms (such as fever or low body temperature, not feeding well, neurological status, breathing patterns, capillary refill time and possibly others) to support case capture should be further investigated.

There is currently no consensus standard case definition of stillbirth. The methods to investigate cause of death or stillbirth towards confirmation of the possible role of GBS should be characterized, considering acceptability of post-mortem examinations, ideally using minimally-invasive procedures.

ii. Secondary/exploratory investigations:

Secondary analyses should include serotype-specific vaccine efficacy and efficacy against vaccine-included serotypes only; vaccine efficacy against early- and late-onset GBS disease separately; the relationship between time of immunization and time of delivery; the influence of maternal factors (e.g., past GBS exposure and pre-vaccination GBS sero-status, HIV infection, malaria, malnutrition, maternal age, multiparity) on immunogenicity and trans-placental antibody transfer. Separate safety and immunogenicity trials may need to be conducted in special populations.

If GBS-confirmed stillbirth is not included in a primary composite endpoint, it should be a separate secondary endpoint.



The demonstration of a vaccine effect on the GBS-related invasive disease in the mother (chorioamnionitis, intra-amniotic infection, post-partum endometritis, bacteraemia, puerperal sepsis and others) would have a high value, but it is not expected that pre-licensure trials would be powered to show significant effects on maternal morbidity.

Compatible disease syndromes in the context of maternal and/or neonatal colonisation but in the absence of confirmed GBS etiology would likely not constitute an ideal primary endpoint because of possible alternative aetiologies but would be of interest, as successful bacterial isolation is not expected in all invasive infections, especially when peripartum antibiotics have been given. In that context occurrence of preterm labour, stillbirth and overall mortality not confirmed to be caused by GBS should be monitored, even if it is likely that only large post-licensure studies may allow estimation of a vaccine effect on these rare but important outcomes.

The effect of vaccination on GBS maternal colonization over time during pregnancy and colonization at birth in mothers and neonates should be assessed. Monitoring of pre-labour GBS colonization in a trial without provision of IAP to mothers found to be colonized would likely pose an ethical challenge. Alternatives may be to evaluate colonization at birth only if agreeable by local ethics committees, or for this to be investigated in a separate study where screening-based IAP is the standard of care.

iii. Diagnostic algorithm for standard data collection related to endpoint case definitions

Clinical management and diagnostic algorithms supportive of standardized data capture relevant to protocol-defined endpoint case definitions and case ascertainment needs should be developed; availability of testing capacity supporting differential diagnosis of GBS-like disease syndromes should be ensured. Samples for bacterial cultures from potential cases should be obtained before antibiotic administration, which should be documented. The role of sensitive molecular methods (PCR) should be defined. Feasibility should ideally be assessed before a vaccine efficacy trial starts, informing capacity strengthening needs.

V. Value proposition

The assessment of the public health value of vaccine candidates needs to be based on sound evidence including robust estimates of vaccine preventable burden of disease and cost-effectiveness, taking into account different world regions including low and middle income countries. The potential impact of vaccine introduction on standard medical practice including reduction of perinatal antibiotic use should be considered. Mathematical modelling tools can be a useful support in decision-making during clinical development, when interpreting available data, and upon policy decision on implementation and prioritization.



B. PREFERRED PRODUCT CHARACTERISTICS FOR GBS VACCINES

Parameter	Preferred Characteristic	Notes
Indication	Prevention of laboratory-confirmed GBS stillbirth and invasive GBS disease in neonates and young infants.	See section IV.3 for further considerations on primary and secondary/exploratory endpoints.
Target population	Pregnant women, in the second or third trimester of pregnancy.	<p>Vaccination timing in pregnancy should maximize antibody transfer to the fetus and offspring protection, including for those born preterm. Evidence shows delaying vaccination into the late third trimester is associated with reduced levels of antibody transfer to the fetus (16). Vaccination during the early pregnancy period should be avoided, as the first months of pregnancy are associated with an increased risk of spontaneous abortion which would obscure the vaccination safety assessment.</p> <p>Given the difficulties related to access to obstetric care and the determination of precise gestational age in many LMICs, a vaccine that can be delivered over a range of gestational ages is preferred.</p> <p>HIV infection should not be a contra-indication to vaccination.</p>
Schedule	A one dose regimen is highly preferred.	A two dose regimen, with a first priming dose possibly delivered prior to pregnancy, is not a preference but may need to be considered. The role of additional doses in subsequent pregnancy(ies) should also be investigated, possibly post licensure.
Safety	Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis).	<p>Favourable safety in non-pregnant healthy adults should be shown before proceeding to evaluation in pregnant women.</p> <p>While transient, mild to moderate local symptoms would be acceptable, systemic reactions to vaccination in pregnancy are highly undesirable. Mild, transient reactogenicity with low grade, low rate fever and no serious adverse events related to vaccination, with no adverse impact on the normal course of pregnancy and neonatal health, and development outcomes in infancy.</p> <p>The GAIA (Global Alignment of Immunisation safety Assessment in pregnancy) project coordinated by the Brighton collaboration in collaboration with WHO aims to provide tools aimed to strengthen maternal immunization in pregnancy safety oversight, considering specificities in low-and-middle-income countries. The US FDA also issued recommendations about vaccines intended for use in pregnancy (8, 9).</p>

Parameter	Preferred Characteristic	Notes
Efficacy	Available evidence supportive of 80% protection against combined risk of laboratory-confirmed GBS (all serotypes) stillbirth and invasive disease in the offspring.	<p>Estimation of vaccine included serotype-specific protection is desirable.</p> <p>The vaccine should be protective irrespective of past GBS exposure history (as assessed by the pre-vaccination sero-status).</p> <p>Post-licensure studies or the use of conditional approval may play an important role to fill data gaps about rare endpoints. See section IV.3 for further considerations on primary and secondary/exploratory endpoints.</p>
Strain and serotype coverage	The serotypes in the vaccine formulation must cover at least 90% of the current invasive disease isolates in the target region.	Presently available data suggests that a pentavalent polysaccharide conjugate vaccine covering serotypes Ia, Ib, II, III, V would be expected to offer wide protection. Coverage of serotype IV may be a useful addition given the recently demonstrated data on its virulence potential (17, 18). Serotype VII has been reported to be predominant in Bangladesh (19). The possibility of serotype replacement should be investigated. The risk of escape variants with protein candidate vaccines should also be considered, taking into account sequence diversity data.
Adjuvant requirement	Preference for the absence of an adjuvant.	A formulation including an aluminium salt or another adjuvant with an extensively demonstrated favourable safety profile in pregnancy would likely be acceptable.
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring antibody levels/ functionality in the mother and/or the neonate.	<p>Refer to section IV.2 for further considerations on the role of correlates of protection in the licensure pathway.</p> <p>The longevity of the immune response in infants should be characterized, and the relationship to duration of protection should be investigated.</p> <p>The influence of important maternal comorbidities such as HIV infection and malaria in pregnancy should be evaluated.</p> <p>Collaborative efforts towards the generation of relevant non clinical assays, using open source reference reagents with international standards of quality may greatly contribute to comparability assessments, generation of a regulatory acceptable correlate of protection, ultimately supporting immune bridging steps, clinical development plan simplification and accelerating the pathway to licensure.</p>
Non-interference	<p>Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines recommended for use in pregnancy.</p> <p>Demonstration of non-interference with immune responses to relevant vaccines from the Expanded Program of Immunization in infants of vaccinated mothers.</p>	<p>In LMICs, investigation of co-administration with tetanus vaccine should be investigated as a priority. Co-administration with Tdap, influenza and possibly RSV (if available for maternal immunization in pregnancy before GBS) should also be considered.</p> <p>The presence of a protein carrier in a GBS vaccine candidate and possible interference with specific EPI vaccines should be considered.</p>

Parameter	Preferred Characteristic	Notes
Route of administration	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery.	
Registration, prequalification and programmatic suitability	The vaccine should be prequalified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO defined criteria for programmatic suitability of vaccines should be met (Appendix 1).	
Value proposition	Dosage, regimen and cost of goods amenable to affordable supply. The vaccine should be cost-effective and price should not be a barrier to access including in low and middle income countries.	A GBS vaccine-associated reduction of premature labour and perinatal antibiotic use in routine practice would be of high added value. The vaccine impact on health systems and other aspects of implementation science should be evaluated in large trials, pre or post-approval, as practicable.

Useful links

WHO PPCs do not override existing WHO guidance on vaccine presentation, packaging, thermostability, formulation and disposal, addressed in documents from the WHO Vaccine Presentation and Packaging Advisory Group (VPPAG) (<http://www.who.int/immunization/policy/committees/vppag/en/index2.html>). Guidance about the WHO Prequalification (PQ) process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries (for Programmatic Suitability for Prequalification (PSPQ) criteria is also available elsewhere (http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf).

Guidance from WHO on regulatory expectations about clinical evaluation of vaccines can be found at the following website: http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/035-101.pdf.

More information about WHO activities related to maternal immunization can be gathered at the following websites: http://www.who.int/immunization/research/maternal_immunization and, in collaboration with the Global Alignment of Immunisation Safety Assessment in Pregnancy (GAIA) initiative <https://brightoncollaboration.org/public/what-we-do/Projects/Gaia.html>.

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