

**FULL VALUE OF VACCINE ASSESSMENT**



**GROUP B  
STREPTOCOCCUS  
VACCINE**

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



**World Health  
Organization**



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Group B streptococcus vaccine: full value of vaccine assessment

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# Summary

Group B streptococcus (GBS) is an important cause of disease burden in every region worldwide, contributing to neonatal/ infant infection, deaths, disability, stillbirths and maternal infection. The World Health Organization (WHO) identified the development of GBS vaccines suitable for maternal immunization in pregnancy and use in low- and middle-income countries (LMICs) as a priority in 2015. The purpose of this report, WHO Full value

of vaccines assessment of Group B streptococcus vaccines is to describe the global public health rationale for developing vaccines against disease caused by GBS for maternal immunization, to inform decision making across the continuum of vaccine development and uptake with a line of sight to sustainable public health impact.

Key audiences include:

- 1 vaccine research and development community;
- 2 funders of research and vaccine implementation;
- 3 global policy-makers;
- 4 national policy-making bodies and health planners.

This full value of vaccines assessment (FVVA) provides evidence that:

- The global burden of GBS is higher than previously recognized, and includes GBS neonatal/ early infant meningitis, sepsis, death, and neurodevelopmental impairment, with additional GBS-attributable stillbirth, maternal sepsis and GBS-associated preterm births. The burden is highest in sub-Saharan Africa and South Asia.
- Vaccination could result in substantial declines in global morbidity and mortality due to GBS. A maternal vaccine is likely to be a cost-effective intervention, with a positive global net monetary benefit under most assumptions if the vaccine is affordably priced.
- GBS vaccine development is financially sustainable and likely to be profitable from the manufacturer perspective globally, subject to adoption in high-income countries.
- A maternal vaccination programme would be feasible to implement, requiring increased awareness of GBS as a public health challenge as well as strengthening of health systems for delivery, monitoring and evaluation.
- There are information gaps that if filled could further reduce uncertainty, including prospective data on GBS maternal colonization and preterm births, as well as stillbirths and maternal infections. Health economic data are only available in a few low- and middle-income settings and more data from countries in a range of different settings would improve economic evaluations.
- There is heterogeneity in disease burden, vaccine cost-effectiveness and programmatic preparedness by region and country, emphasizing the need for local assessment and decision-making with tiered and fair vaccine pricing.

Priority areas for further support for GBS vaccine development and implementation preparedness are:

- to define correlates of protection to facilitate vaccine licensure;
- to support country-level assessments and decision-making;
- to develop tools and evaluation frameworks, including surveillance standards;
- to establish ongoing monitoring through routine systems.

# 1. HOW TO USE THIS VALUE OF VACCINES ASSESSMENT FOR GROUP B STREPTOCOCCUS VACCINES

## 1.1 Definition and purpose of a full value of vaccine assessment

A full value of vaccine assessment uses multiple different analyses to describe the health, economic and societal value of a vaccine to a broad range of global stakeholders, including from a low- and middle-income country (LMIC) perspective, and aims to articulate the full direct (individual) and indirect (population) effect of a vaccine (1).

The purpose of this report is to describe the global public health rationale for developing vaccines against disease caused by Group B streptococcus for maternal immunization, to inform decision-making across the continuum of vaccine development and uptake with a line of sight to sustainable public health impact (Fig. 1).

Fig. 1. The continuum of vaccine development



## 1.2 Relationship to preferred product characteristics

Through preferred product characteristics documents, WHO aims to describe the strategic public health goals to guide vaccine development, by defining the medical need and describing how the vaccine will address this from the perspective of LMICs. The preferred product characteristics are presented within the context of the existing global disease burden and epidemiology, as well as through other available interventions.

The optimal development, use, and impact of vaccines are often hindered by a number of interrelated obstacles and information gaps, which are often more acute in LMICs. The FVVA identifies these and assesses information available to communicate the value of a vaccine and to facilitate alignment among key stakeholders. It informs decision-making related to investment in vaccine development intended for use in LMICs, as well as country-level decision-making related to introduction, especially in LMICs. As such, an FVVA is likely to have most impact when published well in

advance of licensure, during clinical development. Elements that may be presented in an FVVA but not a preferred product characteristic include: estimates of the cost of vaccine research and development and financial sustainability analysis from a manufacturer perspective; estimates of the potential impact and cost-effectiveness of a vaccine in relation to the preferred product characteristics; challenges to, and costs of, implementation for the vaccine; and guidance on potential pricing of vaccines.

WHO FVVAs aim to assess the global value of vaccines by including the value of LMIC markets (1); they do not necessarily aim to be as comprehensive and detailed as value of vaccine assessments compiled by other organizations. To account for changes in the vaccine development pipeline, WHO FVVAs do not name, compare or rank individual candidate products or product developers; however, where available they provide links to sources where such information can be found.

The *WHO preferred product characteristics for GBS vaccines (2)* and the GBS FVVA, taken together, aim to encourage innovation and the development of vaccines for use in settings most relevant

to global unmet public health need. They can help raise further interest and funding to address major gaps in knowledge and to support vaccine development, especially for LMIC use.

### 1.3 Target audiences for full value of vaccines assessments

For this particular assessment, the main target audiences include:

- 1 the vaccine research and development community;
- 2 funders of research and vaccine implementation;
- 3 global policy-makers;
- 4 national policy-making bodies and health planners.

The different sections of the document may be of greater relevance to different groups; it is advisable that the document be read as a whole and the modules relevant to specific target audiences then selected as required.

This document may also be useful to other audiences with an interest in immunization and can be adapted accordingly.

## 2. THE GLOBAL PUBLIC HEALTH NEED FOR A GROUP B STREPTOCOCCUS VACCINE

### 2.1 Description of Group B streptococcus disease

Group B streptococcus, also known as *Streptococcus agalactiae*, is a  $\beta$ -haemolytic Gram-positive bacterium. GBS bacteria are part of the normal microbial flora in humans, and colonization with GBS (often referred to as GBS carriage) in the rectum and vagina is commonly found. GBS can occasionally cause serious disease, particularly, but not exclusively, in young infants. GBS was first recognized as a cause of puerperal sepsis in 1938 (3), emerging subsequently as an important cause of neonatal meningitis and sepsis (4).

Invasive GBS disease (iGBS) can present as meningitis, sepsis or bacteremic pneumonia and is confirmed by laboratory identification of GBS from a normally sterile site in the presence of clinical symptoms. In infants, early-onset iGBS occurs between birth and 6 days of life; late onset between 7 and 89 days. The case fatality rate of iGBS in infants was estimated to be 8.4% overall, with significant variation according to country income group and region, being lowest in high-income countries and highest in Africa (5). Infants surviving iGBS may experience long-term consequences associated with neurodevelopmental impairment;

moderate to severe neurodevelopmental impairment was estimated to affect 1 in 5 survivors in a 2017 systematic review (6). GBS infection is also an important cause of stillbirth (7) and is associated with preterm birth (8). Mothers may also be affected by GBS sepsis in pregnancy and the post-partum period (9). Invasive GBS disease that is not associated with pregnancy also occurs in adults (e.g. (10, 11)), but addressing the prevention of such cases is beyond the scope of this document.

Group B streptococcus bacteria have a polysaccharide capsule and are classified into ten serotypes (Ia, Ib, II–IX) based on this capsule. As with other encapsulated bacteria such as *Neisseria meningitidis* and *Streptococcus pneumoniae*, the capsule is both a virulence factor and a promising vaccine antigen. Further characterization of the population structure of GBS using molecular techniques, including multilocus sequence typing and whole genome sequencing, is increasingly used. Indeed, there is a global genomic survey of GBS (12). The main characteristics of GBS are described in Table 1 below.

**Table 1. Main features of Group B streptococcus infection and disease**

Feature	Summary and evidence	Notes
Age distribution	Primarily a peripartum disease of the fetus and neonate/young infant (<3 months of age) with additional maternal disease burden.	GBS also causes invasive disease in non-pregnant adults, with clinical diagnoses including skin and soft-tissue infections, bacteraemia, osteomyelitis, urosepsis and pneumonia. In addition, GBS is implicated in post-caesarean section invasive surgical site infection (13).
Antimicrobial resistance issues	Pan-susceptibility to first-line (penicillin), but concerning resistance to other commonly used antibiotics gentamicin, clindamycin and erythromycin (14).	Antibiotic resistance variation may exist by region, GBS disease type, and/or serotype, but more data is needed. Global implementation of IAP in place of a vaccine could theoretically add considerable selection pressure to GBS and bystander (i.e. non-targeted) pathogens.
Disruption of health systems	None	Potential for maternal vaccination to strengthen health system links between antenatal care and EPI.

Feature	Summary and evidence	Notes
Epidemic and outbreak potential	None	Occasional nosocomial outbreaks of late onset iGBS described in high-income settings (15).
Gender distribution	Some evidence of excess risk in male infants in high-income settings (16). Maternal disease can also occur and may be vaccine preventable (9).	
Herd immunity	GBS is part of normal microbial flora; it is unlikely that interventions in pregnant women will influence population transmission or lead to herd immunity.	Reduction of maternal colonization by an effective vaccine will result in fewer colonized infants in a neonatal unit and less nosocomial transmission.
Morbidity	2015 global estimates: <ul style="list-style-type: none"> <li>• 319,000 infants aged &lt;3 months with iGBS (UR: 140,000–653,000)</li> <li>• plus at least 10,000 (UR: 3000–27,000) children with moderate to severe disability related to GBS meningitis.</li> <li>• 33 000 (UR: 13 000–52 000) maternal cases</li> <li>• 57 000 (UR: 12 000–104 000) GBS attributable stillbirths.</li> </ul>	See Table 3 for outcomes considered in this FVVA and section 6.4 for updated 2020 burden estimates.
Mortality	Global CFR of 8.4% for infant iGBS (5). 2015 estimate of 90 000 (UR: 36 000 – 169 000) early infant deaths.	CFR variable by region, early versus late onset and access to care (section 6).
Natural immunity	Evidence of natural immunity to GBS capsule in mothers is associated with reduced infant GBS disease risk (17).	Further work on immune correlates of protection critical for vaccine licensure (18).
Predictability of disease occurrence	Endemic disease burden worldwide.	There is incomplete surveillance and burden is uncertain in many countries/regions (section 6).
Transmission	Ascending infection from mother to fetus and vertical transmission from mother to infant are well established. Transmission routes for late onset iGBS are incompletely understood but include maternal and external sources.	Maternal GBS vaccination is unlikely to lead to population-wide reductions in transmission.
Types, strains, and serotypes	GBS is an encapsulated bacteria with 10 serotypes; 6 serotypes (Ia, Ib, II, III, IV, V) cause most disease (19).	GBS can also be characterized by MLST and whole genome sequencing independent of serotype.

CFR: case fatality rate; EPI: Expanded Programme on Immunization; FVVA: full value of vaccine assessment; GBS: Group B streptococcus; IAP: intrapartum antibiotic prophylaxis; iGBS: invasive GBS disease; MLST: multilocus sequence typing; UR: uncertainty range.

## 2.2 Current methods of surveillance, diagnosis, prevention and treatment

Cases of iGBS in neonates/infants and their mothers are diagnosed clinically through active or passive surveillance and confirmed by laboratory testing. The pathway for case ascertainment from a WHO perspective is summarized in [Fig. 2 \(20\)](#). There are clearly differences in the availability and quality of surveillance for GBS around the world, as reflected in the uncertainty in disease burden estimates ([section 6](#)). Case ascertainment is influenced by care-seeking, access to care and clinical assessment, ability to take appropriate samples and the quality of laboratory methods for pathogen detection ([21](#)). The paucity of aetiological data for infections in women, stillbirths and infants in regions where most births occur is an ongoing challenge. A systematic assessment of the burden of disease due to GBS, published in 2017, noted that the “inverse data law” applied to GBS, whereby the highest burden falls on vulnerable populations in LMICs, yet this is also where the least data are gathered ([21](#)).

Antibiotic therapy is used for treatment of suspected and confirmed cases in infants (and mothers) and, in some settings, as prevention through intrapartum antibiotic prophylaxis (IAP). There is global concern for the development of antimicrobial

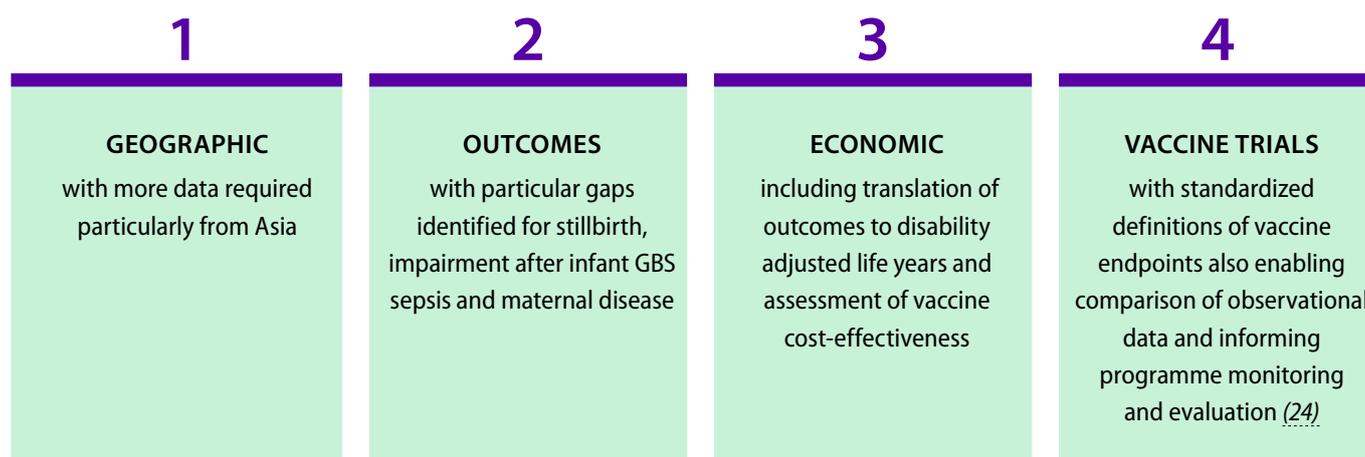
resistance in many pathogens. Currently for GBS, first-line penicillin retain high susceptibility. There is some evidence of concerning resistance to other commonly used antibiotics, including gentamicin, clindamycin and erythromycin, which should be monitored ([14](#)).

The administration of IAP is usually targeted according to known maternal GBS colonization and/or peripartum clinical risk factors. IAP has been shown to be effective in reducing early-onset neonatal disease in high-income settings ([22](#)). Current IAP provision ([23](#)) is estimated to prevent 29,000 (UR (uncertainty range): 0–51,000) cases of early onset iGBS each year ([24](#)). However, IAP is ineffective against late-onset neonatal GBS disease and is unlikely to reduce GBS-attributable stillbirth and GBS-associated preterm birth. IAP has not been implemented at scale in LMICs, and there are concerns about the feasibility of such an approach, given that it is resource intensive and that many births occur outside of a health-care setting. Furthermore, widespread IAP raises concerns about encouraging the development of antibiotic resistance ([25](#)) and disrupting the newborn microbiota ([26, 27](#)).

## 2.3 Major gaps in knowledge or research evidence

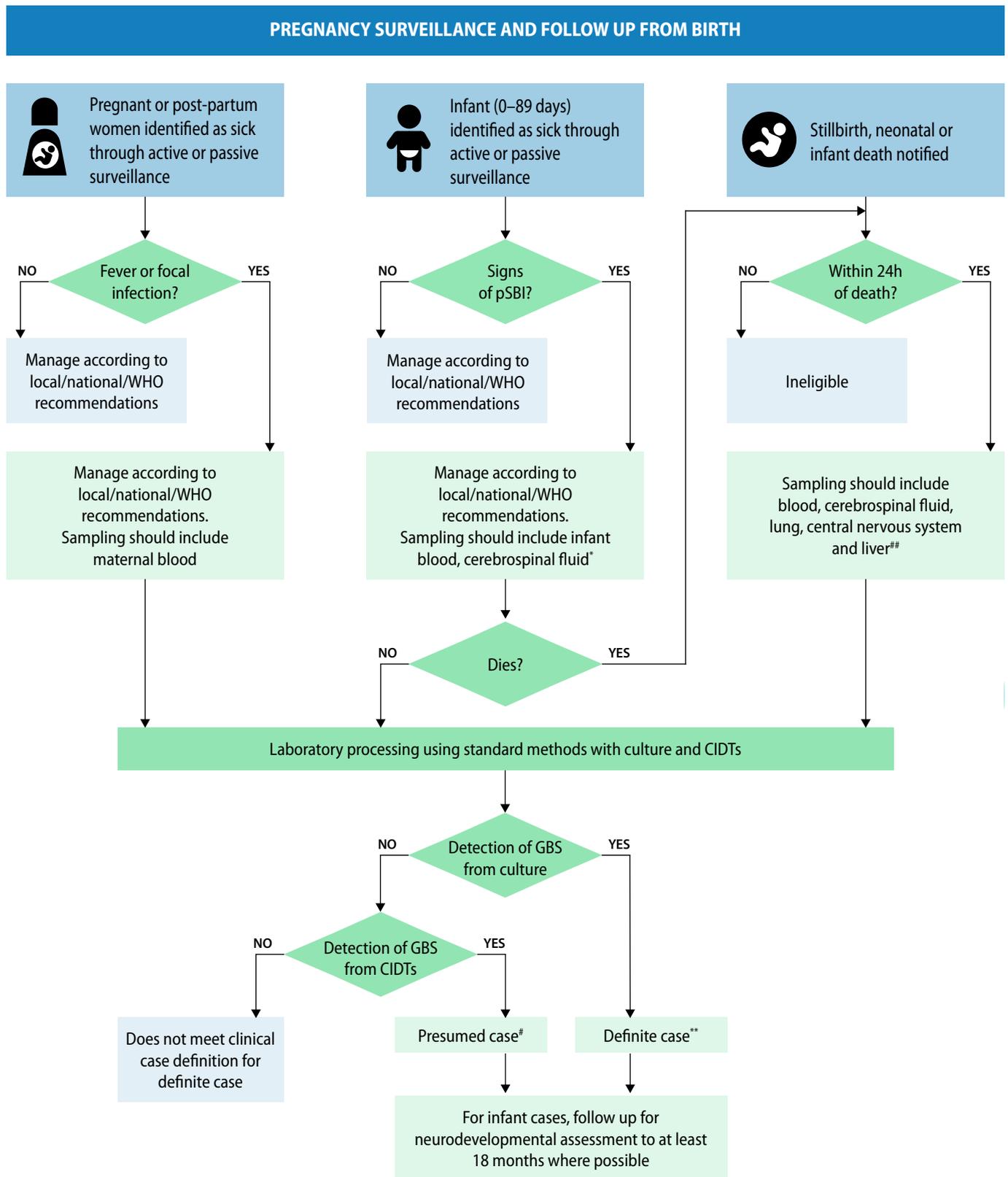
The first systematic estimates of the worldwide GBS burden were presented in a series of coordinated publications ([28](#)). These established that there is a large burden of GBS disease globally

and that a substantial proportion of this disease is potentially vaccine preventable with a maternal immunization programme ([24](#)). These studies also highlighted data gaps in four domains:



WHO is continuing to lead work aimed at standardizing case definitions and vaccine endpoints ([20](#)).

Fig. 2. Case ascertainment of invasive GBS disease in pregnant and postpartum women, stillbirths and infants (0–89 days). Adapted from Seale et al. (20)



CIDT: culture independent diagnostic tests; pSBI: possible serious bacterial infection.

\* Unless clinical contraindication.

\*\* GBS isolates should be stored, to allow later typing, ideally using whole genome sequencing.

# Dependent on establishment of specificity of the particular CIDT (based on nucleic acid amplification) used.

## Blood, cerebrospinal fluid and lung should be prioritized for sampling.

### 3. GROUP B STREPTOCOCCUS VACCINES, A STRATEGIC PRIORITY FOR WHO

The world has made great strides in child survival during the past two decades, with the global number of neonatal deaths declining from 5.0 million in 1990 to 2.4 million in 2019 (29). However, the decline in neonatal mortality from 1990 to 2019 has been slower than the decline in post-neonatal mortality in children under 5 years of age. Infections remain an important cause of neonatal death.

The Sustainable Development Goals include a specific target 3.2 on childhood mortality (30):

*By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births.*

In its 2015 and 2016 meetings, the Product Development for Vaccines Advisory Committee, which informs the WHO Strategic Advisory Group of Experts (SAGE) on vaccine research and development matters and contributes to prioritize topics for the involvement of WHO's Initiative for Vaccine Research, identified the development of Group B streptococcus vaccines suitable for maternal immunization in pregnancy and use in low- and middle-income countries as a priority (31, 32). WHO recognized the major unmet public health need for a GBS vaccine, particularly for infants in LMICs.

The stated WHO strategic goal (2) is:

*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.*

This is further reinforced by WHO and partners in their global road map "Defeating meningitis by 2030" (33), a bold and comprehensive plan approved by the World Health Assembly in November 2020 (34). The road map includes GBS as one of four focal pathogens, together with *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* which in combination cause the majority of bacterial meningitis cases globally and are potentially vaccine preventable. The road map is organized into five interconnected pillars:

1. prevention and epidemic control;
2. diagnosis and treatment;
3. disease surveillance;
4. support and care for people affected by meningitis;
5. advocacy and engagement.

Within each pillar are strategic goals and milestones, some of which are specific to GBS – including supporting the development and implementation of a GBS vaccine – with others being broadly applicable to all forms of meningitis.

### 3.1 Preferred product characteristics

As described above, this FVVA complements the preferred product characteristics for a GBS vaccine, as defined by WHO in 2017 (2, 35) and summarized in Table 1. These characteristics are

carried forward in the FVVA analysis of vaccine impact, cost-effectiveness, financial sustainability and implementation challenges (section 7–10).

**Table 2. Preferred product characteristics for a Group B streptococcus vaccine**

Parameter	Preferred characteristic
Indication	Prevention of laboratory-confirmed GBS stillbirth and invasive GBS disease in neonates and young infants.
Target population	Pregnant women, in the second or third trimester of pregnancy.
Schedule	A one-dose regimen is highly preferred.
Safety	Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis).
Efficacy	Available evidence supportive of 80% protection against combined risk of laboratory-confirmed GBS (all serotypes) stillbirth and invasive disease in the offspring.
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.
Adjuvant requirement	Preference for the absence of an adjuvant.
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring antibody levels/ functionality in the mother and/or the neonate.
Non-interference	Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines recommended for use in pregnancy. Demonstration of non-interference with immune responses to relevant vaccines from the Expanded Programme of Immunization in infants of vaccinated mothers.
Route of administration	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for WHO prequalification 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 (36). WHO-defined criteria for programmatic suitability of vaccines should be met.

GBS: Group B streptococcus.

## 4. METHODOLOGY

### 4.1 Research designed to address major data gaps

WHO and researchers at the London School of Hygiene & Tropical Medicine agreed to engage in developing an FVVA for GBS vaccines. The project, supported by a grant from the Bill & Melinda

Gates Foundation, was designed to fill key data gaps (section 2.3) and structured into four complementary work streams with the following aims:

#### Work stream 1

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To update estimates of the burden of GBS disease that is potentially preventable by GBS vaccination, with particular attention to collection of new data on GBS-attributable neurodevelopmental impairment, including studies in LMICs.

#### Work stream 3

---

To review the expected impact of GBS vaccine introduction on standard medical practice, the capacity of different service delivery models and the effect of different vaccination schedules on vaccine uptake, as well as the monitoring and evaluation requirements and provide a summary of the latest evidence from ongoing operational research.

#### Work stream 2

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To ascertain the impact and cost-effectiveness of a maternal immunization programme with GBS vaccines globally and by region.

#### Work stream 4

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To assess the return on investment and financial sustainability for vaccine developers of developing and commercializing a GBS vaccine delivered by maternal immunization.

The following keystone peer-reviewed publications have been produced for each work stream:

Work stream 1: Gonçalves BP et al. (37);

Work stream 2: Procter SR et al. (38);

Work stream 3: Mantel C et al. (39);

Work stream 4: Malvolti et al. (40).

Additional papers providing new underpinning evidence is presented in a 2021 supplement of *Clinical Infectious Diseases* (41).

### 4.2 Stakeholder analysis and involvement

WHO facilitated broad engagement with stakeholders both through the development of this FVVA and the Defeating meningitis by 2030 road map (33). For the GBS FVVA, a Scientific Advisory Group was regularly convened, with members having particular scientific and policy expertise in relation to GBS and representing different regions. A core activity of Work stream 3 was to conduct a global stakeholder online survey to ascertain the existing level of awareness and management of GBS disease and its prioritization in different countries. This survey was conducted in late 2019 and targeted representatives of national paediatric associations, gynaecology and obstetrics associations, national

immunization technical advisory groups, national regulatory agencies, academia, and UN organizations (39). The development of the Defeating meningitis by 2030 road map culminated in a meeting of a broad group of stakeholders in September 2019 in London, the United Kingdom of Great Britain and Northern Ireland, to finalize the shared strategy. The meeting was attended by representatives from ministries of health, government agencies, pharmaceutical companies, nongovernmental and civil society organizations, academia, funding agencies, UNICEF and WHO; the 110 participants came from 29 countries and all regions of the world (42).

# 5. DEVELOPMENT OF THE VACCINE

## 5.1 Biology of a maternal vaccine against Group B streptococcus

Proof of principle that maternally-derived GBS anticapsular IgG was an important factor in preventing iGBS in neonates was first demonstrated in the 1970s (43), specific to serotype III. This suggested that developing a maternal vaccine targeted against the capsule to protect neonates against GBS disease could be feasi-

ble. A maternal vaccine to prevent GBS in the fetus and neonate depends on efficient placental antibody transfer, thus measuring antibodies in cord or infant sera, in addition to the mother's serum is important.

## 5.2 Technical platforms under consideration

Two main approaches are being taken currently for GBS vaccine development. The most common approach is a multivalent capsular polysaccharide-protein conjugate vaccine covering between three and six capsular types, designed to target the majority of disease-causing serotypes (19). Both CRM197 (the non-toxic mutant of diphtheria toxin) and tetanus toxoid are being used

as carrier proteins. Protein subunit vaccines are an alternative approach. If appropriately targeted to proteins conserved across all GBS serotypes, such vaccines may have higher strain coverage compared to capsular based conjugate vaccines. One candidate targets the N-terminal domains of the Alp-protein family.

## 5.3 GBS vaccine development pipeline

Leading GBS vaccine candidates – both polysaccharide-protein conjugate and protein subunit vaccines – have reached phase 2 clinical trials. The Defeating meningitis road map includes specific milestones that: by 2026, at least one affordable vaccine against GBS is licensed and WHO-prequalified for maternal

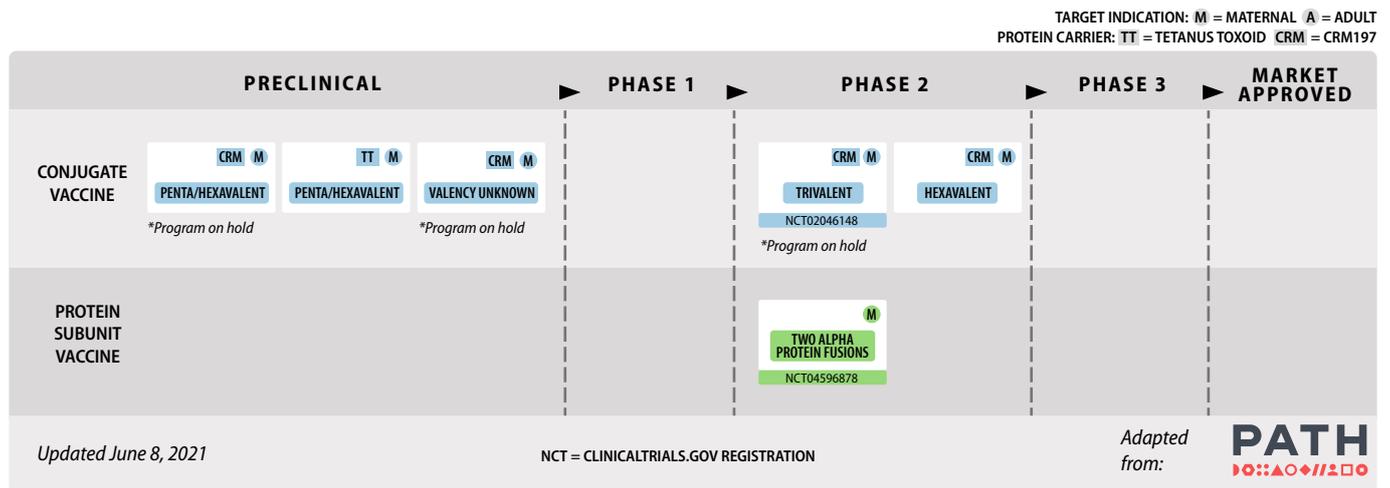
immunization during pregnancy; and by 2030 at least 10 countries will have introduced the vaccine (33) (Fig. 3). This timeline is dependent on the key issues identified in clinical development and regulatory pathways (section 5.5 below).

## 5.4 Preclinical development: key issues

GBS vaccine candidate testing in animal models is essential to demonstrate safety and immunogenicity before human testing (44). In addition, favourable outcomes in suitable reproduc-

tive toxicology animal models are required before studies in pregnant women are initiated (2).

Fig. 3. GBS vaccine pipeline



## 5.5 Clinical development and regulatory pathway: key issues

Phase 1 and 2 trials should initially recruit non-pregnant women of child-bearing age to characterize the safety and immunogenicity profile of a GBS vaccine and to ascertain the schedule, optimal vaccine dose and whether an adjuvant is required. With good outcomes in non-pregnant women, trials could proceed in pregnant women (45, 2).

The strongest evidence to provide proof-of-vaccine efficacy to support licensure would come from a randomized, double-blind placebo-controlled trial with a well-defined, specific primary endpoint. Ideally the endpoint would be laboratory-confirmed GBS stillbirth and invasive GBS disease in neonates and young infants. Design issues for a randomized controlled trial are discussed fully in the WHO preferred product characteristics (2). It is acknowledged however, that a phase 3 trial for a GBS candidate vaccine may be prohibitively large (40,000–180,000 women-infant dyads) because iGBS disease and other outcomes of interest are rare (18). Therefore, alternative licensure pathways may be considered, with a potentially crucial role for studies that can identify robust correlates of protection/biomarkers associated with risk reduction.

In a systematic review of correlates of protection for GBS (17), it was concluded that anti-GBS-capsular polysaccharides IgG con-

centrations between 1–10 µg/mL are protective for GBS serotypes Ia and III. Such concentrations are well within responses seen in phase 1 and 2 vaccine trials reported to date (46, 47, 48, 49). It seems likely that GBS conjugate vaccines act to induce antibodies that facilitate killing of GBS bacteria by opsonophagocytosis, but a protective opsonophagocytosis titre has not yet been defined (17). Caution should be applied in extrapolating protective antibody thresholds between settings, because coinfection (e.g. with HIV or malaria) may impair placental antibody transfer. WHO is leading consultations on the pathway to licensure via immune correlates of protection and has highlighted 15 steps to facilitate and accelerate this process (18). A 2021 expert workshop convened by the Bill & Melinda Gates Foundation advanced this agenda (50).

Pre-licensure clinical studies should also assess potential interference with other vaccines given in pregnancy and the routine schedule of the Expanded Programme on Immunization. This has been shown to be a (potential) issue particularly for polysaccharide-protein conjugate vaccines given in the routine schedule, specifically *Haemophilus influenzae* type b (Hib), meningococcal and pneumococcal conjugate vaccines (51). Such effects on immunogenicity may depend on the carrier proteins but are unpredictable and must be studied before widespread use.

## 5.6 Vaccine efficacy: key issues

The vaccines in development are designed to provide broad coverage against disease-causing GBS strains, although there are well-recognized limitations to global GBS surveillance (section 2) which may have biased these assessments of coverage. Immunogenicity studies indicate the potential for vaccine effectiveness to be influenced by co-infection (e.g. with HIV (48)) and prevalence of GBS colonization. A potential risk for capsular-based conjugate vaccines is that vaccination against only specific serogroups/

types increases selective pressure leading to capsular switching (demonstrated by Bellais et al. (52) to occur for GBS) or capsular replacement. Substantial replacement has been observed following the introduction of pneumococcal conjugate vaccines (53) but not following meningococcal or Hib vaccines (54). Strong post-licensure surveillance in a range of different settings will be required to elucidate these issues.

## 5.7 Vaccine safety: key issues

A 2014 review of vaccine safety in pregnancy by the Global Advisory Committee on Vaccine Safety concluded that:

*There is no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated virus, bacterial vaccine, or toxoid. (55).*

While safety assessments of GBS vaccines must not be compromised there are no current indications of concern for conjugate or protein-based vaccines.

## 5.8 Major gaps in knowledge or research evidence

Possible pathways to licensure for GBS vaccines have not yet been agreed by regulators. Substantial programmes of work are ongoing to build additional capacity for conducting trials of a GBS vaccine, including sites in LMICs, and to provide the evidence

required to establish immune correlates of protection that are robust enough to support vaccine licensure. Well-designed clinical trials of GBS candidate vaccines will provide answers to many of the key issues highlighted above.

# 6. ESTIMATION OF DISEASE BURDEN

## 6.1 Modelling approach

The estimation of disease burden in 2020 was based on a natural history model for GBS in pregnancy (Fig. 4) starting from maternal colonization and including all relevant outcomes for the woman and the infant (Table 3). The approach considered the current implementation of IAP (not shown in Fig. 4) and adjusted for IAP use (23) when modelling early onset iGBS risk.

As a vaccine would be targeted to pregnant women and may not prevent colonization, a transmission dynamic model of GBS colonization and disease in the entire population was not considered relevant nor, given that this would introduce many more uncertainties, desirable.

## 6.2 Data inputs

Data inputs were systematically reviewed from published and unpublished literature (37). Underpinning data, by country, were obtained from key sources: on births from the United Nations World Population Prospects 2019 (57); on stillbirths from the WHO Global Health Observatory data repository (58); and on preterm birth rates from a review by Chawanpaiboon et al. (59). In an update to previous estimates (21), new data were specifically collected and analysed to enable estimation of the risk of neurodevelopmental impairment in children who survive GBS sepsis and also longer-term outcomes after meningitis from both high-income countries (60) and LMICs (61). New data on stillbirths from Africa and one study performed in Bangladesh informed uncertainty in estimated numbers of stillbirths caused

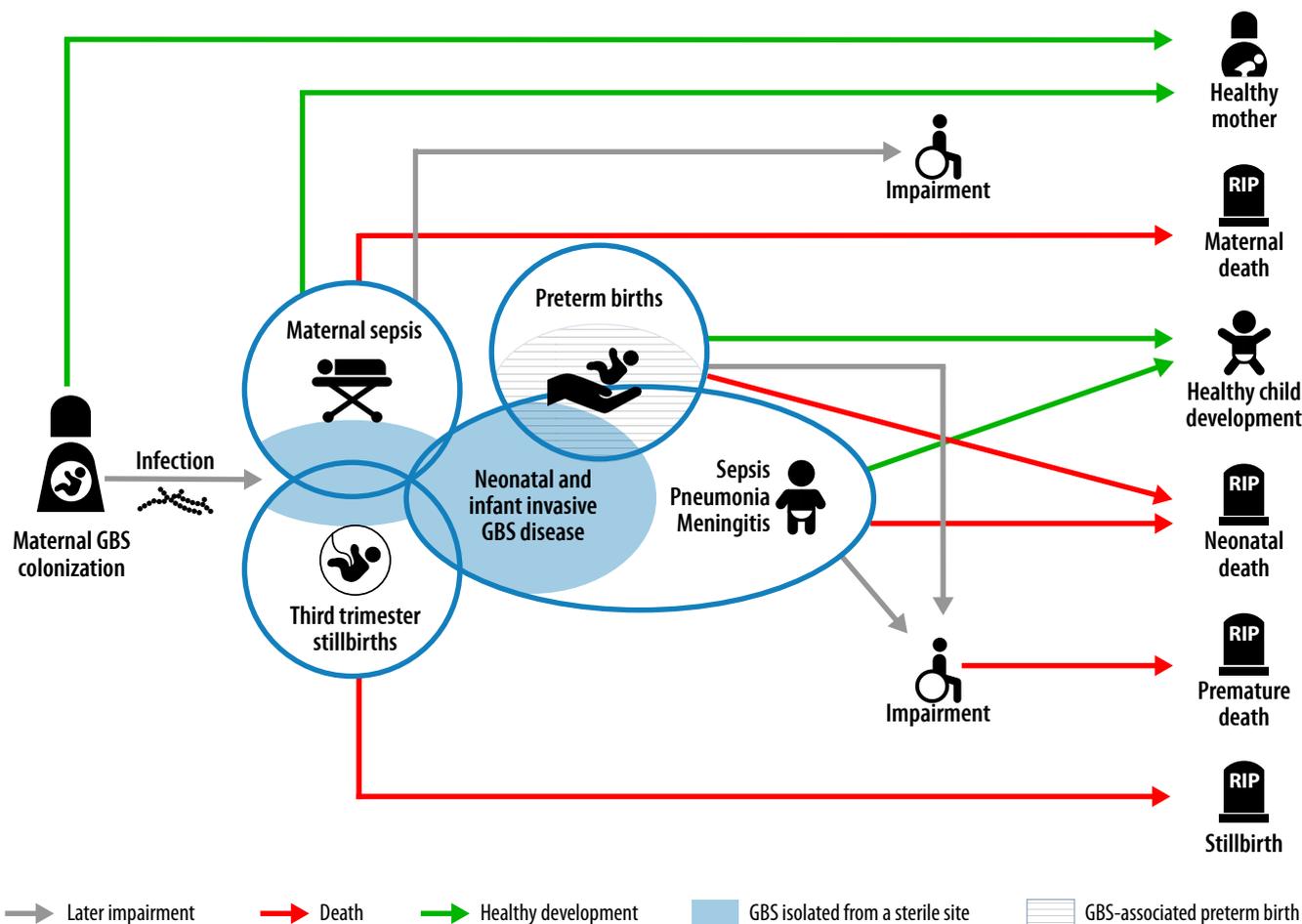
In an advance to the method previously used in GBS disease burden estimation (24) a Bayesian framework was applied, including meta-analyses for the relevant inputs corresponding to each step of the disease process (37). This approach accounted for the hierarchical data structure, with explicit modelling of heterogeneity, and coherent propagation of uncertainty step by step. For example, uncertainty in the number of early-onset invasive GBS cases reflected uncertainties in both the proportion of population at risk, determined by maternal GBS colonization prevalence, and the risk of disease in infants born to GBS colonized mothers.

The GATHER statement (56) was followed for transparent model development and reporting of estimation.

by GBS (7). Although some new data are available on maternal iGBS, this remains a major data gap. Excess preterm births associated with maternal GBS colonization were estimated, which was not included in the previous burden estimation work (24).

The regional case fatality rate for early onset iGBS with skilled birth attendance varied from 6% (95% credible interval (CI): 4–10%) in developed countries to 23% (95% CI: 12–38%) in Africa. There was less variability in late onset iGBS CFR with 6% (95% CI: 4–9%) in developed and 10% (95% CI: 5–19%) in Africa. A mortality rate of 90% was assumed for iGBS neonatal cases occurring in the absence of skilled birth attendance (37, 24).

Fig. 4. Group B streptococcus Natural History Model and case definitions\*



Parameter	Case definitions used for estimates
Group B <i>streptococcus</i> maternal colonization	Isolation by culture of GBS from either the vagina (high or low), rectum or peri-anal region at any time during pregnancy
Maternal GBS disease	Laboratory isolation of GBS from sterile site in pregnant or postpartum woman (up to 42 days postpartum), with clinical signs of sepsis
Stillbirth GBS invasive disease	Birth of a fetus weighting > 100 g and/or ≥ 28 weeks' gestation age with no signs of life and evidence of GBS invasive disease from a normally sterile site such as fetal blood, lung aspirate or cerebrospinal fluid
Neonatal and infant GBS invasive disease	Laboratory isolation of <i>Streptococcus agalactiae</i> from a normally sterile site in an infant aged 0 to 89 days with signs of clinical disease, including meningitis, sepsis or bacteremic pneumonia
Neurodevelopment impairment in children after GBS invasive disease	Cognitive and/or motor, vision or hearing impairment in survivors of invasive infant GBS disease isolated from a normally sterile site
Preterm birth associated with GBS maternal colonization	Delivery prior to completion of 37 weeks' gestation from mother with maternal GBS colonization isolated from vaginal, cervical and/or rectal swabs

\* Source: Gonçalves et al. (37) (after Lawn et al. (21))

## 6.3 Outcomes

A range of clinical outcomes were included, as noted in [Fig. 4](#) and [Table 3](#).

**Table 3. Outcomes considered in the Group B streptococcus burden estimation and assessment of vaccine impact\***

Clinical outcome	Measurement	Included in principal analyses of vaccine impact?	Notes
Maternal colonization	Proportion	No	Maternal colonization is part of the disease pathway but not the disease outcome of relevance.
Early onset iGBS in neonates 0–6 days	Cases, deaths, NDI, QALYs	Yes	Early onset iGBS was estimated separately to account for impact of intrapartum antibiotic prophylaxis.
Late onset iGBS in infants 7–89 days	Cases, deaths, NDI, QALYs	Yes	Region-specific multiplication factor applied to early onset iGBS in order to estimate late onset iGBS.
GBS-attributable stillbirth	Deaths, QALYs	Yes	Additional data since 2017 review included from CHAMPS following standardized procedures to characterize GBS in the causal chain leading to stillbirth.
GBS-associated preterm birth	Cases, deaths, QALYs	No	Studies have associated maternal GBS colonization with an increased risk of preterm birth.
Maternal sepsis due to GBS	Cases	No	While an important outcome, data are not sufficient for robust estimates.

\* Quality adjusted life years are used to summarize the burden of disease that could be averted through vaccination by including death and disability resulting from GBS infection.

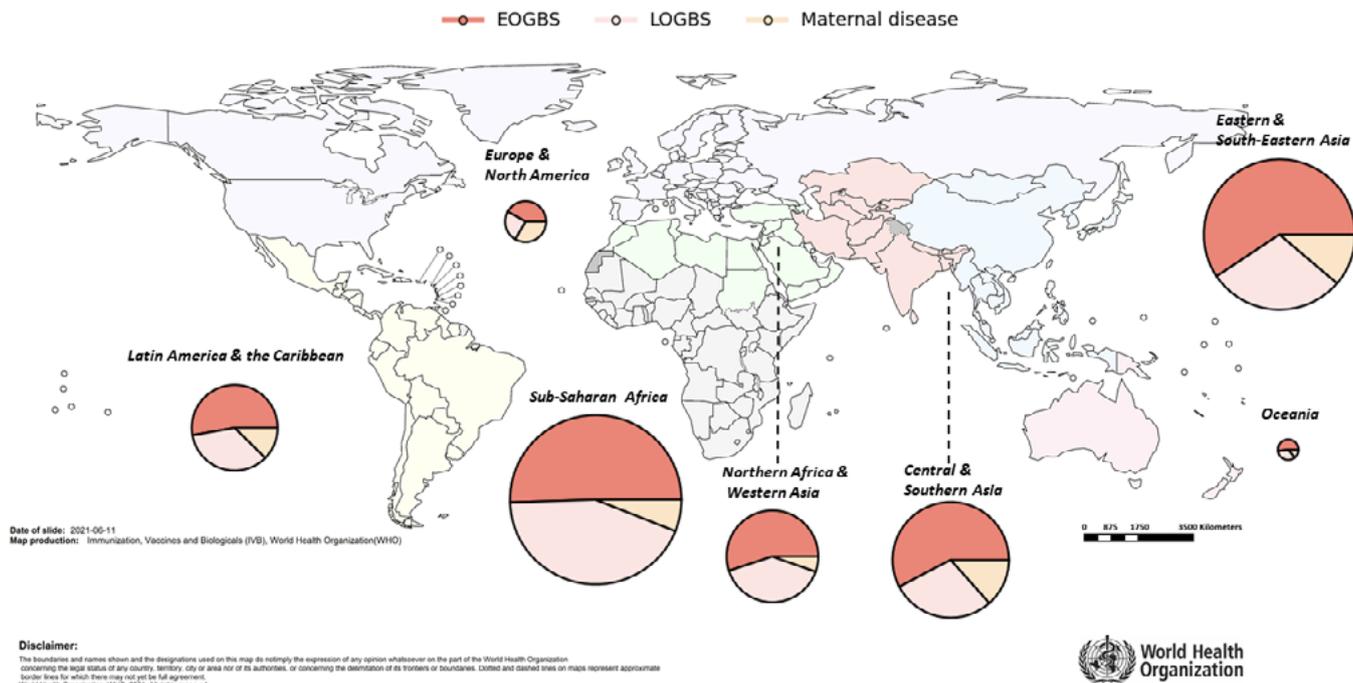
GBS: Group B streptococcus; iGBS: invasive GBS disease; NDI: neurodevelopmental impairment; QALY: quality adjusted life years.

## 6.4 Disease burden estimates of Group B streptococcus

The updated estimates identify a larger burden of GBS disease than previously quantified. There are 231,000 (UR: 114,000–455 000) early onset iGBS cases and 161,000 (UR: 70,000–394,000) late onset iGBS cases, which result in 91,000 (UR: 44,000–187,000) deaths and 37,000 (UR: 14,000–96,000) survivors with neurodevelopmental impairment each year. This assumes that early onset iGBS cases born without a skilled birth attendant have 90% risk of

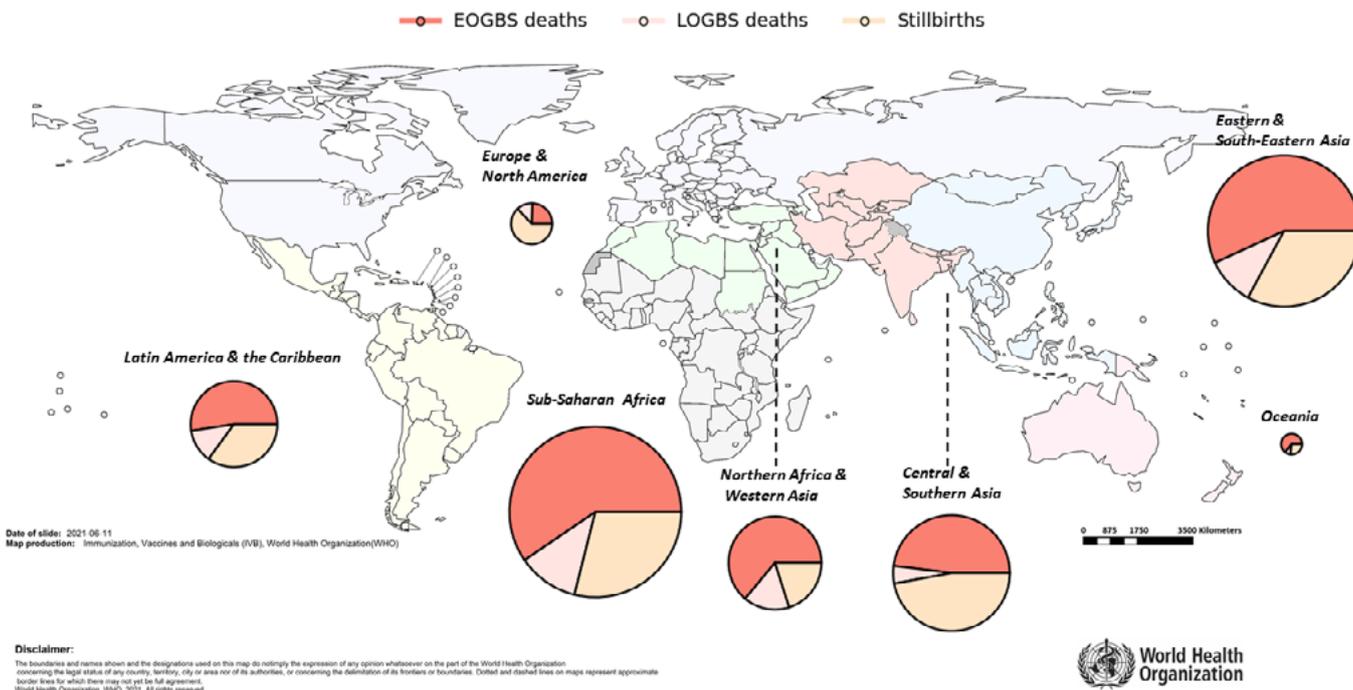
mortality due to lack of antibiotics for treatment. Stillbirths represent a major mortality burden with 46,000 (UR: 20,000–111,000) GBS-attributable stillbirths occurring each year. Although there is large uncertainty, 3.5% of preterm births globally are associated with maternal GBS colonization, with a central estimate of 518,000 (UR: 36,000–1,142,000) preterm births annually.

Fig. 5. Global cases and deaths due to GBS disease by region: neonatal iGBS cases and maternal disease



Source: Gonçalves et al. (37).

Fig. 6. Global cases and deaths due to GBS disease by region: deaths due to neonatal iGBS and stillbirth\*



Source: Gonçalves et al. (37).

## 6.5 Group B streptococcus and antimicrobial usage

WHO is leading a programme of work to assess the impact of vaccination on antimicrobial resistance (62). Further analysis of the possible impact of a GBS vaccine on antimicrobial usage and antimicrobial resistance was considered but not taken forward at this stage for the following reasons:

- There are currently high levels of susceptibility to first and second line antibiotics used for treatment and IAP (14).
- The volume of antimicrobials used for IAP is currently relatively low and it does not seem feasible to roll it out globally. A GBS vaccine would thus only displace a relatively small volume of antimicrobial usage.
- At this stage, WHO is focusing on priority pathogens for which vaccines would have a direct impact on antimicrobial resistance; i.e. by reducing the incidence of disease from resistant pathogens. Examples include typhoid and pneumococcal conjugate vaccines.

## 6.6 Major gaps in knowledge or research evidence

A reliance on modelled estimates of disease burden is inevitable when many countries do not have high quality surveillance systems for infant infections and deaths. Strengthening surveillance, including microbiological confirmation, is one of the five pillars of the Defeating meningitis road map (33). Further studies, in particular well-designed prospective studies, with more comprehensive exposure measures (including other bacteria) are necessary, especially to further elucidate the (causal) association between GBS infection and preterm birth. Additional data on GBS-attributable stillbirth, especially from Asia and sub-Saha-

ran Africa, would be welcome and there are still few studies outside of high-income settings on maternal sepsis (or other serious infections) due to GBS.

GBS prophylaxis may still have an important role in selecting for resistance in “bystander” pathogens, i.e. pathogens other than GBS that are not directly targeted but nonetheless exposed to antibiotics, in settings with high IAP use (currently mainly high-income settings). The effect of this on resistance remains an important area for continued monitoring.

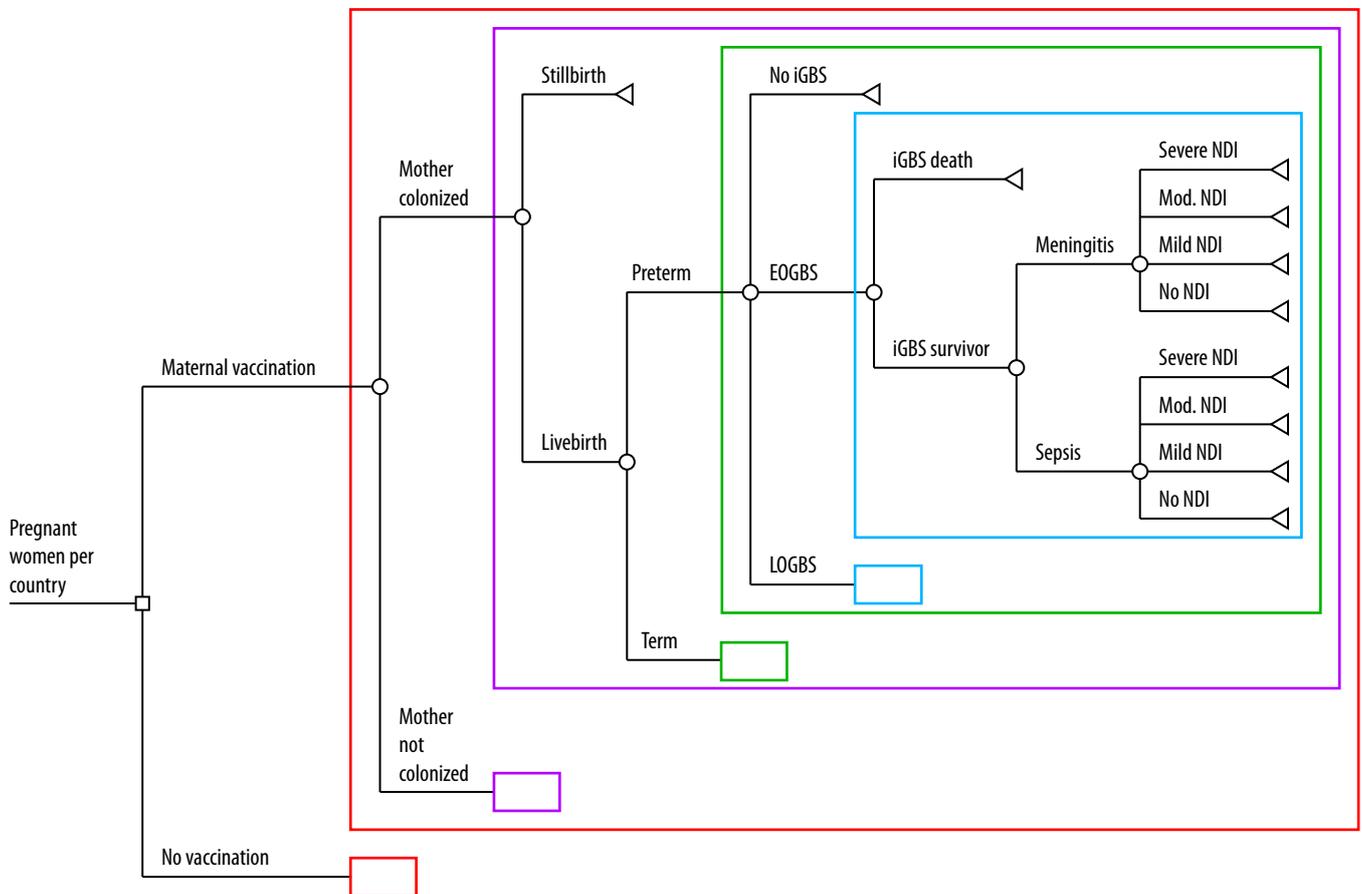
# 7. IMPACT OF THE VACCINE ON DISEASE BURDEN

## 7.1 Modelling approach

A decision tree model was built (Fig. 7) to reflect the natural history of GBS; this is illustrated in Fig. 4 (38). The model was used to compare scenarios with a maternal GBS vaccine against a no-vaccine counterfactual, assuming that current IAP practice continues

in both scenarios. The analysis thus measures the added benefit of vaccination and does not consider potential health-care savings from reduced IAP in the context of a vaccine.

Fig. 7. Decision tree model used to estimate the impact and cost-effectiveness of maternal GBS vaccination



## 7.2 Data inputs

The vaccine characteristics given in the WHO preferred product characteristics (2), were assumed for the purpose of modelling potential impact of GBS vaccine, i.e. a single dose maternal vaccine delivered in the second or third trimester of pregnancy with effectiveness of 80% (against all strains).

Vaccine coverage was based on each country's antenatal care, fourth visit (ANC4) coverage. This is a conservative assumption; higher levels of vaccine coverage are possible but will likely require additional investment in expanding access to antenatal care. The proportion of GBS-associated preterm births that are potentially prevented was based on the likely timing of vaccination from antenatal care data (63) and the distribution of prematurity by gestational age (64).

The burden of disease data were sourced from a study conducted by Gonçalves et al. (37), as described in section 6. The disease burden assessment assumed that births with early onset iGBS that were not attended by a skilled birth attendant have a 90%

risk of mortality due to lack of antibiotic treatment. However, many of these births are likely to be associated with women who also would not normally receive maternal vaccines. Hence in the base case for the vaccine impact assessment, it was assumed that vaccine-preventable cases experience the region-specific case fatality rate rather than the higher 90% rate. If vaccine coverage can be expanded, particularly to pregnant women without access to health care, the potential impact of vaccination on mortality may be substantially increased. This will require additional investment in access to health services among marginalized communities which has not been costed here.

The excess risk of mild and moderate or severe sequelae due to GBS was determined by Gonçalves et al. (37) using an assumed counterfactual risk among children with no history of invasive GBS from a Danish cohort study (60). As moderate and severe neurodevelopmental impairment are combined in the study conducted by Gonçalves et al. (37), the proportion that was severe was assumed to be 33%, based on the same Danish study.

## 7.3 Modelled outcomes

The model was used to estimate the incremental benefits of a maternal GBS vaccination programme in terms of cases, deaths and stillbirths prevented and quality adjusted life years (QALYs) gained.

QALYs were calculated as follows. Neonatal deaths and stillbirths due to GBS were assigned life years lost according to the average life expectancy of their country (65); this may be an overesti-

mate if GBS mortality is linked to populations with a higher mortality risk from other causes. Of the survivors with neurodevelopmental impairment, utility decrements from mild, moderate and severe sequelae (66) were applied to each year of life using country-specific average life-expectancy. Preterm births were assigned an independent utility decrement of 0.066 (uncertainty range (UR): 0.035–0.098) (67), again applied to each year of life for the country-specific life expectancy.

## 7.4 Estimated vaccine impact on disease burden

The annual numbers of mothers vaccinated and the outcomes averted in the base case are shown in Table 4.

**Table 4. Numbers of mothers vaccinated and outcomes averted (with uncertainty ranges in parentheses) by a Group B streptococcus vaccine, globally and by Sustainable Development Goal region**

Region	Annual GBS outcomes averted through vaccination* (thousands)						
	Mothers vaccinated (Millions)	EOGBS	LOGBS	GBS deaths	GBS stillbirths	Moderate/severe NDI	GBS associated preterm births**
Central and Southern Asia	22.8	22.8 (11.6, 43.6)	11.3 (2.9, 33.1)	4.2 (1.8, 9.6)	6.6 (1.6, 23)	3.3 (0.9, 10.2)	34.7 (2.3, 78.5)
Eastern and South-Eastern Asia	25.5	30.6 (14.5, 62.4)	15.2 (3.9, 45.7)	5.6 (2.3, 13.4)	3.1 (0.8, 10.9)	4.4 (1.2, 14.1)	28.7 (2.1, 66.1)
Europe and Northern America	11.7	3.4 (1.6, 5.9)	2 (0.8, 4.2)	0.3 (0.1, 0.7)	0.6 (0.2, 1.5)	0.3 (0.1, 0.6)	33.2 (2.4, 72)
Latin America and Caribbean	9.5	8.9 (4.7, 16.8)	5.9 (1.9, 20.4)	1.9 (0.8, 4.7)	1.3 (0.2, 8.4)	1.5 (0.4, 4.7)	18.5 (1.3, 39.2)
Northern Africa Western Asia	7.8	17.9 (8.6, 36)	12.9 (5.2, 33)	4.8 (2.1, 10.8)	1.3 (0.6, 3.1)	3 (0.9, 9.1)	23.8 (1.8, 52.4)
Oceania	0.5	0.4 (0.2, 0.9)	0.3 (0.1, 1.4)	0.1 (0, 0.3)	0.1 (0, 0.3)	0.1 (0, 0.2)	1.5 (0.1, 3.3)
Sub-Saharan Africa	21.9	42.3 (20.1, 86.5)	36.4 (14, 101)	13.6 (5.6, 32.2)	9.3 (4.1, 18.5)	7.5 (2.3, 23.5)	44.4 (3.2, 97.4)
<b>Global</b>	<b>99.8</b>	<b>126.8</b> <b>(63.3, 247.7)</b>	<b>87.3</b> <b>(38.1, 209.4)</b>	<b>31.1</b> <b>(14.4, 66.4)</b>	<b>23</b> <b>(10, 56.4)</b>	<b>20.2</b> <b>(6.4, 60.2)</b>	<b>185.2</b> <b>(13.5, 407.3)</b>

\* Base case vaccine assumptions: coverage based on ANC4, 80% efficacy against iGBS and GBS stillbirth.

\*\* Scenario analysis including 80% vaccine efficacy against GBS-associated preterm births.

This translates into 4,100,000 (UR: 2,300,000–7,800,000) undiscounted QALYs gained per year globally through averting neonatal iGBS and its resulting death and disability, and GBS-attributable stillbirths. Prevention of GBS-associated preterm births and

consequent disability could gain a further 830,000 (UR: 60,000–2,100,000) QALYs, and is of higher relative importance in Europe and North America, where the incidence of early onset iGBS is lower.

## 7.5 Major gaps in knowledge or research evidence

A large burden of disease could be prevented through the implementation of a maternal GBS vaccine. The characteristics of the vaccine modelled here are based on a hypothetical vaccine that meets the criteria set out in the WHO preferred product characteristics (2); a GBS vaccine that reaches licensure may deviate from

this. The coverage assumptions are based on ANC4 and not coverage of an existing vaccine. Uncertainty in disease burden estimates (section 6) are propagated through this analysis of potential vaccine impact.

# 8. ECONOMIC ANALYSIS OF THE VALUE OF A GROUP B STREPTOCOCCUS VACCINE

## 8.1 Modelling approach and outcomes

The model described in section 8 was also used to estimate the incremental costs of a maternal GBS vaccination programme and the net monetary benefit, where the net monetary benefit is equal to the QALY gain, multiplied by the cost-effectiveness threshold minus the incremental costs. A positive net mon-

etary benefit indicates a cost-effective intervention. Country-specific cost-effectiveness thresholds as determined empirically by (68), (69) were used conservatively. An alternative threshold of  $1 \times$  gross domestic product per capita was also considered.

## 8.2 Data inputs

Vaccine delivery cost inputs were assigned based on a country's World Bank income designation and according to data from a systematic review of vaccine delivery costs (70). Vaccine prices in the base case were assumed to be US\$ 50 for high income countries; US\$ 15 for upper-middle-income countries and US\$ 3.50 for all other LMICs. These prices were based on both benchmarking to other vaccines and analysis of cost of goods supplied (40) and are also used in section 9.

A health payer perspective was taken for health-care costs. A regression model was used to estimate GBS specific acute health-care costs (systematically reviewed in Salman et al. (71) relative to total per capita health expenditure. Survivors with moderate to severe sequelae were assumed to have ongoing annual health-care costs of between 3% and 25% of acute costs (sampled from a uniform distribution).

All costs were in US\$ 2019.

## 8.3 Normative assumptions

Policy-makers in different settings are likely to have different frameworks for decision-making; these are reflected in the range of scenarios suggested by WHO (1) and national guidelines for economic evaluations of vaccines. Therefore a range of normative assumptions – i.e. those assumptions on which policy-makers will take a value judgement – are presented in Table 5. For ease

of presentation, most and least favourable assumptions are grouped together.

The additional potential benefits of prevention of GBS-associated preterm births is considered in a scenario analysis.

**Table 5. Least and most favourable normative assumptions**

Assumption about	Least favourable	Most favourable
Discounting	3% discounting of costs and benefits	3% discounting of costs, 0% discounting of benefits
Inclusion of stillbirth quality adjusted life years	Excluded	Included
Cost-effectiveness threshold	Woods (2016) (68) & Ochalek (2020) (69) empirically estimated	1 x gross domestic product per capita

## 8.4 Vaccine cost-effectiveness

There is a positive global net monetary benefit in the vaccination base case under all normative assumptions. The global net monetary benefit ranges from US\$ 1 billion to US\$ 18 billion under least/most favourable assumptions. The value of stillbirth QALYs contributes between US\$ 1 billion and US\$ 7 billion to the global net monetary benefit depending on other assumptions. Inclusion of stillbirth QALYs is consistent with global initiatives to better quantify the burden of stillbirth (72) and develop strategies to reduce this burden.

Under the most favourable assumptions, the net monetary benefit is positive in all regions (Fig. 8); under the least favourable assumptions, it is negative in three regions, but the uncertainty intervals overlap zero, suggesting that with more competitive prices particularly in middle-income countries the net monetary benefit may become positive in all regions.

In scenario analyses, the inclusion of a vaccine effect on GBS-associated preterm birth leads to a positive net monetary benefit under most and least favourable assumptions in all regions.

## 8.5 Threshold vaccine price

The threshold vaccine price by region under least and most favourable assumptions was investigated (Fig. 9). Under the most favourable assumptions, the range of vaccine prices was always positive and the central estimate was above US\$ 70 in all regions. Under

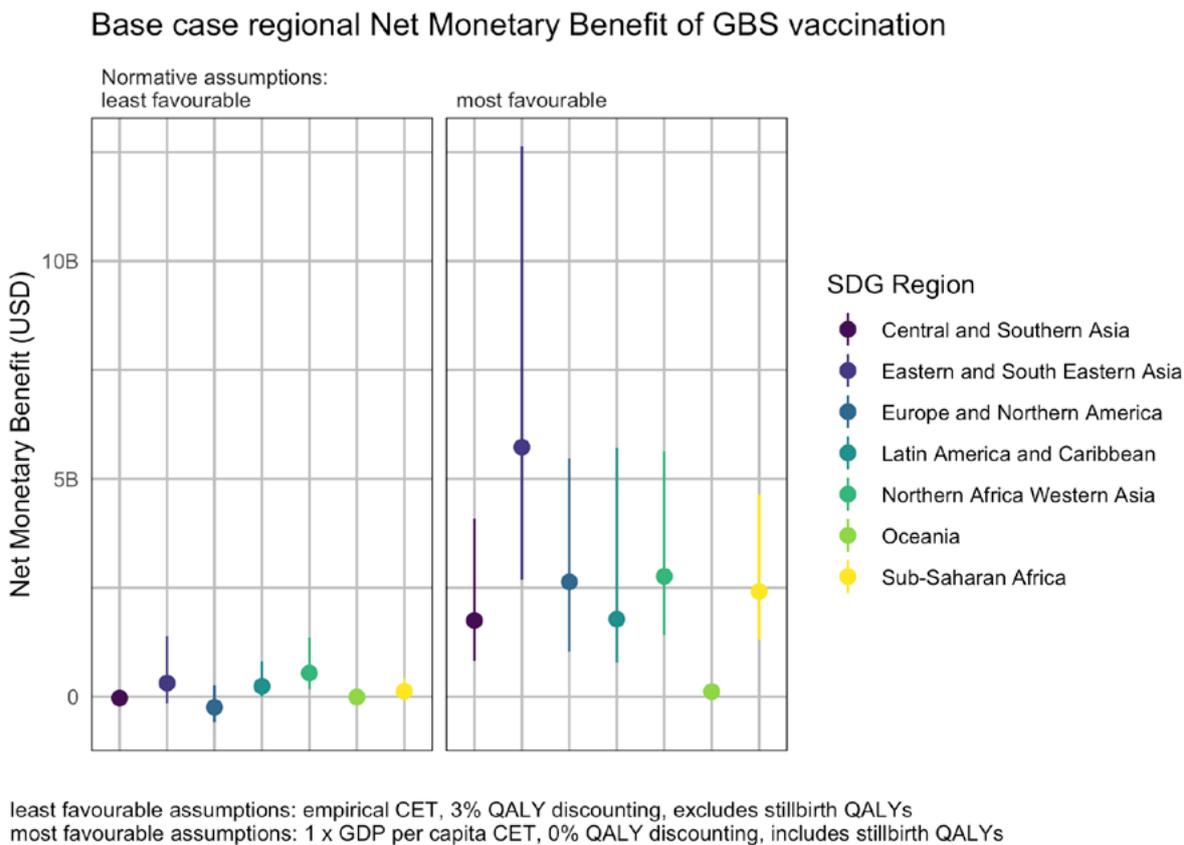
least favourable scenarios, the range in some regions included negative values (i.e. there is no price at which a vaccine would be cost-effective) but the central estimate of threshold price exceeded the assumed vaccine price in all regions apart from Europe.

## 8.6 Major gaps in knowledge or research evidence

This is the first global analysis of GBS vaccine cost-effectiveness. Previous studies in particular high-income country contexts (73, 74, 75) and LMIC contexts (76, 77) support that a competitively priced GBS vaccine would be a cost-effective intervention. The uncertainty in disease burden estimates is propagated through this global cost-effectiveness assessment. If a GBS vaccine were to reduce preterm births, the net monetary benefit would be positive

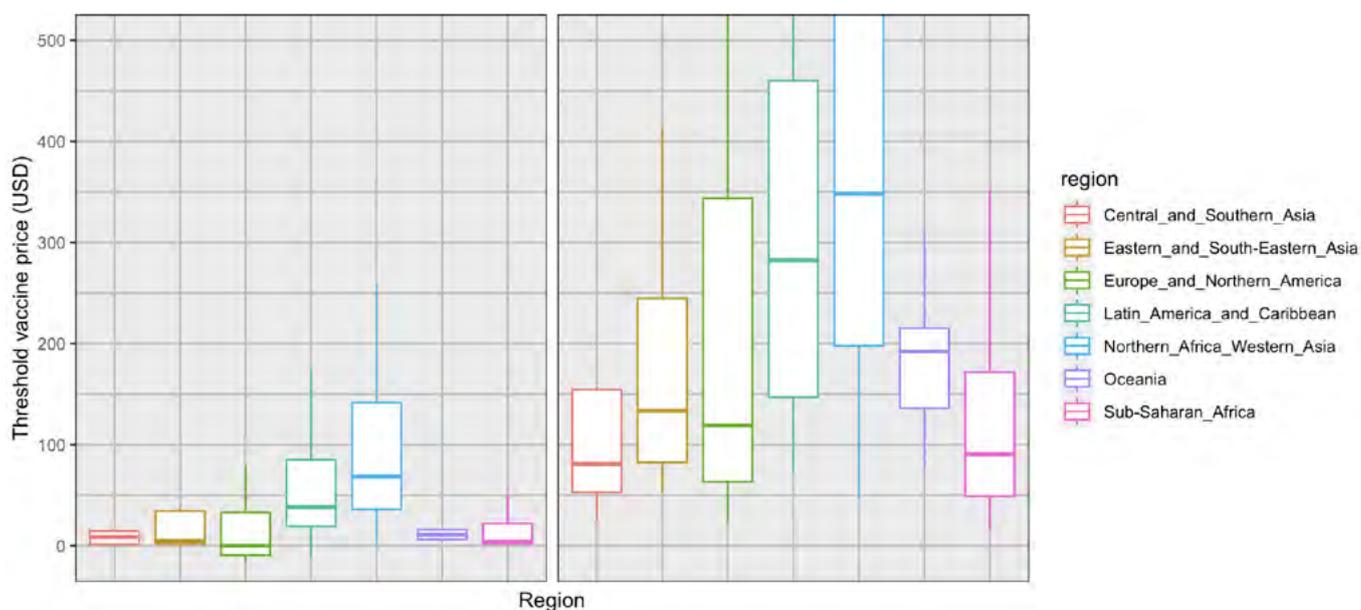
in most settings. While it is desirable to reduce this uncertainty, a preterm effect may only be established through a vaccine probe study. Few studies have ascertained the long-term health and social costs of disability and decrements to quality of life resulting from neonatal iGBS and this is an area for further improvement that could be supported by the Defeating meningitis by 2030 road map.

**Fig. 8. Net monetary benefit of GBS vaccines by least and most favourable normative assumptions and Sustainable Development Goal region\***



\* Source: Procter et al., 2021 (38).

**Fig. 9. Threshold vaccine price by region under least and most favourable assumptions (censored at US\$ 500\*)**



\* Source: Procter et al., 2021 (38).

# 9. RETURN ON INVESTMENT AND FINANCIAL SUSTAINABILITY OF A VACCINE

It is essential for vaccine manufacturers to understand the potential financial outcomes that can be expected from the successful

development of a GBS vaccine so that they are prepared to commit to the costs of such development and manufacture.

## 9.1 Defining the market

A GBS vaccine would fill an unmet global public health need, thus a vaccine is required that can attain global registration. The burden of disease is highest in LMICs and a GBS vaccine is an attractive proposition for reducing neonatal deaths. However, a GBS

vaccine is also likely to appeal to many high-income countries where GBS control lags behind that of other childhood infections and the potential to charge higher prices in high-income countries may be a driver for vaccine manufacturers to invest.

## 9.2 Vaccine demand forecast

Vaccine characteristics, as set out in the WHO preferred product characteristics (2), were used as the foundation for a vaccine demand forecast for GBS vaccines (40). Standard population-based forecasting methodology (78), (79), (80) was used with:

- date of adoption based on country data on burden of disease (section 6), fiscal space, assessment of programmatic readiness (section 10), vaccine introduction history, and eligibility for Gavi support;

- anticipated coverage based on ANC4;
- 5% wastage rate; and
- 25% buffer stock.

The total global demand for GBS vaccines is expected to reach approximately 110 million doses per year by 2040 and stabilize thereafter (Fig. 10).

## 9.3 Methodology for financial analysis

A financial analysis was performed to assess, from a manufacturer standpoint, the return on investment on GBS vaccine development, the potential need for non-market financial incentives and the potential alternative financing avenues that could be mobilized (40). The financial analysis employed a basic discounted cash flow methodology (81) to calculate the net present value of the project. Standard discounted cash flow evaluations discount the financial flows generated by a single project by employing the weighted average cost of capital that captures the specific risk of

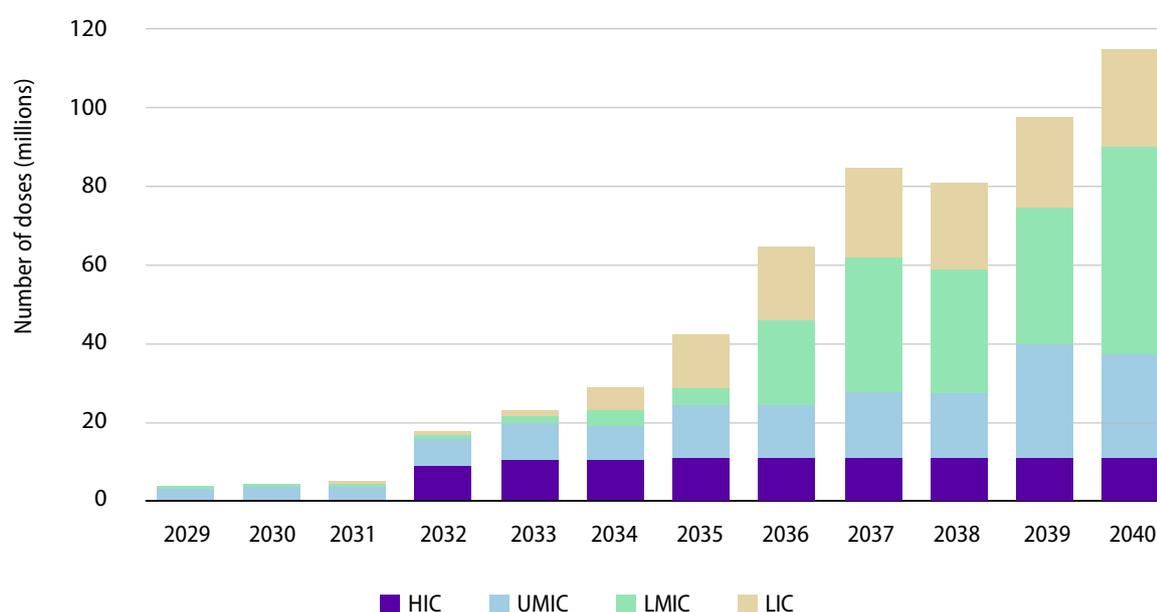
the business in analysis via the estimate of the cost of equity for that type of business as per the capital asset pricing model. The expectation of additional returns in reward for projects that can be considered riskier than the average portfolio is captured by increasing the discount rate beyond the weighted average cost of capital in what is defined as a “hurdle rate”. The analysis covers the period 2020–2040 in order to consider a sufficient number of years pre- and post-commercialization, assuming vaccine licensure in 2028. Full methods are given by Malvolti et al. (40).

Key assumptions include:

- a one-dose vaccine given in the 2<sup>nd</sup>/3<sup>rd</sup> trimester of pregnancy as outlined in the WHO preferred product characteristics (2) (alternative schedules are considered but not reported here);
- vaccine licensure in 2028 with first introduction in 2029 (178 countries to introduce by 2040 and 16 countries to introduce after 2040 (Fig. 9));
- vaccine prices by income strata (US\$ 50.00/US\$ 15.00/US\$ 3.50) (section 7) based on benchmarking prices and an analysis of cost of goods supplied;
- clinical development investments (as described in Table 6);
- a proportion of 14% of total revenues used as the selling, general and administrative expense rate; and
- 10.5% discounting used to reflect the “hurdle rate”.

The combined investment total is thus US\$ 226 million under the assumption that an immunogenicity trial is sufficient for licensure and US\$ 378 million if a full efficacy trial is required.

Fig. 10. Forecast of vaccine demand 2029–2040, by country income group\*



\* Vaccine licensure assumed to occur in 2028; first introduction in 2029.

HIC: high income country; UMIC: upper-middle-income country; LMIC: lower-middle-income country; LIC: low-income country.

Table 6. Estimated clinical development investments required for a Group B streptococcus vaccine from a manufacturer’s perspective

Investment	Amount US\$ million	Notes
Phase 1–2 trial	23.6	
Phase 3 immunogenicity trial	52.3	In the base case, an immunogenicity and safety trial of 7000 participants is assumed to be sufficient for licensure. Cost of US\$ 4612 per subject including regulatory and manufacturing costs.
Phase 3 efficacy trial	204.5	In an alternative scenario, an efficacy trial with 40,000 participants is required with same cost assumptions as above.
Manufacturing facility investment	150	

## 9.4 Outcomes of financial analysis

The key summary outcome of the financial analysis is the net present value. If the net present value is positive, then the initial investment costs can be recovered, rewarding the capital

invested at an appropriate rate based on the specific risk of the business and generating a surplus.

## 9.5 Results of financial analysis

In the base case the net present value was US\$ 742 million (note that the calculation includes 12 years of positive cash flows and not residual value). The net present value is sensitive to assumptions of competition; the base case assumes only one manufacturer reaches market. With a second or third manufacturer the net present value reduces to US\$ 531 million and US\$ 88 million respectively, as competitors gain market share at the expense of the first and lower overall revenue and financial sustainability for each business. When an efficacy trial is required, the net present value decreases significantly compared to the base case. The results are highly dependent on revenue from high-income countries, which comprises about two thirds of a manufacturer's

revenue in the first decade, emphasizing the requirement for global vaccine registration.

This analysis concludes that the business case for the development of a GBS vaccine can be considered financially sustainable and a solid commercial proposition. A GBS vaccine initiative can likely guarantee a sizeable return on investment for a manufacturer. There is no need for further incentives beyond the market. Nonetheless, the role of donors or financers can still prove very important in de-risking the development of the GBS vaccine that, especially at this stage, is still affected by many levels of uncertainty.

## 9.6 Major gaps in knowledge or research evidence

These results should encourage manufacturers to prioritize GBS vaccine development. The financial analysis contains assumptions that are not all possible to verify but are consistent with other elements of the FVVA and considered reasonable. While

still viable under this scenario, the need for a phase 3 efficacy trial increases manufacturer risk; defining alternative pathways to licensure ([section 5.5](#)) is thus again emphasized.

# 10. IMPLEMENTATION OF THE VACCINE IN LOW RESOURCE SETTINGS

Issues affecting implementation of a GBS vaccine in low-income settings were considered in four domains: policy formulation; service delivery; acceptance and demand for vaccine; and monitoring and evaluation (39). Each domain was informed by a comprehensive literature search (including grey literature), with an

additional online stakeholder survey to ascertain knowledge and perceptions of GBS disease and its prevention. An important source of information was the WHO report, *Maternal immunization and antenatal care situation analysis report of the MIACSA project 2016–2019* (82).

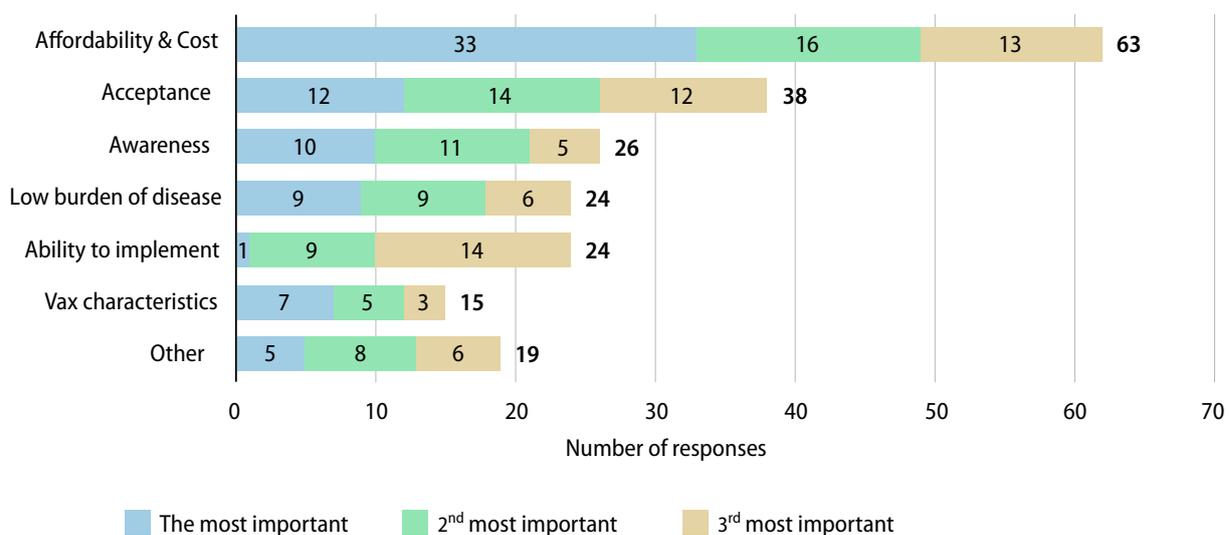
## 10.1 Policy formulation

Policy on the use of a GBS vaccine will be supported by evidence-based recommendations published by WHO SAGE once vaccine licensure is imminent. In addition, Gavi, the Vaccine Alliance, will consider which new vaccines to add to its portfolio through its vaccine investment strategy (83). However, each country will require national policies and targets. It is essential that regional bodies and national immunization technical advisory groups are well informed and have access to available evidence required for good decision-making on GBS vaccine policy. The stakeholder survey (39) showed high awareness of GBS disease and its prevention among paediatricians and obstetricians, but low awareness among public health specialists, especially in LMICs. Perceived barriers to GBS vaccine implementation are shown in Fig. 11.

Affordability and cost were important perceived barriers to GBS vaccine implementation. Note that section 8 and 9 of this FVVA consider tiered vaccine pricing by income level which, in addition to donor support, may help to overcome this.

The burden of disease was perceived to be lower in Asia and prevention of GBS was not seen as a priority in this region. Improved estimates of the global and regional burden of disease are presented in section 6 of this report, but GBS-specific data are still scarce in many countries and it is likely that national immunization technical advisory groups will require better local data to justify GBS vaccine implementation in their countries. WHO could therefore provide further support by defining standards to strengthen surveillance, although generating high quality local data may be challenging in many LMICs.

Fig. 11. Survey respondents view of barriers to inclusion in national immunization programmes



## 10.2 Service delivery

Tetanus toxoid-containing vaccines are the only vaccines provided during pregnancy in most LMICs, with influenza vaccines increasingly offered, mainly in middle-income countries. A platform for maternal immunization therefore exists in LMICs, with vaccines being given either in antenatal care settings or immunization clinics. Based on data reported in the *Maternal immunization and antenatal care situation analysis report of the MIACSA project 2016–2019* (82), the timely delivery of GBS vaccination in the 2<sup>nd</sup> or 3<sup>rd</sup> trimester is likely to be easier when delivered along with antenatal care in a “one stop shop” approach with regular antenatal care visits (84). Survey results, also taken from the

MIACSA report, identified that vaccine procurement and distribution were mainly the responsibility of a country’s national immunization programme (84). GBS vaccination will likely require collaboration between national immunization programmes and for antenatal care/maternal and neonatal health providers to be strengthened (85, 86). Furthermore, the financial and human resources dedicated to antenatal care and maternal immunization would need to be improved in many LMICs in order to successfully deliver a GBS vaccination programme – a weakness identified by the MIACSA project (84).

## 10.3 Acceptance and demand for vaccine

The likelihood of pregnant women accepting a GBS vaccine has not been extensively studied in LMICs. Although pregnant women themselves were not surveyed about their hypothetical acceptance of a GBS vaccine, most health professional and policy-maker respondents from LMICs thought there was a high or medium likelihood of pregnant women accepting a vaccine based on their recommendation (39). A reasonable amount of literature exists on factors influencing acceptance of antenatal care in general (systematically reviewed by Downe et al. (87)), and on the acceptance of vaccination during pregnancy (systematically reviewed by Wilson et al. (88)). While most research is undertaken in high-income settings, overall, it appears that such factors are contextual and likely to vary between and within countries (39). Given this context-dependence, the development of concep-

tual frameworks that could be used to support LMICs that wish to measure demand and acceptance should be encouraged. As an example, the tailoring immunization programmes for maternal influenza vaccination (TIP FLU) tool provides a framework for diagnosing demand and supply side barriers and facilitators for vaccination during pregnancy, building on an understanding of the behavioural, social and environmental factors that influence vaccination behaviours and demand in a given context (89). This knowledge can be used to design appropriate interventions to improve uptake. To assist with risk communication for vaccine use during pregnancy, estimates of background rates of stillbirths, neonatal deaths and congenital malformations are available (90) and could be collated for use in settings where there is an absence of high-quality local data.

## 10.4 Monitoring and evaluation

Monitoring and evaluation are essential activities of vaccine implementation, generating evidence on performance (vaccine coverage), impact and safety that informs strategic and operational decisions for programme optimisation. With the maternal tetanus (and in some cases influenza) programme as part of a national immunization programme, each LMIC has an existing platform which could be leveraged, adapted and strengthened for monitoring and evaluation of GBS vaccines (as summarized in Table 7). In previous vaccine introductions, it has been important to demonstrate vaccine impact on specified disease outcomes (see Fig. 4, Table 3 for relevant GBS outcomes) in early adopting countries. If vaccine is licensed on the basis of immunogenicity/correlates of

protection without an efficacy trial, then such demonstration projects in countries with enhanced surveillance are likely to be critical for the successful roll-out in other LMICs.

As other maternal vaccines (tetanus toxoid-containing vaccine and influenza vaccine) are being rolled out more widely, and with further products such as respiratory syncytial virus vaccines under development, there may be synergies in strengthening monitoring and evaluation and service delivery for maternal immunization, including both national immunization programme and antenatal care providers (82).

**Table 7. Summary of monitoring and evaluation components and adaptations required to incorporate a GBS vaccine**

M&E component	Existing system	Adaptations required for GBS vaccine	Comments
Vaccine coverage	NIP usually monitor coverage, with some input from MNH for maternal vaccines. Coverage is reported to WHO and UNICEF annually (91).	Existing systems could be adapted to report GBS vaccine coverage. Surveys could be used to validate administrative coverage estimates.	Strengthening collaboration between NIP and MNH may be required, depending on delivery system chosen.
Impact assessment – stillbirth	Data on stillbirths are not systematically collected in many LMICs (e.g. through CRVS). Stillbirth is not an outcome that is linked to impact assessment of other vaccines.	LMICs are increasingly undertaking maternal and neonatal death audits as part of MPDSR activities. These systems could be adapted to examine the impact of GBS vaccine in the absence of CRVS.	The INDEPTH Network (92) which has 49 field sites in LMICs could potentially be used (with appropriate resources) to investigate stillbirth before and after vaccination to assess impact of GBS vaccine.
Impact assessment – neonatal iGBS	About one third of LMICs report in MIACSA survey that they conduct surveillance of neonatal sepsis, but this may not include laboratory-confirmation.	WHO commissioned a feasibility study on establishing a multi-country GBS surveillance network in LMICs and is developing surveillance standards. PREPARE GBS (93) includes LMICs.	A new GBS surveillance network would require appropriate resources. Surveillance activities are among the key milestones in the Defeating meningitis road map (33).
Impact assessment – maternal sepsis	No assessment of surveillance of maternal sepsis in LMICs has been performed.	There are no existing networks covering this group. The WHO Invasive Bacterial Disease Surveillance network covers infants aged 1–59 months, but has appropriate laboratory capacity.	Establishing sentinel surveillance sites could be feasible approach.
Safety monitoring	Mechanisms and technical capacity to monitor the safety of vaccination during pregnancy in LMICs is currently limited.	A road map for establishing or strengthening maternal immunization safety monitoring in LMICs is available (94).	The Global Alignment of Immunization Safety Assessment in Pregnancy (95) project could also be used to strengthen capacity.

CRVS: civil registration and vital statistics; GBS: Group B streptococcus; LMIC: low- and middle-income country; M&E: monitoring and evaluation; MIACSA: maternal immunization and antenatal care situational analysis; MNH: maternal and neonatal health; MPDSR: maternal and perinatal death surveillance and response; NIP: national immunization programme.

## 10.5 Major gaps in knowledge or research evidence

Many of the operational issues highlighted above are feasible to address with appropriate planning and support in the time horizon until GBS vaccines are available. The development of tools and frameworks to support LMICs in addressing issues of optimal service delivery, likely GBS vaccine acceptance and moni-

toring and evaluation should be a priority. Synergies with other maternal immunization programmes, including new vaccines on the horizon should be investigated. The economic analysis (section 9) does not include costs of systems strengthening, but this is likely important to quantify and include in the future.

# 11. PRINCIPAL FINDINGS AND CONCLUSION

## 11.1 Principal findings

The research summarized in this FVVA shows that:

- The global burden of GBS is higher than previously recognized, and includes GBS neonatal/ early infant meningitis, sepsis, death, and neurodevelopmental impairment, with additional GBS-attributable stillbirth, maternal sepsis and GBS-associated preterm births. The burden is highest in sub-Saharan Africa and South Asia.
- Vaccination could result in substantial declines in global morbidity and mortality due to GBS. A maternal vaccine is likely to be a cost-effective intervention, with a positive global net monetary benefit under most assumptions if the vaccine is affordably priced.
- GBS vaccine development is financially sustainable and likely to be profitable from the manufacturer perspective globally, subject to adoption in high-income countries.
- A maternal vaccination programme would be feasible to implement, requiring increased awareness of GBS as a public health challenge as well as strengthening of health systems for delivery, monitoring and evaluation.
- There are information gaps that if filled could further reduce uncertainty, including prospective data on GBS maternal colonization and preterm births, as well as stillbirths and maternal infections. Health economic data are only available in a few low- and middle-income settings and more data from countries in a range of different settings would improve economic evaluations.
- There is heterogeneity in disease burden, vaccine cost-effectiveness and programmatic preparedness by region and country, emphasizing the need for local assessment and decision-making with tiered and fair vaccine pricing.

The relationship of the findings reported in this FVVA to the vaccine development pipeline and key stakeholders is illustrated in [Table 8](#) and [Fig. 12](#).

## 11.2 Next steps

Further discussion at global level will be helpful to assess additional evidence and information that is being generated and to translate this information into action and policies that will enable the research and development community to develop a GBS vaccine optimized for use in low resource settings as well as national decision-makers to prepare their countries to introduce GBS vaccine in pregnant women.

The pathway to licensure for a GBS vaccine has not yet been agreed by regulators. Evidence to support licensure based on immunogenicity studies and correlates of protection is a priority and much work in this area is ongoing. The financial sustainability analysis suggests that this will increase the attractiveness of GBS vaccine development to manufacturers.

A reliance on modelled estimates of disease burden is inevitable when many countries do not have high-quality surveillance systems for infant infections and deaths. Uncertainty in disease burden estimates are propagated through the analyses of potential vaccine impact. Additional data on GBS-attributable stillbirth, especially from Asia, would be welcome, and few studies have been conducted on maternal sepsis due to GBS outside of high-income settings. Strengthening surveillance, including microbiological confirmation, is important for good local decision-making before vaccine introduction and monitoring vaccine impact. Surveillance is one of the five pillars of the Defeating meningitis by 2030 road map (33), which will provide technical support for countries.

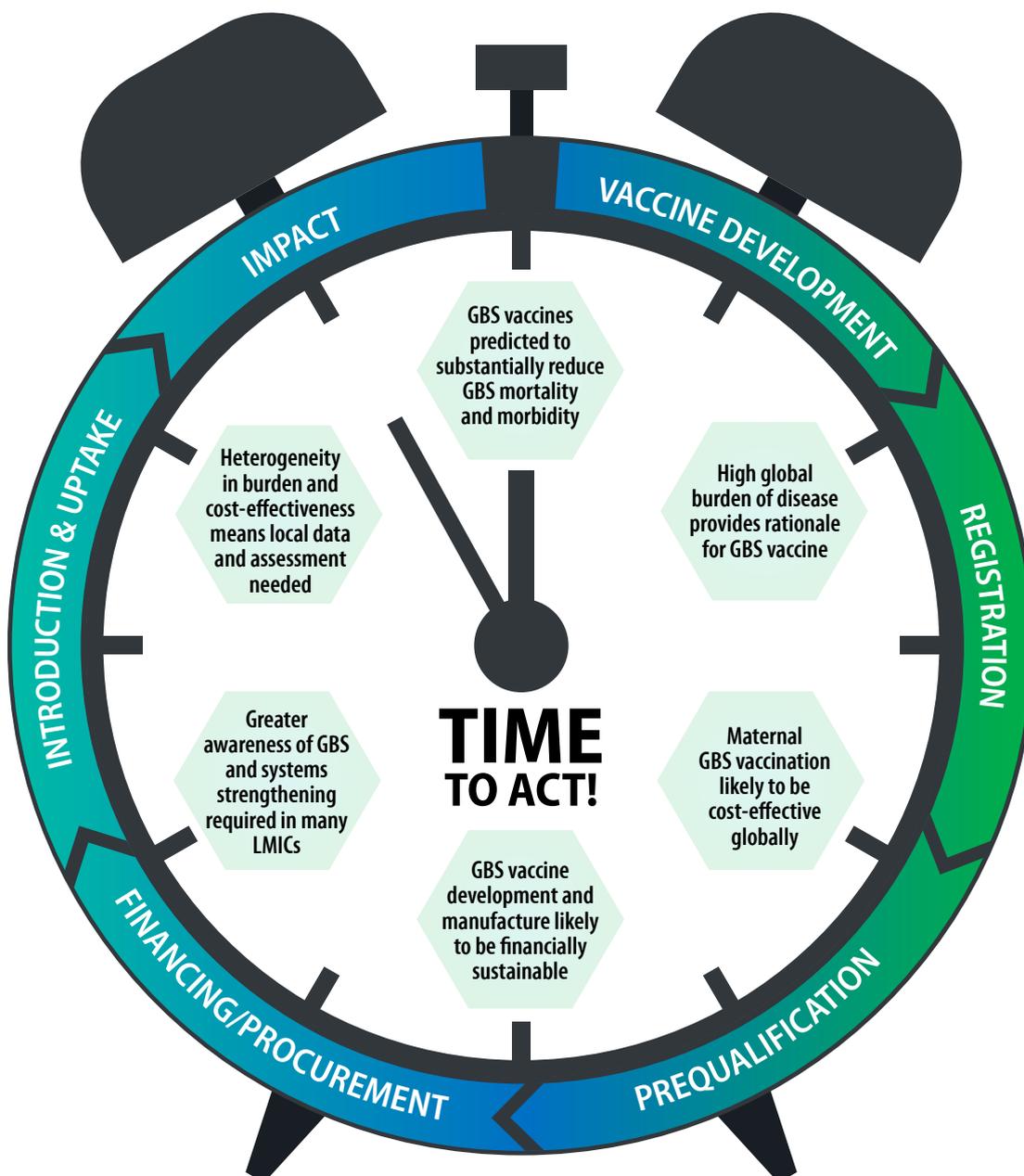
Further studies, in particular well-designed prospective studies, with comprehensive exposure measures are necessary, especially to further elucidate the association between GBS infection and maternal sepsis, stillbirths and preterm births. If a GBS vaccine were to reduce preterm births, the net monetary benefit would be positive in most settings. There was insufficient evidence to develop an extended cost-effectiveness analysis (96) to examine the equity implications of a GBS vaccine, but this is an important area for further research.

The development of tools and frameworks to support LMICs in addressing issues of optimal service delivery, likely GBS vaccine acceptance, and monitoring and evaluation should be a priority. Synergies with other maternal immunization programmes should be investigated, including new vaccines in development.

**Table 8. Principal findings, the quantitative data behind these, interpretation and next steps for different stakeholders**

Principal finding	Quantitative assessment	Interpretation	Next steps
New estimates of global neonatal/ infant infections in 2020 illustrates high burden of GBS disease	Annual burden: iGBS (392,000, UR 184,000–849,000), deaths (91,000, UR 44,000–187,000), stillbirth (46,000, UR 20,000–111,000), neurodevelopmental impairment (37,000 new cases, UR 14,000–96,000) and GBS associated preterm births (518,000, UR 36,000–1,142,000)	Disease burden provides strong rationale for vaccine development for all stakeholders	Technical and financial support is required to strengthen country-level surveillance and burden assessments, including health economic data
Vaccination could result in substantial declines in global morbidity and mortality due to GBS	3,841,000 QALYs gained per year globally (base case)	Maternal GBS vaccination will substantially reduce burden of disease	Global Policy makers should recommend Funders and Countries to prioritise GBS vaccines
A maternal vaccine is likely to be a cost-effective intervention, with a positive global net monetary benefit under most assumptions	Global net monetary benefit of US\$ 1–17 billion	Vaccination is likely to be cost-effective at competitive prices	Industry should provide GBS vaccines at fair prices. Funders of vaccine implementation and National policy makers should invest in GBS vaccines if prices are competitive
GBS vaccine development is financially sustainable and likely profitable, subject to adoption in high-income countries	Net present value: US\$ 742 million (base case)	High NPV will motivate Vaccine Researchers & Developers (R&D) to take GBS vaccine candidates through to registration	Vaccine R&D and funders should discuss how to accelerate vaccine development for use in low resource settings
Awareness of GBS is low in many LMICs and systems strengthening needed for vaccine implementation, monitoring & evaluation	N/A, findings supported by literature reviews and surveys	Countries and national policy makers may not recognise the potential value of GBS vaccines	National level stakeholders and Funders should jointly address core success factors of future vaccine introduction and secure funding for sustainable use
There is clear global value in a GBS vaccine but heterogeneity by region and country	Regional variation in disease burden (section 6) and vaccine cost-effectiveness (section 8) shown in report	Such heterogeneity emphasizes the need for regional and country-level data, assessment and decision making	National level stakeholders should prepare for assessment and decision making with support from funders

Fig. 12. Illustration of the relationship of FVVA findings to the vaccine development pipeline and key audiences



### 11.3 Conclusion

This FVVA presents some of the important challenges and opportunities for the development and implementation of GBS vaccines suitable for maternal immunization, summarizing the latest research findings on disease burden, potential vaccine cost-effectiveness, financial sustainability and operational issues. This evidence can be used by a range of stakeholders to prioritize activities and accelerate progress towards development and use of a GBS vaccine.

tiveness, financial sustainability and operational issues. This evidence can be used by a range of stakeholders to prioritize activities and accelerate progress towards development and use of a GBS vaccine.

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