Vaccine 41 (2023) S41–S52

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Vaccine value profile for Group B streptococcus

Caroline L. Trotter [a,*], Mark Alderson [b], Ziyaad Dangor [c], Margaret Ip [d], Kirsty Le Doare [e], Eve Nakabembe [f], Simon R. Procter [g], Musa Sekikubo [f], Philipp Lambach [h]

[a] Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES, UK
[b] PATH, 2201 Westlake Avenue, Suite 200, Seattle, WA 98121, USA
[c] WITS VIDA Research Unit, University of the Witwatersrand, Chris Hani Baragwanath Hospital, 30 Chris Hani Road, Diepkloof, Soweto, 1862 Johannesburg, South Africa
[d] The Chinese University of Hong Kong, Sha Tin, New Territories, Hong Kong, China
[e] St George's, University of London, Cranmer Terrace, London SW17 0RE, UK
[f] Makerere University School of Medicine, P.O. Box 7072, Kampala, Uganda
[g] London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK
[h] World Health Organization, Avenue Appia, Geneva CH-1211, Switzerland

ARTICLE INFO

Article history:
Available online 6 October 2023

Keywords:
Group B streptococcus
Vaccines, maternal immunisation
Vaccine value profile

The development of this Vaccine Value Profile has been commissioned by WHO's Immunization, Vaccines and Biologicals (IVB) department on the recommendation of IVB's Product Development for Vaccines Advisory Committee, to an independent contractor. All authors are independent subject matter experts and the authors alone are responsible for the views expressed in this manuscript.

ABSTRACT

Group B streptococcus (GBS) is a major global cause of neonatal meningitis, sepsis and pneumonia, with an estimated 91,000 infant deaths per year and an additional 46,000 stillbirths. GBS infection in pregnancy is also associated with adverse maternal outcomes and preterm births. As such, the World Health Organization (WHO) prioritised the development of a GBS vaccine suitable for use in pregnant women and use in LMICs, where the burden of disease is highest. Several GBS vaccines are in clinical development. The WHO Defeating Meningitis by 2030 has set a target of 2026 for vaccine licensure.

This 'Vaccine Value Profile' (VVP) for GBS is intended to provide a high-level, holistic assessment of the information and data that are currently available to inform the potential public health, economic and societal value of pipeline vaccines and vaccine-like products. This VVP was developed by a working group of subject matter experts from academia, non-profit organizations, public private partnerships and multilateral organizations, and in collaboration with stakeholders from the WHO regions of AFR, AMR, EUR, WPR. All contributors have extensive expertise on various elements of the GBS VVP and collectively aimed to identify current research and knowledge gaps. The VVP was developed using only existing and publicly available information.

1. The global public health need for a vaccine

Group B streptococcus (GBS) also known as *Streptococcus agalactiae*, emerged as an important human pathogen in the 1960s [1]. While the bacteria are part of the normal microbiota of the human gastrointestinal tract, GBS is recognized as a major cause of bacterial meningitis and sepsis in newborns and young infants [2]. Disease in neonates aged 0–90 days is classified into early-onset disease (EOD) occurring between 0 and 6 days and late-onset disease (LOD) occurring between 7 and 90 days. Infants who survive invasive GBS disease, may suffer from long term sequelae, including neurodevelopmental impairment (NDI) [3]. GBS is also an important contributor to stillbirth [4] and associated with preterm births [5]. GBS is a cause of invasive disease in pregnant women [6] and non-pregnant adults, particularly the elderly [7].

The proof of concept that a vaccine given to pregnant women could prevent invasive GBS disease in their babies was established in the 1970s [8] but progress toward a GBS vaccine has been slow. The development of a GBS vaccine suitable for use in pregnant women and use in LMICs was prioritised by Product Development for Vaccines Advisory Committee (PDVAC) in 2015 and 2016 [9,10]. The stated WHO strategic goal 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.*" [11] In 2021, GBS vaccines were the subject of the first of a planned series of Full Value of Vaccine Assessments published by WHO [12]. Table 1 summarizes the key epidemiological features of GBS disease.

* Corresponding author.
E-mail addresses: clt56@cam.ac.uk (C.L. Trotter), malderson@path.org (M. Alderson), Ziyaad.Dangor@wits.ac.za (Z. Dangor), margaretip@cuhk.edu.hk (M. Ip), kiledoar@sgul.ac.uk (K. Le Doare), drevena@yahoo.co.uk (E. Nakabembe), simon.procter@lshtm.ac.uk (S.R. Procter), msekikubo@yahoo.com (M. Sekikubo), lambachp@who.int (P. Lambach).

https://doi.org/10.1016/j.vaccine.2023.04.024
0264-410X/

Table 1
Summary of epidemiology and potential indirect public health impact.

Feature	Summary and evidence
Epidemiology	
Reservoir	• GBS was first identified as a bovine pathogen causing bovine mastitis in 1887. Cattle remain an important mammalian reservoir of GBS. • GBS emerged as a human pathogen in the 1960s [1] and since then GBS infections have become a leading cause of neonatal infections globally[2]. o In infants, GBS disease can cause meningitis, sepsis and pneumonia [13] o In the fetus, GBS infection can lead to stillbirth[4] and is associated with preterm births[5] o In pregnant women GBS is a cause of sepsis and urinary tract infections o In the elderly, GBS infections can cause sepsis, skin and soft tissue infection, meningitis and endocarditis [7] • Approximately 18% of pregnant women globally are colonised with GBS [14]. o If the mother is colonised with GBS during pregnancy, there is a 50% chance the neonate will become colonised, and a 1% chance of the neonate developing invasive disease, in the absence of intrapartum antibiotic prophylaxis [15]. o GBS commonly resides in the gastrointestinal tract then spreads to the genital tract. For this reason, infants may ingest GBS laden fluids whilst in utero or during delivery. • GBS also has a fish reservoir and is found in both seawater and freshwater fishes. GBS is also a fish pathogen in aquaculture and the consumption of raw fish has been associated with human infections caused by ST283 strains [16].
At-risk populations	• At-risk populations for GBS include pregnant women[6], the unborn fetuses of colonised women[4], neonates 0-90 days [13], especially those born before 37 weeks gestational age[5], less commonly older infants and the elderly[7]. • HIV exposed infants are also at higher risk of GBS disease than unexposed infants, with estimates from a systematic review and meta-analysis reporting an odds ratio of 2.29, (95% CI 1.31-4.38, p=0.005). Sub analyses showed that HIV-exposed neonates were not at increased risk of EOD (OR 1.31, 95% CI 0.84-2.04 p=0.240) but were 4.43 times more likely to have LOD (95% CI 1.81-10.85 p=0.001). There was no association identified between maternal HIV infection status and rectovaginal GBS carriage.[17]
Mortality	• *Infants* o The global case fatality rate estimated in 2017 was 8.4% (6.6-10.2%)[13]. In 2020 there were an estimated 91,000 (UR: 44,000–187,000) deaths globally from early and late-onset invasive GBS (iGBS) in infants[18]. Case fatality rates are higher in preterm babies with iGBS compared to term babies with iGBS but there is not necessarily an increased risk of death comparing preterm babies with and without iGBS [19]. • *Fetus (stillbirth)* o Stillbirths represent a major mortality burden with 46,000 (UR: 20,000–111,000) GBS-attributable stillbirths occurring globally each year [4]. • *Pregnant women* o There is a paucity of evidence on GBS deaths in pregnant women, a 2017 systematic review reported 0.2% CFR with confidence intervals overlapping zero[6]. • *Non-pregnant adults* o The overall CFR is estimated at 9.98% (95% CI, 8.47-11.58). CFR is highest in Africa at 22.1% (95% CI, 12.3-33.6). Serotype V is the most prevalent serotype globally and in North America accounting for 43.5% (n = 12,926) and 46.7% (n = 12,184) of cases, respectively. Serotype Ia was the second and serotype III was more prevalent in Europe (25.0%) and Asia (29.5%). In particular, older age (i.e., ≥65 years) has been associated with increasing iGBS disease mortality (up to 50%).[7]
Morbidity	• *Infants* o The pooled incidence of iGBS disease in infants was estimated in 2017 to be 0.49 per 1000 livebirths (95% CI 0.36-0.47). for the year 2020, there were an estimated 231,000 (UR: 114,000–455,000) early onset iGBS cases and 161,000 (UR: 70,000–394,000) late onset iGBS cases. There is also a considerable burden of long-term morbidity in survivors. A 2017 systematic review demonstrated that of GBS meningitis survivors, 32% (95% CI 25-38%) had neurodevelopmental impairment (NDI) at 18 months of follow-up, including 18% with moderate to severe NDI[3]. The studies included in this review revealed an absence of follow-up beyond 2 years of age and a paucity of data pertaining to outcomes following sepsis. More recent studies have addressed these gaps in a range of settings [19–23]. Globally, an estimated 40,000 (14,000- 112,000) iGBS survivors develop moderate and/or severe NDI each year [18] • *Pregnant women* o Global estimate of GBS sepsis in pregnant or postpartum women of 33,000 cases per year (UR 13,000-52,000) [18] • *Non-pregnant adults* o Invasive GBS (iGBS) disease is a major clinical entity in adults: the most common presentation is primary bacteraemia, followed by skin and soft tissue infection, pneumonia, urosepsis, endocarditis, peritonitis, meningitis, and empyema. An increase in the incidence of iGBS in adults over time has been observed and relapse is relatively frequent. Most of the cases in older adults are linked to underlying medical conditions such as diabetes mellitus, obesity, liver cirrhosis, stroke, cancer, and cardiovascular disease and with immunosenescence [7]. There are no global burden of disease estimates.
Geographical and seasonal distribution	• *Colonization* o A 2017 systematic review revealed regional variation in maternal colonisation rates [14]. The Caribbean had the highest prevalence of colonization (35% [95% CI, 35%–40%]), and Southern Asia and Eastern Asia had the lowest prevalence of GBS colonization (13% and 11%, respectively). • *Disease* o Around 15% of the world's population resides in Sub-Saharan Africa, but about half of the burden of GBS cases and deaths occur there. [18]

Table 1 (*continued*)

Feature	Summary and evidence
	• *Case fatality rates* o Overall case fatality rate from infant iGBS was estimated at 8.4% (95% CI, 6.6%–10.2%) in 2017[13] . CFR in Africa (18.9% [95% CI, 13.7%–24.0%]) was 4 times higher than in developed countries (4.7% [95% CI, 3.3%–6.1%])[13] • *Non-pregnant adults* o The incidence rate for iGBS among non-pregnant adults was 2.86 cases per 100,000 population (95% CI, 1.68–4.34) overall, this varied by region with 5.90 cases per 100,000 population (95% CI, 4.30–7.70) in North America, 1.50 (95% CI, 1.10–2.00) in Europe, 1.50 (95% CI, 0.70–2.60) in Asia, 0.90 (95% CI, 0.70–1.20) in South America and 0.40 (95% CI, 0.30–0.60) in Africa. There was only one study from South America, two from Africa (one South Africa, one Reunion) and three from Asia. [7]
Gender distribution	• *Infant GBS* o Sex might be associated with susceptibility to iGBS as higher incidence has been described in male compared to female infants in the UK and France [24]. There was no clear evidence of a difference in mortality or sequelae in in cohort studies of infant iGBS disease from Denmark and The Netherlands.[19]
Socio-economic status vulnerability(ies) (equity/wealth quintile)	• There is a paucity of good evidence on socio-economic vulnerabilities. • *Infants* - Lower socioeconomic status of the mother is a risk factor for GBS disease in the infant in one study from the USA[25]. • *Pregnant women* - women from lower socioeconomic groups were reported to be more likely to carry GBS in the USA, South Africa[26]. However, other studies in The Gambia[27] and Kenya [28]report an association with higher socioeconomic class and GBS colonisation.
Natural immunity	• Carol Baker first highlighted natural immunity from infection in the 1970s. Her work demonstrated that infants who developed GBS serotype III disease had significantly lower serotype III-specific IgG in maternal serum than infants without disease also born to women recto-vaginally colonised by that serotype. Subsequent studies have shown similar results for serotypes Ia, Ib, and V in maternal serum. While antibody-mediated risk reduction estimates have been reported from different studies for the most frequent serotypes (Ia, III, V), rigorous estimates of protective thresholds have not been established. An inverse association between levels of antibodies and neonatal risk of invasive disease has also been shown for some protein candidate antigens, but not others. [29,30]
Pathogenic types, strains, and serotypes	• GBS is characterised by 10 serotypes (Ia, Ib, II-IX) o Serotype III accounts for 60% of all infant invasive disease cases reported globally [31] o Serotype V is seen in 40% of non-pregnant adult infections[7] • Multi-locus sequence type (MLST) classification shows that clonal complex (CC) 17 is the most common cause of neonatal infections and is exclusively made up of serotype III strains. GBS strains from this CC is overrepresented in LOD disease due to presence of the hvgA gene which has meningeal tropism in neonates.[32]
Potential indirect impact	
Anti-microbial resistance (AMR) threat	• Penicillin is the first line of treatment for GBS infections. Resistance to penicillin remains low but there are a number of reports of reduced penicillin susceptibility from Japan, Canada and Korea. Erythromycin and clindamycin are alternative treatments for patients with penicillin allergies; resistance to these antimicrobials is high. Resistance to other antibiotic classes including aminoglycosides and fluoroquinolones is rising. Vancomycin (last resort antibiotic) remains effective.[33] • The US CDC has identified AMR in GBS as "concerning". [34] • IHME have estimated that there are in excess of 150,000 GBS deaths per year associated with AMR. This does not seem consistent with total deaths due to GBS estimated in 2020.[35] • Administration of intrapartum antibiotic prophylaxis (IAP) may have unintended consequences. The evidence remains unclear but there are theoretical risks that IAP could increase antibiotic resistance in GBS strains and there may be downstream health consequences of altered infant microbiota caused by IAP.[36]
Epidemic and outbreak potential	• Invasive GBS disease in young infants is generally considered a sporadic disease. • Outbreaks of GBS infection in adult and paediatric wards as well as in the community can occur, though they may go unrecognised. • A meta-analysis of published reports of healthcare associated GBS clusters was undertaken by Collin et al in 2019. 26 studies were included for data-analysis, which included adult and paediatric outbreaks. 22 studies described neonatal GBS clusters, with 17 of these clusters occurring in neonatal intensive care units (NICUs) or special care nurseries with other cases arising from maternity units. Premature and low-birth weight infants were most susceptible. Adult GBS outbreaks in the meta-analysis were reported from haemodialysis units and oncology units. Findings were consistent with horizontal transmission.[37] • Community outbreaks have been associated with handling of fresh-water fish and the GBS strain ST283. Most recently, the Centre for Health Protection in Hong Kong is currently investigating an outbreak of invasive group B streptococcus (type ST283) which has been linked to environmental and food samples taken from a local market[38].
Transmission route /potential	• Maternal colonisation poses the greatest risk of infants developing EOD due to inhalation or ingestion of GBS laden fluids whilst travelling down the birthing canal.[15] • Evidence for the route of transmission for LOD remains scarce with anecdotal reports of breastmilk transmission and environmental contamination.[39,40]
Acquired/ herd immunity	• Given that colonisation with GBS is widespread in the population, interventions in pregnant women (who represent <5% of the population) are considered unlikely to lead to herd immunity.
Co-associated mortality	• The risk of invasive GBS disease among infants from multiple births is high (17%-40%), if one infant had already developed iGBS disease. Recurrent neonatal and young infant invasive GBS disease can occur after completed appropriate treatment of the primary infection in 1.4%- 2.8% of cases of neonatal invasive GBS infection.[41–43]

(*continued on next page*)

Table 1 (*continued*)

Feature	Summary and evidence
Economic burden	
Health facility costs/out of pocket costs/ productivity costs	• A systematic review found that the costs of treating all-cause sepsis and meningitis in neonates and infants <1 year of age ranged from $55 to $129,632 for sepsis and $222 to $33,635 for meningitis. Low- and middle-income countries (5 studies) reported lower costs than high-income countries (15 studies, of which 13 studies from the USA) for both sepsis and meningitis [44]. • A GBS vaccine cost-effectiveness study in the USA estimated the GBS specific short-term treatment costs at $20,741 for a term infant and $53,728 for a pre-term infant with meningitis and $21,787 to $56,438 for sepsis, respectively. The long-term costs were estimated at $489,377 for meningitis and $511,631 for sepsis.[45] • A study from England estimated the mean health and social care cost for infants with iGBS disease over the first 2 years of life at $16,233, two times higher than infants without iGBS disease.[46] • A GBS vaccine cost-effectiveness study in the Netherlands estimated the total annual direct healthcare and productivity loss costs associated with iGBS disease at $5,474,320.[47] • A GBS vaccine cost-effectiveness study in the Gambia estimated the provider treatment costs at $17,542 and the out-of-pocket costs for treatment at $5270 per annum.[48]

Abbreviations used in table not defined elsewhere: CDC – Centers for Disease Control, USA; IHME Institute for Health Metrics and Evaluation

1.1. Current methods of surveillance, diagnosis, prevention, and treatment

A global survey of GBS disease in 2017 identified few country-wide ongoing surveillance networks [2]; these were based predominantly in high income countries and focussed on monitoring of GBS-associated meningitis. Where surveillance is undertaken, this usually takes the form of clinician notification to the lead public health surveillance organisation, with laboratory confirmation of GBS from a sterile site. A range of microbiological methods are used for diagnosis of GBS including PCR and latex agglutination to identify serotype, but conventional culture remains the gold standard because of high specificity and the ability to investigate antimicrobial susceptibility and further characterise isolates, including by whole genome sequencing. The utility of whole genome sequencing has been demonstrated in the identification of hospital outbreaks of GBS in neonates and adults [37]. WHO perspectives on case ascertainment and case definitions of GBS, particularly in the context of vaccine efficacy trials, are detailed by Seale et al [49]. Ten GBS capsular envelope polysaccharide (CPS)-based serotypes have been described, however, the majority of invasive disease in young infants is caused by a few of these serotypes (predominantly Ia, Ib, II, III, IV, V) [13].

The major risk factor for early onset GBS disease is colonisation in the pregnant woman. Intrapartum antibiotic prophylaxis (IAP), of one or more doses of antibiotics prior to delivery of the infant, can be used to prevent early onset GBS disease [50]. There are currently 2 different approaches used to identify pregnant women that require IAP: the culture-based strategy used in countries such as the United States, Canada and parts of Australia and the risk factor-based strategy used in the United Kingdom, the Netherlands and South Africa, among others. The former identifies GBS colonization at 35–37 weeks of gestation (using a rectovaginal swab); intravenous benzylpenicillin or ampicillin is then offered to colonized women during labor. The second strategy is based on the presence of clinical risk factors including preterm labor (<37 weeks), prolonged rupture of membranes, maternal pyrexia (temperature > 38 °C), previous infant with GBS disease and GBS bacteriuria. There are no randomised trials that directly compare the two strategies. While the incidence of early-onset GBS disease (EOGBS) (0–6 days) has declined significantly in many settings that have adopted IAP, a Cochrane review concluded that "there is lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal early onset GBS disease"[51]. In low- and middle-income settings, there are concerns about the feasibility of widespread IAP implementation [50]. Moreover, the incidence of LOGBS has been unaffected by the introduction of IAP strategies [50]. Other prevention strategies are urgently required to decrease morbidity and mortality from invasive neonatal GBS disease.

Treatment of invasive GBS disease also relies upon antimicrobial therapy. Penicillin is the first line of treatment for GBS infections. Resistance to penicillin remains low but resistance to erythromycin and clindamycin has risen sharply in recent years.

1.2. Summary of knowledge and research gaps in epidemiology, potential indirect public health impact and economic burden

- A reliance on modelled estimates for disease burden is necessary when not all settings have good GBS surveillance. Surveillance, of all-cause sepsis and meningitis as well as culture-confirmed GBS, should be strengthened. Surveillance is one the key pillars of the Defeating Meningitis by 2030 roadmap [52].
- Data on stillbirth attributable to GBS are still sparse, further studies on stillbirth causes of death are required, particularly in Asia and sub-Saharan Africa.
- Greater understanding of the association between GBS and preterm birth could be generated through well designed prospective studies that consider multiple exposures. This is important because if a GBS vaccine could reduce the risk of preterm birth, it is more likely to be cost-effective.
- There are few studies of maternal GBS disease outside of high-income settings, this outcome was not included in the global economic analysis due to lack of data.
- The contribution of IAP to AMR is thought to be small given volume of treatments globally, but further research is required to elucidate this relationship.
- The picture on invasive disease in non-pregnant adults is dynamic, and further research is required to elucidate disease burden and routes of transmission, including from a One Health perspective given zoonotic outbreaks of GBS disease.

2. Potential target populations and delivery strategies

GBS vaccines are being developed for maternal immunisation, following the WHO strategic goal stated in section 1. There are existing recommendations for tetanus and influenza vaccines to be given in pregnancy and depending on the country, other vaccines, such as pertussis may be offered routinely to pregnant women. The target population of a GBS vaccine in pregnant women

Table 2
Overview of potential target and key population(s) and associated delivery strategy(ies).

Target and key population(s)	Delivery strategy(ies)
Pregnant women	• Currently, the WHO recommends tetanus toxoid and influenza vaccination for pregnant women. Generally tetanus vaccines are administered between 27 and 36 weeks of pregnancy. Increasingly, pertussis and COVID vaccines are offered in pregnancy and there are other new maternal vaccines in the pipeline, such as respiratory syncytial virus (RSV). • For GBS, a 1 dose regimen is preferred, given in the 2nd/3rd trimester of pregnancy. This was outlined in the WHO preferred product characteristics[11]. This could align with routine antenatal care visits and with current immunization schedules. • Countries that recommend > 4 antenatal care (ANC) contacts are more likely to have > 90% protection against tetanus at birth[53]. However, in many low resource settings women do not attend for the recommended minimum number of antenatal care visits and are at risk of being missed in vaccination efforts. Strengthening of antenatal care services and increased collaboration between immunization programmes and maternal and child health services is therefore warranted[54].
People living with HIV	• As immunity is often impaired in the context of HIV infection, it may be necessary to amend the dose or number of doses of vaccine given to pregnant women living with HIV[55]. A trial of a GBS conjugate vaccine in pregnant women in Malawi and South Africa showed that lower levels of serotype-specific maternal antibody was transferred to infants in women with HIV compared to those without HIV [56].

is universal with no differentiation between high- and low-income settings. Invasive GBS disease in non-pregnant adults is not a priority for vaccine development but a licensed product could potentially be used in outbreaks or other very high-risk settings (see Table 2).

3. GBS and its consideration as a public health priority by global, regional or country stakeholders

The first ever WHO Full Value of Vaccines Assessment was published in November 2021 with GBS vaccines as the topic [12]. This followed from WHO declaring GBS vaccines as a priority in 2015 and 2016 and demonstrates that much progress has been made to gather new and synthesize available evidence on the value of GBS vaccines. In addition to WHO leading the global drive for a GBS vaccine, other key international stakeholders include the Bill & Melinda Gates Foundation, who provided financial support for the Full Value of Vaccines Assessment and have convened a series of meetings to move forward the agenda on correlates of protection for GBS, with a line of sight to vaccine licensure based on immunogenicity rather than efficacy studies. Individual countries and stakeholders within these countries have differing awareness and preparedness of/ for a GBS vaccine. The Full Value of Vaccines Assessment identified the need for greater awareness and local assessment of both need and implementation readiness, particularly in LICs (see Table 3).

4. Existing guidance on preferences/preferred product attributes for vaccines against GBS

The preferred product characteristics for a GBS vaccine were published by WHO in 2017[11]. This document defined preferential characteristics but did not define minimal characteristics for a GBS vaccine (see Table 4).

5. Vaccine development

5.1. Probability of technical and regulatory success:

The WHO Product Development for Vaccines Advisory Committee (PDVAC) recognised the high technical feasibility for successful development of GBS vaccines in 2015 and 2016. Current GBS vaccine candidates are either polysaccharide conjugate vaccines with multiple GBS serotypes included or protein vaccines; both are designed to provide broad coverage against multiple strains. Both approaches are well established and both conjugate and protein-based vaccines have an excellent safety record, including in pregnant women.

As indicated in the PPC[11], a pre-licensure pivotal randomized controlled clinical efficacy trial may be difficult to perform on the grounds of cost and feasibility because the incidence of iGBS is low and large numbers of pregnant women would need to be recruited. Therefore alternative strategies to support licensure need to be

Table 3
Overview of non-commercial stakeholders engaged, their interest and potential demand

Stakeholders engaged	Summary of position/interest	Potential demand and uptake
WHO global	• GBS vaccine development prioritised in 2015/16 [9,10] • There is a high global burden of GBS disease [18]. • Vaccination could result in substantial reduction in morbidity and mortality[12]. • A maternal vaccine is likely to be a cost-effective intervention at realistic prices[12]. • GBS vaccine development is sustainable and likely profitable, if adopted in HICs[57]	• A Full Value of Vaccines Assessment for GBS vaccines was published in 2021 to encourage the engagement of vaccine developers and funders; global policymakers and national policy-making bodies and health planners. • Global demand for GBS vaccines estimated to reach approx. 110 million doses/year by 2040[57] • Cost-effectiveness and program preparedness varied by region and country, requiring local assessment and decision-making [12].
WHO regional	• Implementation of the roadmap for Defeating Meningitis [52] will be driven by regional offices. There are particular strategic goals for GBS.	• The COVID-19 pandemic has affected the timelines for roadmap implementation but momentum within regions is gathering pace.
HIC, LIC and LMIC professionals (paediatricians, obstetricians, immunization and public health specialists)	• 49% of 101 stakeholders in a survey considered introduction of GBS vaccine a priority	• A survey conducted on stakeholders' awareness of GBS disease and priority to vaccination from 101 respondents from 66 countries inc. paediatricians, obstetricians, immunization and public health specialists. Knowledge of GBS disease greatest in Americas (68%), Europe (66%), lowest Asia (13-38%) Perception highest among paediatricians [54].
GBS charities, action groups and parent voices	• GBS charities and action groups have long called for a GBS vaccine.	• N/A

Table 4
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs reported in [11].

Product attribute	Preferential characteristic
Indication	• Prevention of laboratory-confirmed GBS stillbirth and invasive GBS disease in neonates and young infants.
Target population(s)	• Pregnant women, in the second or third trimester of pregnancy.
Outcome measure(s) and target efficacy	• Available evidence supportive of 80% protection against combined risk of laboratory-confirmed GBS (all serotypes) stillbirth and invasive disease in the offspring.
Safety profile	• Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis). [58]
Number of doses and schedule	• A one dose regimen is highly preferred to ensure maximum reach
Route of administration	• Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery.
Duration of protection	• Not stated*
Co-administration with other vaccine	• 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 Program of Immunization in infants of vaccinated mothers.
Product stability and storage	• Not stated
Vaccine presentation	• Not stated

* Although the duration of protection required is not stated in the PPC, the assumption used elsewhere in the WHO Full Value of Vaccines Assessment is that vaccination will be required for each pregnancy.

Table 5
Overview of parameters that inform scientific feasibility of developing an effective vaccine for LMIC public market use.

Parameter	Issues and evidence
Diagnosis/case ascertainment	• WHO perspectives on case ascertainment of GBS in context of vaccine trials published in 2019 [49].
Biomarkers/ Correlates of risk and/or protection	• Studies have shown that infants who developed GBS disease had significantly lower serotype-specific IgG in maternal serum than infants without disease also born to women colonised by that serotype[8]. However, rigorous estimates of protective thresholds have not been established. Efforts are ongoing to develop standardized assays for IgG and opsonophagocytic killing and an international reference serum (for serotypes Ia, Ib, II, III, IV and V) is being prepared. It is likely that any serocorrelate will need to be based on infant rather than maternal serum, and efforts are ongoing in large seroepidemiological studies to determine protective thresholds using standardised assays[29,30,59].
Sero-epidemiological data	• There are a limited number of seroepidemiology studies reported in the literature. Three large studies in the US, UK and South Africa are ongoing[52]
Clinical endpoints	• Regulatory authorities have indicated a willingness to consider provisional licensure of a GBS vaccine based upon a correlate of protection (IgG). The link to a clinical outcome is based upon the seroepidemiology studies described above.
Controlled Human infection model (CHIM)	• No model exists.
Opportunity for innovative clinical trial designs	• Pivotal licensure studies are likely to be based on a correlate of protection that may be an aggregate based upon data from multiple serotypes.
Regulatory approach(es), including potential accelerated approval strategies	• Initial licensure, based upon the most advanced candidates, is likely to be in high-income countries following a stringent NRA review followed by WHO PQ for Gavi-supported countries. Target countries/ regions for initial licensure are US, UK Europe and South Africa. • Initial licensure is likely to be based on immunogenicity (correlate of protection) and safety with a commitment for post-licensure effectiveness studies.
Potential for combination with other vaccines	• A combination maternal vaccine is possible. Combinations could include tetanus, diphtheria, acellular pertussis and RSV vaccines. Other causes of neonatal sepsis/meningitis may be considered (e.g., *Klebsiella pneumoniae*).
Feasibility of meeting presentation and stability requirements	• The ultracold requirements of one of the more advanced candidate vaccines (Minervax) candidate vaccine may be a barrier to LMICs.
Vaccine platform	• The two most advanced vaccine approaches, conjugate vaccines and protein vaccines, have a good track record for large scale manufacturing and technology transfer. Conjugate vaccines are amenable to inclusion of additional serotypes if needed.
Large scale Manufacturer capacity / interest	• The two lead GBS vaccine candidates are being developed by a multi-national vaccine manufacturer (Pfizer) and a small biotech company (Minervax). Several other entities, including LMIC vaccine manufacturers, have preclinical GBS vaccine candidates.

considered. It is now generally accepted that a serocorrelate of protection could be used to accelerate licensure of a proposed vaccine together with a phase IV effectiveness study. Several different correlates have been proposed over the past 20 years[29], with ongoing studies seeking to add further evidence [52]. Post-licensure evidence of effectiveness from a range of settings would be required, including populations in LMICs where further investments in surveillance are required (see Table 5).

5.2. Overview of the vaccine candidates in the clinical pipeline

There are several GBS vaccine candidates in development (Table 6 and Fig. 1). In some cases, product development seems to be on hold or terminated.

The leading candidates are in Phase 2 trials in pregnant women, having demonstrated acceptable safety and immunogenicity in Phase 1 trials. The consensus in the field is that maternal IgG

Table 6
Summary of clinical trials of vaccine candidates.

Candidate	Antigen platform	Developer/ manufacturer	Phase of development, population, and location	Route of administration, no. of doses, schedule	Presentation and stability	Clinical trial refs
Hexavalent conjugate vaccine	Polysaccharide conjugate (serotypes Ia, Ib, II, III, IV and V)	Pfizer	Phase 2, healthy non-pregnant adults in USA	Intramuscular, single dose	Liquid, stable at 4C.	NCT03170609 NCT03765073 NCT04766086 NCT04258995
alpha-like protein fusion	Recombinant protein vaccine (2 fusion proteins)	Minervax	Phase 2, healthy female non-pregnant adults in UK; healthy pregnant women in South Africa & Uganda	Intramuscular, 2 doses superior to 1.	Liquid, requires ultra-cold storage.	NCT04596878 NCT05005247 NCT03807245
Trivalent conjugate vaccine (discontinued)	Polysaccharide conjugate (serotypes Ia, Ib and III)	GlaxoSmithKline	Phase 2, healthy female non-pregnant adults in Belgium; healthy pregnant women in USA; healthy pregnant women in Belgium and Canada	Intramuscular, single dose	Liquid, stable at 4C.	NCT01193920 NCT01446289 NCT02046148 NCT01150123

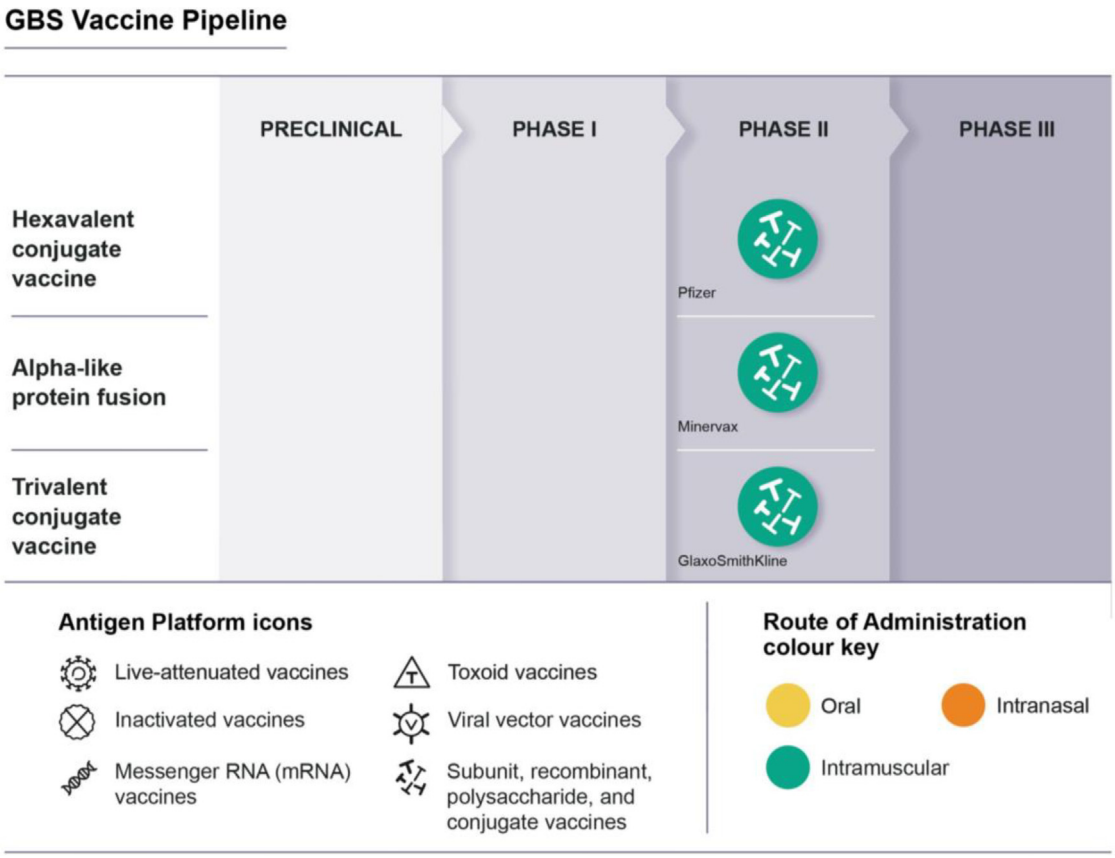

Fig. 1. Overview of the vaccine candidates in the clinical pipeline.

may reasonably predict protection in the neonate and therefore a pivotal Phase 3 trial will be based upon immunogenicity and not efficacy. Manufacturers would be obliged to conduct post-approval real-world evidence studies to confirm clinical benefit. A pivotal Phase 3 trial is likely to involve several thousand pregnant women (estimates of 50,000–60,000 women at an incidence of invasive neonatal disease of 1:1000 livebirths [30] with the primary endpoint being a high percentage (80–90%) of women achieving the defined IgG threshold correlate of protection for each of the serotypes or proteins in the candidate vaccine. The Defeating Meningitis by 2030 roadmap includes specific milestones that [52]: 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.

6. Health impact of a vaccine on burden of disease and transmission

Consistent with the PPC, estimates of the health impact of GBS vaccines have focussed on the impact of maternal immunisation on morbidity and mortality in pregnant women and their babies. A series of country-level estimates have been undertaken, which

report the health and economic impact of a GBS maternal vaccine; these are reviewed in section 7. Two studies have examined the health impact of a GBS vaccine worldwide (Table 7).

Global estimates of the incidence and case fatality rates of invasive GBS disease in young infants, and prevalence of GBS associated stillbirths were first reported in a series of systematic reviews and meta-analyses published in 2017. Using these estimates, the potential health impact of a maternal GBS vaccine was projected. Based on 2015 disease burden estimates, a maternal GBS vaccine with 80% efficacy and 90% coverage could have prevented 229,000 (uncertainty range; UR: 114,000–507,000) infant and maternal GBS cases, 41,000 (UR: 8,000–75,000) stillbirths, and 67,000 (UR: 12,000–123,000) infant deaths[2]. This is in contrast to the effect of intrapartum antibiotic prophylaxis (IAP) in high and some middle-income countries, which would have prevented an estimated 29,000 infants (UR: 0–51,000) with EOD and 3,000 (UR: 0–108,000) infant deaths in 2015 [2].

Revised estimates of the global burden of GBS disease for the year 2020 using Bayesian modelling were published in 2021 [12,18]. Using the assumptions of a single dose maternal vaccine with 80% effectiveness and coverage based on the proportion of women receiving four antenatal care visits in each country, a maternal GBS vaccine would result in approximately four million undiscounted QALYs gained per year. A maternal GBS vaccine would have prevented an estimated 126,800 (UR: 63,300–247,700) EOD cases, 87,300 (UR: 38,100–209,400) LOD cases, 31,100 (UR: 14,400–66,400) GBS deaths, 23,000 (UR: 10,000–56,400) stillbirths, 20,200 (UR: 6,400–60,200) cases of moderate/severe neurodevelopmental impairment in infant survivors mainly from sub-Saharan Africa and Asia [12]. If a vaccine is also effective against GBS-associated prematurity this could also avert a further 185,200 (UR: 13,500–407,300) GBS associated preterm births. These modelled estimates have wide uncertainty ranges. Ultimately the effect of a GBS vaccine on outcomes such as stillbirth and preterm birth may be best quantified using a vaccine probe study.

A number of maternal, perinatal and infant factors need to be considered when estimating the impact of a maternal GBS vaccine. Maternal serotype specific GBS colonisation is an absolute risk factor for invasive EOD, maternal disease and stillbirths, is associated with an increased risk of prematurity, and may in part contribute to LOD. Infant GBS disease may lead to adverse long-term outcomes including neurodevelopmental impairment. The availability of IAP preventative strategies, the predicted vaccine coverage, vaccine efficacy, and timing of dose in relation to gestational age need consideration as these will influence vaccine impact.

6.1. Summary of knowledge and research gaps in modelling health impact on disease burden and transmission

The following priority knowledge and research gaps need to be addressed to further inform the value assessment of this vaccine:

- Better evidence on GBS stillbirth rates in Africa and Asia;
- Better understanding of the role of GBS colonisation in the natural history of preterm birth;
- Better underlying data on disease burden through surveillance in a range of settings, which may require establishing/ strengthening surveillance and point of care diagnostic tests in settings with limited microbiological services; and
- Better evidence on QALY gained or DALY loss amongst survivors of GBS.

7. Social and/or economic impact of a vaccine

The Full Value of Vaccine Assessment includes the first global economic analysis of the value of a GBS vaccine [12]. This reports

Table 7
Overview of modelling studies that measure health impact on disease burden and transmission.

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/ interpretation
What is the global burden of GBS in pregnancy and the potential impact of a GBS vaccine?	• Meta-analyses combined via stepwise estimates of disease burden. • Reduction in cases of infant and maternal disease, stillbirths and infant deaths.	• Based on a series of systematic reviews that inform estimates of disease burden. • Utilized GATHER framework.	• Global use of GBS vaccine given to pregnant women. • Based on 80% efficacy against invasive disease and stillbirth. • Uniform vaccine coverage of either 50% or 90% globally.	A maternal vaccine with 80% efficacy and 90% coverage could prevent 229,000 (UR: 114,000–507,000) infant and maternal GBS cases, 41,000 (UR: 8,000–75,000) stillbirths, and 67,000 (UR: 12,000–123,000) infant deaths per year.[2]
What is the potential health impact and cost-effectiveness of a maternal GBS vaccine globally?	• Bayesian meta-analyses of disease burden combined with static vaccine impact model. • Reduction in invasive GBS cases, stillbirths, deaths and NDI and overall gain in QALY.	• Based on prior systematic reviews and updated data on stillbirths, sepsis, and neuro-developmental impairment outcomes to inform estimates of disease burden. • Utilized GATHER framework.	• Based on 80% vaccine efficacy against infant disease and stillbirth. • Vaccine coverage rates based on proportion of women receiving 4 ANC visits. • Single-dose vaccine in 2nd/3rd trimester. • Vaccine in addition to current IAP policy.	A maternal GBS vaccine could prevent 126,800 (UR: 63,300-247,700) EOD cases 87,300 (UR: 38,100-209,400) LOD cases 31,100 (UR: 14,400-66,400) GBS deaths 23,000 (UR:10,000-56,400) stillbirths, 20,200 (UR: 6,400-60,200) cases of moderate/severe neurodevelopmental impairment, and 185,200 (UR: 13,500-407,300) GBS associated stillbirths per year based on the estimated burden of disease in 2020. [12]

Table 8
Overview of modelling studies that measure anticipated socio-economic impact of the vaccine published in the last 10 years.

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/ interpretation
What is the global value of a maternal GBS vaccine?	Cost-effectiveness analysis with net monetary benefit as key outcome measure	Complements disease burden and vaccine impact sections of FVVA. Decision tree model. A range of normative assumptions (least and most favourable) and threshold prices explored.	CEA threshold values based on Woods/ Ochalek or 1 x GDP per capita for each QALY gained. Vaccine characteristics as per WHO PPC in Table 4 [11]. No effect on preterm in base case. Pricing $3.50, $15, $50 in low, middle, high income settings	A maternal GBS vaccine is likely to be cost-effective at a global and regional level if fairly priced.[12].
Cost-effectiveness of maternal immunization against neonatal iGBS in the Netherlands	Cost-effectiveness analysis considering added value of GBS vaccination on top of risk-based IAP.	Decision tree model used. Univariate sensitivity analysis performed on key epidemiological and economic parameters	Trivalent vaccine assumed in base case. 20,000 euros per QALY threshold. VE 52% early onset GBS, 64% late onset GBS. Societal perspective	A maternal GBS vaccine could be cost-effective when implemented in addition to the current risk factor-based IAP prevention strategy in the Netherlands. Threshold price in base case 58 euros (including administration costs).[47]
Cost-effectiveness of a maternal GBS vaccine in The Gambia	Cost-effectiveness analysis in absence of IAP.	Decision tree model Univariate sensitivity analysis	1 and 3 x GDP per capita/ DALY used as CEA threshold. VE 70% base case (50-90% simulated), Health payer perspective,	A hexavalent vaccine would considerably reduce the current burden of GBS disease in The Gambia but to be cost-effective, the vaccine price per dose would need to be $12/dose or less.[48]
Cost-effectiveness analysis of maternal immunisation against GBS in the UK	Cost-effectiveness of maternal immunisation in combination with risk-based IAP was compared risk-based IAP alone from a health-provider perspective	Decision tree model. Univariate and multivariate sensitivity analysis reported.	CEA threshold of £20,000 per QALY gained. VE 85% in base case. Health payer perspective	In the base case GBS vaccine likely to be cost-effective at £55 per dose (excluding administration costs) and will prevent substantial burden of disease.[60]
Cost-effectiveness of maternal GBS immunization in low-income sub-Saharan Africa	Cost-effectiveness of maternal immunisation in absence of IAP.	Decision tree model. Probabilistic sensitivity analysis	Four countries chosen as representative (Ghana, Nigeria, Uganda, Guinea-Bissau). 0.5 GDP per capita/ DALY averted used as CEA threshold. VE range of 50-90%. Health payer perspective.	GBS vaccine could be a cost-effective intervention in these settings if competitively priced.[61]
Cost-effectiveness of maternal GBS immunisation in the USA	Cost-effectiveness analysis comparing: • No prevention • Current screening/IAP • Maternal immunization • Maternal immunization + IAP when indicated for unimmunized women • Maternal immunization + screening/IAP for all women	Decision tree model. Univariate, multivariate and probabilistic sensitivity analyses.	• VE of 70% (lower in preterm babies) • Healthcare payer and societal perspectives. • Vaccine price of $107.12 in public sector, and $135.80 in the private sector.	"GBS maternal immunization, with IAP as indicated for unvaccinated women, could be an attractive alternative to screening/IAP if a pentavalent vaccine is sufficiently effective."[45]
Cost-effectiveness of maternal GBS immunisation in the USA	Cost-effectiveness of maternal immunisation in addition to screening and IAP.	Decision tree model. Univariate sensitivity analysis.	• VE of 75% (lower in preterm babies) • Societal perspective. • Vaccine cost of $100 per dose. • No CET specified.	The cost-effectiveness of immunisation (in addition to screening and IAP) was estimated to be $91,321 per QALY.[62]
Cost-effectiveness of GBS immunisation in South Africa	Cost-effectiveness analysis comparing four scenarios: 1. Doing nothing 2. Maternal immunization 3. Risk factor-based IAP 4. Maternal immunization + Risk factor-based IAP	Decision tree model. Univariate, multivariate and probabilistic sensitivity analyses.	VE of 50-90% (lower in preterm babies)Healthcare payer and societal perspectives.Vaccine cost of $10-30 in public sector (higher in private sector)	"Vaccination would substantially reduce the burden of infant GBS disease in South Africa and would be very cost-effective by WHO guidelines. Vaccination plus RFB-IAP is more effective and more costly than vaccination alone, and consistently very cost-effective."[63]

Table 9
Overview of expectations of evidence that are likely to be required to support a global / regional / national policy recommendation, or financing.

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
Health impact	Prime indicators will be future deaths averted and future cases averted. See section 6. Vaccine profile as per PPC	Full Value of Vaccine Assessment for GBS vaccines.[12]
Value for money	Tiered vaccine pricing by income strata; vaccine use globally in high-, middle- and low-income settings	See section 7 and [12]. See Table 8 for other cost-effectiveness analyses.
Equity and social protection impact	There are particular benefits of a GBS vaccine for women and their babies. The highest burden of iGBS is in infants in LMICs and prevention through vaccination free at the point of delivery will prevent potentially catastrophic health expenditures.	None available
Economic impact	Prevention of GBS will reduce acute treatment costs and costs of care for long term sequelae	There are few studies on the costs of care and broader economic impact of GBS on families. [46,64]
Global Health Security impact	No impact on Global Health Security as this is not an epidemic disease. Likely impact on AMR through reduced IAP and treatment. A vaccine would also directly reduce infections caused by both resistant and susceptible GBS bacteria.	Estimates of the impact a vaccine may have on AMR are not yet available
Other impact	DALYs averted. Preterm births averted (subject to more evidence on attributable risk)	
Implementation feasibility	Synergies with other maternal immunisation programmes	Section 9, GBS Full Value of Vaccines Assessment[12], MIACSA [53,65].
Alternative interventions	IAP is the only alternative intervention	There are concerns about the feasibility of rolling out IAP in low-income settings. IAP is considered in several milestones of the Defeating Meningitis roadmap[52].
Vaccine cost	Analyses to date assume tiered vaccine pricing, with lowest costs in low-income settings. True price or cost of goods unknown.	GBS FVVA[12]
Operational costs	Evidence required to quantify the incremental in-country operational costs per vaccinated person	Not yet estimated specifically for GBS. Recent systematic review on delivery costs for maternal immunisation synthesises evidence on unit costs by country income strata [66].
Additional implementation costs	Evidence required regarding additional costs for vaccine introduction	Not yet specifically estimated for GBS. The Full Value of Vaccines Assessment recognises that health systems strengthening is required for implementation[12].

Table 10
Assessment of access and implementation feasibility.

Indicator	Evidence/Expectation for access and implementation feasibility (ranked with reference to Appendix A)
Possibility of implementation within the existing system	• Utilisation of the current systems for maternal immunisation is possible given existing tetanus and diphtheria routine immunisation in LMICs[65]. • However, monitoring and evaluation systems may need to be strengthened. This is especially important to capture data on safety[69]. • Ranking = high
Commercial attractiveness	• A recent financial analysis suggests that GBS vaccines are an attractive commercial prospect with global demand potentially reaching 110million doses by 2040 and a net present value exceeding £700 million with one manufacturer reaching market[12,57]. • Ranking = high
Clarity of licensure and policy pathway	• A phase III efficacy trial may be prohibited by cost and feasibility given low incidence[11]. An alternative pathway to licensure based on safety and immunogenicity is likely to be sought. WHO SAGE will be invited to make a global recommendation on the use of GBS vaccines. [70] • Ranking = moderate
Expected financing mechanisms	• LMICs may not have adequate resources to buy sufficient vaccines. Gavi, the Vaccine Alliance and other potential global donors are the key expected financiers. Tiered vaccine pricing by income level has been proposed in the Full Value of Vaccines Assessment[12]. • Alternate routes of sustainable financing mechanisms for LMICs which may be transitioning from full eligibility of Gavi financing to partial or self-financing need to be considered[71] • Ranking = moderate

that there is a predicted positive global net monetary benefit of a GBS vaccine of between US$1 billion and US$17 billion from the health payer's perspective depending on the normative assumptions used and with tiered vaccine pricing by income level. In addition to this there are multiple papers examining the potential cost-effectiveness of maternal GBS immunisation in a range of settings

(Table 8). All models used a static decision tree, as it was deemed not necessary to consider transmission dynamics when most transmission is from mother to baby. The findings from these studies are broadly consistent and show that with fair pricing GBS vaccines are likely to be a good investment. The results are particularly sensitive to disease incidence, vaccine efficacy and vaccine price.

7.1. Summary of knowledge and research gaps in modelling studies that measure anticipated socio-economic impact of the vaccine

- The global analysis presented in the Full Value of Vaccines Assessment is a big step forward in understanding the value of a GBS vaccine. Uncertainty in disease burden is propagated through the economic model.
- The impact of a GBS vaccine on preterm births is uncertain and may only be established through a vaccine probe study, however if a GBS vaccine were to reduce preterm births, the net monetary benefit would be positive in most settings.
- The long-term health and social costs of disability and decrements to quality of life resulting from neonatal iGBS are not well studied and further work in this area could be supported by the Defeating Meningitis by 2030 roadmap.
- It would be useful to develop a tool to support country-level assessment of GBS vaccine cost-effectiveness.

8. Policy considerations and financing

Policy on the use of a GBS vaccine will be considered by WHO's Strategic Advisory Group of Experts on immunization (SAGE), in accordance with their Evidence-to-Recommendation Framework, once regulatory approval has been obtained by at least one country. In addition, Gavi, the Vaccine Alliance, will consider which new vaccines to add to its portfolio through its vaccine investment strategy. As there was no GBS vaccine product close to licensure, it was not considered in the 2018 Gavi Vaccine Investment Strategy (VIS). The FVVA report provides the building blocks for a future analysis, including the 2023 Gavi VIS. A WHO policy recommendation is a pre-requisite for WHO Prequalification, and both WHO policy and PQ are needed for financing by Gavi (see Tables 9 and 10).

Some additional principles that may impact policy and vaccine introduction decision-making:

- National decision-making bodies frequently require evidence of vaccine safety and effectiveness in the local population before considering their use in the public sector, even for vaccines already licensed locally, or in other countries.
- For some countries the possibility of government uptake of a vaccine will be greatly enhanced if it is manufactured locally, particularly for countries with national policies of self-reliance in vaccine production.

9. Access and implementation feasibility

Given that the highest burden of invasive GBS disease in infants occurs in LMICs (section 6), it is crucial that access to GBS vaccines for LMICs is not delayed. The WHO preferred product characteristics for Group B streptococcus vaccines strategic goal (section 1) calls for a vaccine for use in all countries, of all income strata. However, settings with the highest burden of disease generally have the least amount of available data. Therefore, strengthening surveillance systems, as previously undertaken for pneumococcal and rotavirus would allow governments in low-income settings to provide quality estimates and monitor vaccine impact [67]. High income settings, including USA, UK and Europe, are likely to have a crucial role in driving the licensure of a GBS vaccine (section 5) and markets in high income countries add to the appeal of vaccine development by global vaccine manufacturers. A financial and global demand analysis to inform decisions for funding and clinical development of maternal GBS vaccines[57], included in the Full Value of Vaccines Assessment[12], suggests that a vaccine with a widespread recommendation, and adoption across high, middle and low income settings is a viable commercial prospect. Relative to previously licensed vaccines, it is important to reduce the time lag between vaccine licensure and the actual roll out of GBS vaccination in the communities with the highest burden of disease [68]. Key steps to ensuring that a GBS vaccine can be accessed in LMICs include WHO prequalification; inclusion in Gavi, the Vaccine Alliance's portfolio; increased awareness of GBS as an important public health issue [54]; and systems strengthening for vaccine implementation and post-licensure surveillance [12,53].

10. Conclusion

GBS vaccines were the topic of the first completed Full Value of Vaccines Assessment published by WHO in 2021 [12]. As a result, important knowledge gaps have been filled and there is good available evidence to assess the potential vaccine value for GBS vaccines. The vaccine value assessment also highlights remaining knowledge gaps and next steps for key stakeholders to accelerate progress toward an effective and accessible maternal GBS vaccination programme [12]. The vaccine pipeline is promising, with two leading candidates with differing approaches in phase II trials. Given the expected challenges, in terms of both feasibility and cost, of conducting a phase III efficacy trial, pathways to licensure based on safety and immunogenicity are being sought. The Defeating Meningitis by 2030 roadmap [52] targets 2026 for licensure of a GBS vaccine, with implementation in at least ten countries by 2030. Vaccine rollout in LMICs will require increased awareness of GBS, health systems strengthening for both delivery and monitoring & evaluation and suitable financing, such as adoption by Gavi, the Vaccine Alliance.

11. Data statement

No primary data is presented in this paper. All sources of data are fully referenced.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Caroline Marshall for her assistance with coordinating this paper and Isabel Frost for reviewing a draft and providing helpful comments.

This work was supported by the World Health Organization and the Bill & Melinda Gates Foundation, Seattle, WA [grant number # INV-005318].

This supplement was sponsored by the World Health Organization's Immunization, Vaccines, and Biologicals unit. The authors alone are responsible for the views expressed in each article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.04.024.

References

[1] Eickhoff TC, Klein JO, Daly AK, Ingall D, Finland M, Engl N. J Med 1964;271:1221–8.
[2] Seale AC, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J, et al. Clin Infect Dis 2017;65:S200–19.
[3] Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, et al. Clin Infect Dis 2017;65:S190–9.
[4] Seale AC, Blencowe H, Bianchi-Jassir F, Embleton N, Bassat Q, Ordi J, et al. Clin Infect Dis 2017;65:S125–32.
[5] Bianchi-Jassir F, Seale AC, Kohli-Lynch M, Lawn JE, Baker CJ, Bartlett L, et al. Clin Infect Dis 2017;65:S133–42.
[6] Hall J, Adams NH, Bartlett L, Seale AC, Lamagni T, Bianchi-Jassir F, et al. Clin Infect Dis 2017;65:S112–24.
[7] Navarro-Torné A, Curcio D, Moïsi JC, Jodar L. PLoS One 2021;16:e0258030.
[8] Baker CJ, Kasper DL, Engl N. J Med 1976;294:753–6.
[9] Giersing BK, Modjarrad K, Kaslow DC, Moorthy VS, Bavdekar A, Cichutek K, et al. Vaccine 2016;34:2865–9.
[10] Giersing BK, Vekemans J, Nava S, Kaslow DC, Moorthy V. Vaccine 2019;37:7315–27.
[11] World Health Organization. WHO Preferred Product Characteristics for Group B Streptococcus Vaccines. Geneva: World Health Organization; 2017.
[12] World Health Organization, Group B Streptococcus Vaccine: Full Value of Vaccines Assessment; 2021.
[13] Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, et al. Infant GBS Disease Investigator Group. Clin Infect Dis Off Publ Infect Dis Soc Am 2017;65:S160–72.
[14] Russell NJ, Seale AC, O'Driscoll M, O'Sullivan C, Bianchi-Jassir F, Gonzalez-Guarin J, et al. GBS Maternal Colonization Investigator Group. Clin Infect Dis Off Publ Infect Dis Soc Am 2017;65:S100–11.
[15] Russell NJ, Seale AC, O'Sullivan C, Le Doare K, Heath PT, Lawn JE, et al. Clin Infect Dis 2017;65:S152–9.
[16] Wang R, Li L, Huang Y, Huang T, Tang J, Xie T, et al. Front Microbiol 2017;8:1933.
[17] Cools P, van de Wijgert JHHM, Jespers V, Crucitti T, Sanders EJ, Verstraelen H, et al. Sci Rep 2017;7:13820.
[18] Gonçalves BP, Procter SR, Paul P, Chandna J, Lewin A, Seedat F, et al. Lancet Glob. Health 2022;10:e807–19.
[19] Horváth-Puhó E, van Kassel MN, Gonçalves BP, de Gier B, Procter SR, Paul P, et al. Lancet Child Adolesc. Health 2021;5:398–407.
[20] John HB, Arumugam A, Priya M, Murugesan N, Rajendraprasad N, Rebekah G, et al. Clin Infect Dis Off Publ Infect Dis Soc Am 2022;74:S24–34.
[21] Chandna J, Liu W-H, Dangor Z, Leahy S, Sridhar S, John HB, et al. Clin Infect Dis Off Publ Infect Dis Soc Am 2021:ciab821.
[22] Harden LM, Leahy S, Lala SG, Paul P, Chandna J, Lowick S, et al. Clin Infect Dis Off Publ Infect Dis Soc Am 2021:ciab814.
[23] Bramugy J, Mucasse H, Massora S, Vitorino P, Aerts C, Mandomando I, et al. Clin Infect Dis Off Publ Infect Dis Soc Am 2022;74:S14–23.
[24] O'Sullivan CP, Lamagni T, Patel D, Efstratiou A, Cunney R, Meehan M, et al. Lancet Infect Dis 2019;19:83–90.
[25] Regan JA, Klebanoff MA, Nugent RP. Obstet Gynecol 1991;77:604–10.
[26] Monyama M, Bolukaoto J, Chukwu M, Maloba M, Moyo S, Mavenyengwa R, et al. South. Afr. J Infect Dis 2016;31:74–8.
[27] Le Doare K, Jarju S, Darboe S, Warburton F, Gorringe A, Heath PT, et al. J Infect 2016;72:283–94.
[28] Seale AC, Koech AC, Sheppard AE, Barsosio HC, Langat J, Anyango E, et al. Nat Microbiol 2016;1:16067.
[29] Le Doare K, Kampmann B, Vekemans J, Heath PT, Goldblatt D, Nahm MH, et al. Lancet Infect Dis 2019;19:e162–71.
[30] Vekemans J, Crofts J, Baker CJ, Goldblatt D, Heath PT, Madhi SA, et al. Vaccine 2019;37:3190–8.
[31] Bianchi-Jassir F, Paul P, To K-N, Carreras-Abad C, Seale AC, Jauneikaite E, et al. Vaccine 2020;38:6682–94.
[32] Tazi A, Disson O, Bellais S, Bouaboud A, Dmytruk N, Dramsi S, et al. J Exp Med 2010;207:2313–22.
[33] Hayes K, O'Halloran F, Cotter L. Crit Rev Microbiol 2020;46:253–69.
[34] Centers for Disease Control and Prevention (U.S.), Antibiotic Resistance Threats in the United States, 2019, Centers for Disease Control and Prevention (U.S.); 2019.
[35] Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Lancet 2022;399:629–55.
[36] Patras KA, Nizet V. Front Pediatr 2018;6:27.
[37] Collin SM, Lamb P, Jauneikaite E, Le Doare K, Creti R, Berardi A, et al. J Infect 2019;79:521–7.
[38] Government of Hong Kong, (n.d.) https://www.info.gov.hk/gia/general/202110/18/P2021101800707.htm.
[39] Jauneikaite E, Kapatai G, Davies F, Gozar I, Coelho J, Bamford KB, et al. Clin Infect Dis Off Publ Infect Dis Soc Am 2018;67:854–60.
[40] Nicolini G, Borellini M, Loizzo V, Creti R, Memo L, Berardi A. BMC Pediatr 2018;18:214.
[41] Benitz WE, Gould JB, Druzin ML. Pediatrics 1999;103:e77.
[42] Freudenhammer M, Karampatsas K, Le Doare K, Lander F, Armann J, Acero Moreno D, et al. Front Immunol 2021;12:617925.
[43] Matsubara K, Hoshina K, Kondo M, Miyairi I, Yukitake Y, Ito Y, et al. Infection 2017;45:449–58.
[44] Salman O, Procter SR, McGregor C, Paul P, Hutubessy R, Lawn JE, et al. Pediatr Infect Dis J 2020;39:35–40.
[45] Kim S-Y, Nguyen C, Russell LB, Tomczyk S, Abdul-Hakeem F, Schrag SJ, et al. Vaccine 2017;35:6238–47.
[46] Schroeder E-A, Petrou S, Balfour G, Edamma O, Heath PT. Health Protection Agency Group B Streptococcus Working Group. Eur J Health Econ HEPAC Health Econ Prev Care 2009;10:275–85.
[47] Hahn BA, de Gier B, van Kassel MN, Bijlsma MW, van Leeuwen E, Wouters MGAJ, et al. Vaccine 2021;39:2876–85.
[48] Ahmed N, Giorgakoudi K, Usuf E, Okomo U, Clarke E, Kampmann B, et al. Vaccine 2020;38:3096–104.
[49] Seale AC, Baker CJ, Berkley JA, Madhi SA, Ordi J, Saha SK, et al. Vaccine 2019;37:4877–85.
[50] Le Doare K, O'Driscoll M, Turner K, Seedat F, Russell NJ, Seale AC, et al. Clin. Infect. Dis. 2017;65:S143–51.
[51] Ohlsson A, Shah VS. Cochrane Database Syst Rev 2014.
[52] WHO Defeating Meningitis roadmap. https://www.who.int/initiatives/defeating-meningitis-by-2030.
[53] Giles ML, Mantel C, Muñoz FM, Moran A, Roos N, Yusuf N, et al. Vaccine 2020;38:5268–77.
[54] Mantel C, Cherian T, Ko M, Malvoti S, Mason E, Giles M, et al. Clin Infect Dis Off Publ Infect Dis Soc Am 2021:ciab794.
[55] Dangor Z, Nunes MC, Kwatra G, Lala SG, Madhi SA. Trop Dis Travel Med Vaccines 2017;3:1.
[56] Heyderman RS, Madhi SA, French N, Cutland C, Ngwira B, Kayambo D, et al. Lancet Infect Dis 2016;16:546–55.
[57] Malvolti S, Pecenka C, Mantel C, Malhame M, Lambach P. Clin Infect Dis 2021:ciab782.
[58] Keller-Stanislawski B, Englund JA, Kang G, Mangtani P, Neuzil K, Nohynek H, et al. Vaccine 2014;32:7057–64.
[59] Dangor Z, Kwatra G, Izu A, Adrian P, Cutland CL, Velaphi S, et al. Expert Rev Vaccines 2015;14:1651–60.
[60] Giorgakoudi K, O'Sullivan C, Heath PT, Ladhani S, Lamagni T, Ramsay M, et al. Vaccine 2018;36:7033–42.
[61] Russell LB, Kim S-Y, Cosgriff B, Pentakota SR, Schrag SJ, Sobanjo-ter Meulen A, et al. Vaccine 2017;35:6905–14.
[62] Oster G, Edelsberg J, Hennegan K, Lewin C, Narasimhan V, Slobod K, et al. Vaccine 2014;32:4778–85.
[63] Kim S-Y, Russell LB, Park J, Verani JR, Madhi SA, Cutland CL, et al. Vaccine 2014;32:1954–63.
[64] Aerts C, Leahy S, Mucasse H, Lala S, Bramugy J, Tann CJ, et al. Clin Infect Dis 2022;74:S64–9.
[65] Giles ML, Mason EM, Lambach P, Mantel C. Hum Vaccines Immunother 2020;16:3177–83.
[66] Procter SR, Salman O, Pecenka C, Gonçalves BP, Paul P, Hutubessy R, et al. Vaccine 2020;38:6199–204.
[67] Hasan AZ, Saha S, Saha SK, Sahakyan G, Grigoryan S, Mwenda JM, et al. Vaccine 2018;36:4939–43.
[68] O'Brien KL, Binka F, Marsh K, Abramson JS. Lancet 2016;387:1887–9.
[69] Krishnaswamy S, Lambach P, Giles ML. Hum Vaccines Immunother 2019;15:942–50.
[70] Kobayashi M, Schrag SJ, Alderson MR, Madhi SA, Baker CJ, Sobanjo-ter Meulen A, et al. Vaccine 2019;37:7307–14.
[71] Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Lancet 2021;397:1023–34.