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Status of vaccine research and development of vaccines for GBS

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ABSTRACT

Streptococcus agalactiae (group B streptococcus (GBS)) is the leading cause of neonatal sepsis and meningitis in many countries. Intrapartum antibiotic strategies have reduced the incidence of early-onset neonatal GBS in a number of countries but have had no impact on late onset GBS infection (LOD). In low/middle income settings, the disease burden remains uncertain although in several countries of Southern Africa appears comparable to or higher than that of high-income countries. As disease may be rapidly fulminating cases can be missed before appropriate samples are obtained and this may lead to underestimation of the true burden. Given the rapid onset and progression within hours of birth as well as the deficiencies in IAP strategies and absence of a solution for preventing LOD, it is clear that administration of a suitable vaccine in pregnancy could provide a better solution in all settings; it should also be cost effective. The current leading vaccine candidates are CPS-protein conjugate vaccines but protein-based vaccines are also in development and one has recently commenced clinical trials.

1. About the disease and pathogen

Streptococcus agalactiae (group B streptococcus (GBS)) remains the leading cause of neonatal sepsis and meningitis in many countries and an important cause of disease in pregnant women, immunocompromised adults and the elderly. The highest incidence of all is in the first 3 months of life and this review will focus on this group.

Intrapartum antibiotic (IAP) strategies have reduced the incidence of early-onset neonatal GBS (EOD, defined as disease occurring <7 days of age) where applied, but have had no impact on late onset GBS infection (LOD, 7–90 days of age) and only a limited impact on disease in pregnant women [1]. In low and middle-income country (LMIC) settings, the disease burden remains uncertain although in several countries of Southern Africa appears comparable to or higher than that of high-income countries (HIC) [2,3]. EOD may be rapidly fulminating and cases can therefore be missed before appropriate samples are obtained. This may lead to significant underestimation of the true burden and be a particular issue in many African and Asian countries; comprehensive epidemiological data from such countries are urgently required [4]. A recent meta-analysis emphasized this and reported an overall estimate of GBS incidence of 0.53 per 1000 live births and a mean case fatality ratio of 9.6% (95% CI 7.5–11.8). In African infants the incidence was 1.21 per 1000 live births, with a case fatality of 22% [5].

EOD accounts for approximately 60–70% of all neonatal GBS disease. There are 10 GBS serotypes and ST Ia, II, III and V are responsible for most EOD. Maternal carriage of GBS in the gastrointestinal and/or genital tracts is a pre-requisite for EOD, vertical transmission occurring during or just prior to birth. An estimated 20–30% of pregnant women are colonized with GBS (data derived mostly from HIC [6,7]) and approximately 50% of their babies become colonized and 1% of these babies progress to develop invasive disease. Disease may occur rapidly; signs are evident at birth or within 12 h in over 90% of cases and presentation is typically with pneumonia or sepsis [8].

Two major strategies for targeting women to receive IAP are used: risk factor based (RFB) or swab culture-based. The former is based on the presence of any of the following intrapartum risk factors: delivery at <37 weeks' gestation, intrapartum fever, or rupture of membranes for ≥18 h; while the latter is based on a positive vaginal-rectal swab, typically obtained at 35–37 weeks gestation and cultured for GBS using selective media. For both strategies IAP is also recommended for women with GBS bacteriuria at any time during their current pregnancy or for women who have had a previous baby with EOD [9]. A potential alternative strategy is based on detection of GBS using real time PCR methodology from swabs obtained in labour [7]. This method has the obvious advantage of detecting GBS at the most relevant time for IAP, as screening

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earlier in pregnancy (e.g. 35–37 weeks) can result in both false positive and false negative results.

A number of issues arise with this mode of prevention, including its feasibility in LMIC. In HIC there are issues with compliance, cost and feasibility (especially of PCR in labour) and more theoretical concerns about the excessive use of antibiotics. Of particular importance is that IAP does not decrease LOD. LOD is caused predominantly by serotype III, is acquired perinatally, nosocomially or from community sources, and in up to 50% of cases presents with meningitis, which is associated with significant mortality and long-term morbidity [10,11].

Given the rapid onset and progression of EOD within hours of birth as well as the deficiencies in IAP strategies and absence of a solution for preventing LOD, it is clear that administration of a suitable vaccine in pregnancy could provide a better solution in all settings; it should also be cost effective. A recently published decision-analytic model based on South African data compared four strategies: no intervention, maternal GBS vaccination, RFB-IAP, and vaccination plus RFB-IAP. GBS vaccination alone was predicted to prevent 30–54% of infant GBS cases compared to no intervention. For vaccine prices between $10 and $30, and mid-range efficacy, its cost ranged from $676 to $2390 per disability-adjusted life-year (DALY) averted ($US 2010), compared to no intervention. RFB-IAP alone, compared to doing nothing, prevented 10% of infant GBS cases at a cost of $240/DALY. Vaccine plus RFB-IAP prevented 48% of cases at a cost of $664–2128/DALY. It was concluded that vaccination would substantially reduce the burden of infant GBS disease in South Africa and would be very cost-effective by WHO guidelines [12] (Table 1).

There is also evidence that GBS may contribute to prematurity, birth asphyxia and stillbirths; for example, a recent systematic review estimated it might account for up to 12% of stillbirths [13]. These are important consequences but are difficult to quantify.

2. Overview of current efforts

2.1. EITHER vaccines currently available and their limitations OR Biological feasibility for vaccine development

In the 1930s, Rebecca Lancefield demonstrated that protection against GBS infection in mice could be achieved using capsular polysaccharide (CPS)-specific rabbit sera [14]. CPS remains the best-studied target of GBS, and until recently was the only target for which human vaccine trials have been undertaken. In the 1980s, human trials with plain capsular carbohydrate based vaccines demonstrated that they were well tolerated, including in pregnancy [15], but only modestly immunogenic. GBS polysaccharide-protein conjugate vaccines (predominantly using tetanus toxoid as the conjugate protein) were then developed and have subsequently been administered to healthy adults and pregnant women [16–19]. Essentially all of these clinical vaccine studies were coordinated by a key group of investigators in the USA with funding and sponsorship through the National Institutes of Health and National Institute of Allergy and Infectious Diseases. Multiple studies were undertaken but progress slowed as no vaccine manufacturer appeared willing to progress this candidate to large-scale development, in large part due to perceived issues with the feasibility of maternal immunization.

More recently, a vaccine manufacturer (Novartis, now GSK) has developed and commenced clinical trials with a new CPS conjugate vaccine, based on CRM197 as the conjugate protein. Randomized clinical trials to evaluate the safety and immunogenicity of vaccination during pregnancy are underway; some have been reported as conference abstracts and some results are available on clinicaltrials.gov (NCT01193920, NCT01446289, NCT02046148).

Another manufacturer (MinervaX) has recently commenced phase 1 clinical trials with a protein vaccine (GBS-NN), made from the N-terminal domains of the Rib and AlphaC surface proteins of GBS (NCT02459262).

Additionally and most significantly, the attitude of healthcare workers, the general public, regulators and policy makers towards vaccination during pregnancy has changed. This is exemplified by the World Health Organization's global recommendations on influenza vaccine in pregnant women [20], multiple countries' recommendations on pertussis vaccine in pregnant women and, in the UK, by the high coverage achieved with a pertussis-containing vaccine in pregnancy [21].

2.2. General approaches to vaccine development for this disease for low and middle income country

The leading indication for GBS vaccines is the prevention of neonatal GBS infections (up to 2–3 months of age), including meningitis. Disease occurs too early in life for neonates or infants to mount an effective immune response following vaccination: the majority of infants with GBS disease present on day 1 of life. Therefore, the obvious target for vaccination is pregnant women. Pre-pregnancy or adolescent vaccination may also be considered, but are less feasible, especially in LMIC settings where there is no current platform for vaccination in these groups. The only alternative for prevention of EOD (but not LOD) is IAP, but it is generally believed to be too difficult to implement this in LMICs for logistical reasons. Additionally, evidence from cohort studies suggests that IAP based on swab-based screening at 35–37 weeks is a superior strategy to that based on risk factors [22]; however swab-based screening is significantly more expensive. The South African cost-effectiveness data suggested that GBS vaccination might prevent 30–54% of infant GBS cases while RFB-IAP might prevent only 10% of infant GBS cases [12].

3. Technical and regulatory assessment

The current leading vaccine candidates are capsular polysaccharide-protein conjugate vaccines. Multiple clinical studies have already been completed in order to assess the optimal dosage, schedule, requirement for adjuvant, and the persistence of response, as well as immunogenicity and safety trials in pregnant women. These candidates have so far used conventional carrier proteins (tetanus toxoid, CRM197) [17] (clinicaltrials.gov: NCT01193920). The developmental pathway for conjugate vaccines using such proteins is now well established (e.g. Hib/meningococcal/pneumococcal conjugate vaccines).

A major regulatory issue for this vaccine is that it is being developed specifically for use in pregnant women. This is a new paradigm for regulators as currently no vaccine is licensed specifically for this use. The approach taken for a GBS vaccine and the experience gained will have implications for other vaccines also being developed specifically for pregnancy (e.g. RSV).

Another significant consideration in the development pathway for this vaccine is whether licensure will require large scale randomized placebo controlled trials that demonstrate efficacy against clinical disease, or whether regulatory approval can be based on demonstration of achievement of serological correlates of protection. The latter approach was taken for licensure of meningococcal C [23] and meningococcal B vaccines. Recent guidance lays the groundwork for such an approach for vaccines developed for pregnancy [24].

Serological correlates of protection. Baker and colleagues initially characterized the association between serotype-specific CPS antibody levels and invasive GBS disease in newborns in 1976 [25].

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Table 1
Development status of current vaccine candidates (POC, proof of concept trial).

Developer	Candidate name/identifier	Preclinical	Phase I	Phase II	POC	Phase III
NIH	Tetanus toxoid-CPS conjugates: monovalent (multiple studies), bivalent (one study); CRM197–CPS conjugate: monovalent (one study)	x	x	x	x (trial in pregnant women)	
Novartis/GSK	CRM197-CPS conjugates: monovalent (multiple), trivalent (several)	x	x	x	x (trial in pregnant women)	
Minervax	N-terminal domains of the Rib and AlphaC surface proteins	x	x			
Novartis/GSK	Pilus proteins	x				
Various academic groups	Other protein(s) and/or protein-CPS conjugates	x				

In the majority of subsequent studies lower antibody levels have been found in infants with EOD and LOD, compared with infants who were exposed to mothers colonized with the same ST, but who did not develop disease. Different specific levels have been defined in different studies. For example, in a meta-analysis, the odds of invasive GBS disease were 6.56 (95% CI: 2.10–20.55) and 2.38 (95% CI: 1.20–4.70) times greater in infants whose mothers had antibody levels <2 μg/ml for serotypes III and Ia, respectively, compared to infants whose mothers had antibody levels ≥2 μg/ml [26]. Another analysis yielded a threshold of 1 μg/ml for these STs [27] while other studies have recommended much higher thresholds [28]. There has been considerable controversy regarding the appropriateness of the different ELISA methods used [29]. In general, the different methods used and the absence of reference ranges have confounded the interpretation of antibody studies and highlight an urgent need for standardization.

In a longitudinal study of natural antibody and colonization, thresholds of ≥3 μg/ml for prevention of colonization with GBS ST1a and III and of 1 μg/ml for STV were proposed [30]. This suggests that prevention of colonization may be another potential and achievable benefit of maternal vaccination as colonization is a prerequisite for EOD.

Functional assays have also been widely used and are based on opsonophagocytosis, in which vaccine–induced antibodies promote killing of GBS by polymorphonuclear leukocytes in the presence of complement. Again, standardization of methods is needed in order to facilitate the evaluation and comparison of preclinical and early stage clinical candidates using such assays prior to their advancement to late stage clinical testing.

Further prospective studies in diverse settings are still required to confirm/establish protective levels for the common STs (in addition to STIa, III) for EOD as well as for LOD using standardized methods. Because IgG capsular antibodies are unlikely to be the only determinant of protection, measures of functional antibody are also required. These studies could contribute to the licensure pathway of a GBS vaccine without needing to undertake large-scale efficacy trials in pregnant women.

Should efficacy trials in pregnant women proceed, the main endpoints would include the impact of vaccine against both EOD and LOD, culture proven and ideally, culture negative (clinical sepsis); as well as on maternal disease. Impact (and timing of the impact) of vaccine on GBS colonization (including density and the impact on non-vaccine ST) at delivery, on vertical transmission, on infant colonization and on persistence of antibody duration. Impact on colonization could also serve as a surrogate endpoint for vaccine trials. Finally, an assessment of the impact of vaccine on prematurity, birth asphyxia and stillbirths is also desirable, where possible [31].

4. Status of vaccine R&D activities

In the 1970s and 1980s human trials with plain capsular polysaccharide vaccines, including in pregnant women (STIII), demonstrated them to be well tolerated but modestly immunogenic. Vaccination was generally well tolerated. Better immunogenicity was then shown with conjugate vaccines. Conjugate vaccines were also shown to have efficacy in animal models. Experimental conjugates were subsequently constructed with CPS of GBS serotypes Ia, Ib, II, III, IV, V, VI, VII, VIII. Each GBS conjugate induced high levels of protective antibodies in animals and was shown to be more immunogenic than the unconjugated CPS. Monovalent conjugate vaccines incorporating each of the five major capsular polysaccharides of GBS have now been evaluated in phase 1 and 2 trials and in one study a bivalent conjugate vaccine was assessed (reviewed in [32]).

All published studies have used conjugate vaccines without an adjuvant, with one exception. In this study adsorption of GBS type III CPS-tetanus toxoid (III-TT) conjugate vaccine to alum did not improve the immune response in healthy adult recipients [33]. A limited number of studies have evaluated the duration of protection following immunization. In one study the duration of functional activity following a GBS conjugate vaccine was evaluated among healthy adult responders and showed substantial functional activity at 18 months to 2 years post-immunization [34].

Only one pregnancy trial with a III tetanus toxoid conjugate has been published. A total of 20 women in the USA received the vaccine while ten women received a saline control vaccine. The GBS conjugate vaccine was well tolerated, GBS III-specific IgG rose from 0.18 μg/ml before vaccination to 9.76 μg/ml at delivery, showed excellent transplacental transfer of antibody (cord/maternal ratio: 0.8) and elevated concentrations of antibody persisted in the infants up to 2 months of age. Infant sera promoted significant opsonophagocytic killing of type III GBS in vitro. All infants were born at term and were healthy through to at least 6 months of age. Efficient transplacental transfer of tetanus IgG was also reported, raising the possibility that such conjugates may also offer protection against neonatal tetanus [17].

Phase I and II trials of a trivalent GBS vaccine (CRM197-conjugated capsular polysaccharides of GBS serotypes Ia, Ib and III) have been conducted in >600 non-pregnant and >500 pregnant women in four countries. These have been designed to assess optimal dose, need for adjuvant, immunogenicity in pregnant women (including HIV-infected), placental transfer and persistence in babies. The trivalent vaccine appeared to be well tolerated and immunogenic (results presented on clinicaltrials.gov: NCT01193920, NCT01446289, NCT02046148).

Other vaccine targets include conserved proteins. A number of groups have identified different surface proteins that are both represented on the surface of all strains and serotypes of the bacterium and able to induce opsonically active antibodies. There are a number of obvious advantages with such an approach but until very recently none had entered clinical trials in humans. MinervaX, a privately held Danish biotech company, has recently initiated a Phase I clinical trial with a protein-only vaccine based on a fusion of two immunogenic and protective protein domains from selected

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surface proteins of GBS (N-terminals of AlphaC and Rib) [35,36]. These proteins appear to have a broad distribution among GBS isolates.

Using a reverse vaccinology approach, investigators from Novartis were able to show that a combination of selected surface-exposed proteins might become the basis of a universal GBS vaccine. These protective antigens included proteins subsequently found to constitute pilus-like structures and capable of eliciting high titres of opsonophagocytic antibodies that protect mice in both active and passive immunization models [37]. Clinical trials in humans have not yet commenced.

5. Likelihood for financing

The relatively well-characterized incidence of GBS in high income countries provides the market incentive for development of a vaccine, and historically NIH, and now large pharmaceutical companies, have supported costly clinical studies. This trend is likely to continue until a clear regulatory pathway has been established for vaccine approval in LMICs, and it is established that candidates currently in development are appropriate for LMIC populations. Two cost-effectiveness studies have recently been undertaken in South Africa and the USA. In the US-based study, the cost/QALY ($91,321) for a trivalent GBS vaccine was found to be comparable to other ACIP-recommended vaccines [38]. In the South African study, maternal GBS vaccination was found to be very cost effective per WHO guidelines at prices up to $30/dose [12]. These studies, in addition to more comprehensive data on the burden of disease in LMICs will likely increase awareness of the potential for vaccine impact, and in turn, increase the likelihood for financing.

Conflict of interest

PTH is an investigator for clinical trials done on behalf of St George's, University of London, UK, sponsored by vaccine manufacturers including Novartis, Pfizer and GSK. He has been a consultant to Novartis and Pfizer on group B streptococcus vaccines but receives no funding for this.

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