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REVIEW

A Vaccine Against Group B *Streptococcus*: Recent Advances

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Abstract: Group B *streptococcus* (GBS) causes a high burden of neonatal and infant disease globally. Implementing a vaccine for pregnant women is a promising strategy to prevent neonatal and infant GBS disease and has been identified as a priority by the World Health Organisation (WHO). GBS serotype-specific polysaccharide – protein conjugate vaccines are at advanced stages of development, but a large number of participants would be required to undertake Phase III clinical efficacy trials. Efforts are therefore currently focused on establishing serocorrelates of protection in natural immunity studies as an alternative pathway for licensure of a GBS vaccine, followed by Phase IV studies to evaluate safety and effectiveness. Protein vaccines are in earlier stages of development but are highly promising as they might confer protection irrespective of serotype. Further epidemiological, immunological and health economic studies are required to enable the vaccine to reach its target population as soon as possible.

Keywords: Group B *streptococcus*, *Streptococcus agalactiae*, maternal vaccines, maternal immunisation, neonatal sepsis, infant sepsis

Introduction

Group B *streptococcus* (GBS) is a leading cause of neonatal and infant sepsis and meningitis globally.[1–3] GBS can also cause stillbirths, prematurity and disease in pregnant women, immunocompromised adults and the elderly but the highest incidence of disease is in neonates and young infants.[4]

A systematic review and meta-analysis conducted in 2017 estimated a global incidence of invasive infant GBS disease of 0.49 (95%Cl 0.43–0.56) per 1000 live births.[5] In 2015, GBS was estimated to have caused 319,000 cases of invasive neonatal GBS disease globally, resulting in 90,000 deaths.[3] Serotypes Ia, Ib, II, III and V account for 98% of all rectovaginal colonisation in pregnant women worldwide.[6] The most frequent GBS serotype causing disease in infants is serotype III (61.5%) followed by Ia (19.1%), V (6.7%) and Ib (5.7%).[5] However, the fulminating nature of disease during the first hours of life and the technical difficulties in making an etiological diagnosis in many low- and middle-income settings means that this might represent a significant underestimation of the true GBS disease burden.[7] Epidemiological data on the burden of GBS disease, especially from African countries, where most infant deaths from all-cause sepsis occur, is urgently required.[7] Infant mortality estimates are seven times higher in WHO African region (51 per 1000 live births) compared to WHO European region (7 per 1000 live births).[8]

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Intrapartum Antibiotic Prophylaxis (IAP) has reduced the incidence of early onset disease (EOD, occurring from day 0 to 6 of life) in many countries using these strategies, especially those that screen all pregnant women for GBS rectovaginal colonisation during late pregnancy and give IAP to all GBS-colonised women regardless of presenting risk factors.[9,10] However, IAP coverage is incomplete even in the best of settings,[11] has no impact on late onset disease (LOD, occurring from day 7 to 90 of life), stillbirths and prematurity due to GBS, as well as a limited impact on disease in pregnant women.[10,12] Widespread IAP use might also be an issue in the context of international efforts to control antimicrobial resistance. Furthermore, antibiotics might have an effect on the infant gut flora. Effects of early life events on the neonatal microbiome have been associated with increased rates of allergy, asthma and obesity.[13–15]

Novel Features of a Maternal Vaccine for GBS

A suitable vaccine against GBS given to pregnant women could provide effective protection to those forms of invasive disease that cannot be prevented with IAP or where IAP is not feasible or is incomplete. Furthermore, a vaccine would be more easily accessible than GBS culture in all settings and would avoid the need for antimicrobial administration, avoiding the potential negative consequences of IAP in the long term.

Maternal immunisation is already a successful tool to prevent tetanus,[16] influenza[17] and pertussis[18] in young infants. The placental transfer of maternal antibodies from mother to infant reduces the window of susceptibility to infections during the first months of life.[19] This same rationale has been used to investigate new vaccines against common infections, such as respiratory syncytial virus (RSV) and GBS.[20] A major characteristic of these new vaccines is that they are being specifically designed for pregnant women.[20]

Vaccine Development: Overview of Current Efforts

During the 2015 World Health Organisation (WHO) Product Development for Vaccines Advisory Committee meeting, GBS was identified as a high priority for the development of a vaccine for maternal immunisation because of the major public health burden posed by GBS in low- and middle-income countries (LMIC), and the high technical feasibility for successful development.[21] Recent estimates suggest that an effective GBS maternal vaccine (>80% efficacy), with high (90%) global coverage, could prevent 231,000 infant and maternal GBS cases, 41,000 stillbirths and 66,000 infant deaths annually.[3]

Evidence suggests that maternal immunisation with protein-conjugated GBS capsular polysaccharides may reduce the disease risk in neonates and young infants in a serotype-specific manner.[22–24] In addition, as there are proteins that can be present in different serotypes, protein-based vaccines have the potential to provide protection across the serotype spectrum. These are also under evaluation.[25,26] Table 1 summarizes the development status of current vaccine candidates.

Capsular Polysaccharide Conjugate Vaccines

A number of virulence factors expressed by GBS are involved in colonisation, adherence, invasion and immune

Table 1 Summary of Different Vaccine Candidates

Vaccine Candidate	Preclinical	Phase I	Phase II	Trials in Pregnant Women	Phase III
Monovalent and bivalent conjugates (tetanus toxoid/ CRM197-CPS)	x	x	x	x	
Trivalent CRM197-CPS conjugates	x	x	x	x	
Hexavalent CRM197-CPS conjugates	x	x	x	x	
N-terminal domains of the Rib and AlphaC proteins	x	x			
Pilus proteins	x				
Other proteins	x				
Biotinylated CPS conjugates	x				

evasion[27–29] and these could be used as potential vaccine candidates. One of the most well-studied virulence factors of GBS is its unique sialic acid-rich capsular polysaccharide (CPS) which inhibits complement deposition and protects the bacteria from opsonophagocytosis by immune cells, thus contributing to the evasion of host immune defense mechanisms.[30,31] The CPS also enhances biofilm formation, inhibits the binding of antimicrobial peptides and neutrophil extracellular traps (NET) as well as disturbing bacterial adherence to the epithelium and mucus, thus increasing GBS invasiveness.[32–38]

GBS expresses 10 types of CPS (Ia, Ib, II–IX) that are structurally and antigenically different.[39–41] Variously arranged monosaccharides and a sialic acid residue on the branching terminus of the repeating unit make up the CPS. According to recent meta-analyses, 97% of invasive isolates in all geographical regions are caused by five of the most common serotypes of GBS (Ia, Ib, II, III and V) with serotype III the most commonly found cause of disease in infants.[5] Serotype IV is an emerging and increasing cause of invasive disease, especially in non-pregnant adults, with the potential to become an important cause of neonatal disease, with some cases already reported.[42–45]

As polysaccharides are T-cell independent antigens, the polysaccharide is conjugated to a protein carrier in order to trigger both a protective and a memory B-cell response. Earlier vaccines were conjugated to a tetanus toxoid, such vaccines might have particular value in LMIC where neonatal tetanus is still a concern.[46,47] However, the main carrier protein currently used is CRM_{197}, a nontoxic mutant of diphtheria toxin, which is highly immunogenic. Studies using either carrier protein demonstrated better immunogenicity with high levels of antibodies with CPS-conjugates compared to unconjugated vaccines.[48,49]

The first clinical trials were conducted with monovalent vaccines (Ia, Ib, II, III and V).[48–52] However, single serotypes do not generally produce cross-reactive immunity against other serotypes, thus multivalent vaccines were developed. A phase I/II clinical trial (registered as NCT01193920 at the ClinicalTrials.gov database) of a trivalent (Ia, Ib and III) CRM_{197} conjugate vaccine in pregnant women reported higher levels of CPS-specific antibodies in infants at birth and no safety concerns .[53] In 2017, a clinical trial of a GBS polysaccharide conjugate vaccine targeting serotypes Ia, Ib, II, III and V was started but, more recently, in view of the increase of disease caused by serotype IV, this serotype was added to create an hexavalent vaccine (Ia, Ib, II, III, IV, and V) with the aim to cover at least 98% of GBS isolates causing neonatal invasive disease (NCT03170609).[5,54] In order to verify the clinical safety and immunogenicity of this hexavalent vaccine, further clinical trials will be required. Currently, a phase I/II clinical trial (NCT03765073) is being conducted in South Africa to evaluate the safety, tolerability and immunogenicity of a hexavalent vaccine in healthy non-pregnant and pregnant women.

It has been shown that opsonophagocytosis is the main mechanism for the host to clear GBS infection.[24] A recent Phase II study (NCT01446289) demonstrated that maternal antibodies of pregnant women vaccinated with a trivalent glycoconjugated vaccine composed of CPS Ia, Ib and III result in opsono-phagocytic killing (OPK) titers against each GBS serotype. Analysis of cord sera revealed a strong positive correlation between IgG concentrations and OPK titers, which is predictive of functional activity against GBS infection.[55]

The role of anti-capsular antibodies in preventing GBS maternal colonisation, as well as ascending infection and neonatal transmission was recently evaluated in an animal model.[56] Results show that systemic immunisation with a type III CRM_{197}-glycoconjugate vaccine produces high levels of IgG that can reduce vaginal acquisition of serotype III during pregnancy.[56] Studies in pregnant women showed the same association with natural immunity.[57,58] Further studies will be needed to confirm the same results in vaccinated women.

Few studies have evaluated the number of doses that will be required per pregnancy for full immunity. In one study in healthy, non-pregnant women, no increase in antibody levels was shown after a second dose of a trivalent CRM_{197}-glycoconjugate vaccine administered one month after the first dose.[59] A recent study published in 2019 (NCT02690181) evaluated the safety and immunogenicity of a second dose of a trivalent (Ia, Ib and III) CRM_{197} conjugate vaccine in non-pregnant women over a long period of time (4 to 6 years) after the administration of the first dose. Antibody levels from previously GBS-vaccinated women increased ≥200-fold after a second dose. Women presenting with undetectable antibody levels after first dose also experienced an increase of anti-GBS concentrations after a second dose.[60] These results suggest that further doses might be required in subsequent pregnancies.

Serocorrelates of Protection

Although several vaccine candidates are undergoing preclinical and clinical trials, in order to achieve licensure of

a vaccine for GBS, phase III clinical trials may be required. These would need to be very large in order to demonstrate efficacy in countries able to conduct such trials.[61] As there is a good correlation between immune response and clinical protection, licensure of a GBS vaccine could also be based on antibody measurement, if a specific antibody response can be correlated with protection.[62–65] A review undertaken in 2019 synthesised the scientific evidence to define a serocorrelate of protection against GBS disease based on studies of natural infection.[66] In such a scenario, a phase IV study will be required post-licensure to assess effectiveness. This is the same approach used for meningococcal B vaccine licensure in the United Kingdom.[67]

Assays for Antibody Quantification and Evaluation

The concentration of antibodies against serotype-specific CPS antigens can be quantified using standard immunogenicity assays (IA). However, there are several limitations to using current IA as the concentration measurement is very dependent on how well CPS is immobilized on an ELISA plate. There are other technical difficulties including inconsistent binding of immobilized CPS to the solid phase or a nonspecific serotype-independent binding, of antibodies with lower avidity.[49] There has been much debate about the methods of CPS-binding, for example that used in pneumococcal assays (poly-L-lycine) or the novel biotin-streptavidin methods.[66,68,69] The biotinylated method has the advantage of being able to use mass spectroscopy to determine the exact binding site of the biotin to the CPS, enabling the monitoring of any potential conformational changes to the CPS.[69] However, whether this affects the performance of the assay is unknown.

The radio-antigen binding assay (RABA) had been used successfully to quantify levels of anti-GBS antibody as it measures antibody in its native state;[70] however, as with most assays, there are several limitations, including low detection sensitivity, difficulties in obtaining and using radioisotopes and limited ability to quantify IgG isotopes. Therefore, it is imperative for techniques quantifying capsular serotype-specific antibodies in serum to be sensitive as well as serotype-specific.[71] Multiplex immunoassays (MIAs) based on the Luminex technology are very useful in simultaneously quantifying the concentration of IgG antibodies against the capsule of multiple GBS serotypes. A Luminex-based direct immunoassay (dLIA) was recently developed for pneumococcal CPS.[68] The latter could generate up to 143 test results in a single 96-well plate using similar principles to an ELISA assay for evaluating vaccines in clinical trials. MIAs quantifying IgG antibodies against the six most frequent GBS capsular variants (Ia, Ib, II, III, IV and V) would prove to be extremely useful in the standardisation of the assay used for GBS vaccine development.

The functionality of antibodies may also have a significant role in protection against GBS infections. ELISAs are limited in this aspect as they cannot distinguish between antibodies with low avidity and those with high avidity. Therefore, the opsonophagocytosis killing assay (OPkA) enables the measurement of antibody functionality.[72] For the validation of the pneumococcal vaccine, the granulocytic cell line (HL60) was used, making the assay more reproducible.[73] The assay was also multiplexed, which proved to be advantageous as it was less time-consuming and the amount of serum needed for the assay was reduced.[74,75] Although a multiplexed OPkA for GBS (GBS-MOPA) has been developed for use in newborns, it only targets serotypes Ia, III and V.[76] Therefore, a GBS-OPA targeting all possible vaccine serotypes is necessary for future GBS vaccine development and evaluation.

Protein Vaccines

Although CPS-conjugate vaccines have been demonstrated to induce good immunogenicity, there are still several limitations, including potential immune interference with other types of conjugate vaccines such as *Haemophilus influenzae* type b, meningococcal and pneumococcal conjugate vaccines.[77,78] There is also the possibility of serotype replacement and switching post vaccination, as well as an increase in non-encapsulated GBS strains.[79–81] Alternative vaccine candidates include structurally conserved protein antigens which can induce a strong immune response against most GBS strains. In order to develop a vaccine that can confer broad protection against GBS, several studies have identified proteins common to all GBS strains. Members of the Alp family, including AlphaC, Alp1 (Epsilon), Alp2, Alp3 (R28), Alp4 and Rib, are the most well-known and abundant surface proteins. These proteins are expressed by different serotypes (Table 2).[82–85] Although there have been preclinical vaccine investigations using AlphaC, Alp3 and Rib proteins, the heterogeneity of the Alp sequence restricts the use of Alp proteins as potential vaccine candidates.[86,87] Nonetheless, a protein vaccine

Table 2 Alp Family Proteins Commonly Expressed in Different GBS Serotypes

GBS Serotype	Alp Family Protein Commonly Expressed
Ia	AlphaC, Alp1, Alp2
Ib	AlphaC
II	AlphaC, Rib
III	Rib, Alp2
V	Alp2, Alp3

Notes: This table includes only the Alp family proteins that are mostly expressed by the common serotypes causing infant GBS disease; The uncommon serotypes IV, VI–IX have not been included as their expression of proteins in the Alp family have not yet been characterized. Alp1 can also be referred to as Epsilon and Alp3 as R28.

based on the highly immunogenic N-terminal domains of AlphaC and Rib (GBS-NN) has been studied in a Phase I clinical trial (NCT02459262). The participants included 240 healthy women who were immunised with one or two doses of GBS-NN, generating an elevated level of GBS-NN specific antibodies by over-30 fold in both groups.[82,88] GBS expresses either one of two-allelic serine-rich repeat 1 (Srr1) and serine rich-repeat 2(Srr2) proteins,[89] both of which can bind to fibrinogen Aα chain through the "dock, lock and latch" mechanism, thus contributing to the pathogenesis of GBS meningitis and GBS colonisation of the vaginal surface.[89–91] The antigenic latch domain consisting of 13 amino acids containing both Srr1 and Srr2, was shown to play a significant role in GBS pathogenesis. Murine models have exhibited serotype-independent protection against GBS infection after being vaccinated with the latch-peptide vaccine.[92] C5a peptidase, which is a GBS virulence factor, was also considered as a universal protein vaccine or a carrier for GBS-CPS.[93] C5a peptidase encapsulated within microspheres composed of lactic acid and glycolic acid co-polymer triggered systemic and mucosal immune responses in murine models, thus protecting them against multiple GBS serotypes.[94,95] Another type of surface protein are the pilus proteins, which, in preclinical and human studies, were found to induce immune responses against different GBS serotypes.[30,96,97]

Next Steps, New Perspectives

The most advanced vaccine candidates are hexavalent vaccines including serotypes Ia, Ib, II, III, IV, and V, which are now in phase II trials.[54] Immunogenicity and safety of these candidates has been demonstrated in non-pregnant and, more recently, in pregnant women.[22] Protein vaccines are in phase I trials including human studies in non-pregnant women.[88,92,94-96]

Several obstacles exist in moving the most advanced vaccines into phase III clinical trials. Given the relatively low incidence of GBS disease in Europe and the USA, large numbers of participants would be needed to determine vaccine efficacy.[98] In addition, obstacles exist in determining what concentration of antibody is required to protect the infant for the duration of the period at risk (the 3 first months of life) as there are currently no internationally recognised correlates of protection with which to interpret individual study results.[99] Therefore, a serocorrelate of protection against GBS is needed to accelerate the licensure of a vaccine. The standardisation of reagents to measure antibodies against GBS is crucial for the establishment of serological correlates of protection and for the development of GBS vaccines. The GASTON consortium was recently set up with this aim.[66]

On the other hand, efforts to identify common proteins to all GBS strains have been made in order to find a vaccine that confers protection against all GBS serotypes. Recent use of molecular techniques, such as multilocus sequence type (MLST) and whole-genome sequencing (WGS), have allowed us to better characterise the GBS structure, as well as to identify the virulent lineages such as ST17 hypervirulent strain, strongly associated with serotype III. As it is important to understand the genetic lineages that are more likely to cause GBS disease in order to better define vaccine targets, a global genomic survey of GBS has been established (the JUNO project).[100]

Other Areas for Future Research

As mentioned above, it is important to establish rates of maternal colonisation and GBS disease worldwide, as well as to understand the relationship between colonisation and invasive infection, to assist assessments of vaccine efficacy. Regional serotype distribution is also required, especially from many LMIC were few data are currently available.

Once a vaccine is licensed, the number and timing of doses for optimum coverage during pregnancy and the number of doses required for full protection needs to be determined. There are other knowledge gaps remaining, including the placental transfer of vaccine-induced immune responses in special populations, such as women infected with HIV, malaria, syphilis and hepatitis B, among others. These infections, highly prevalent in LMIC, may alter the immune response to vaccines and impair antibody transfer across the placenta. A phase II trial using a GBS trivalent vaccine (Ia, Ib, III) undertaken in Malawi and South Africa among 270 pregnant women with or without HIV infection (NCT01412801) showed that the immune response to

vaccines and serotype-specific antibody concentrations in infants at birth were lower in the HIV infected group.[101] Maternal immunisation policies require understanding of the role of these endemic infections in generating immune responses that ensure adequate protection of infants in these challenging environments.[102,103]

Finally, cost-effectiveness evaluation is required. Cost-effectiveness studies have indicated that the predominant cost drivers are disease incidence, immunisation coverage and vaccine efficacy.[104] In high income countries, where GBS disease is well characterized, it has been shown that a maternal vaccine would be more cost-effective compared to IAP and doing nothing.[105] A population-based economic analysis in the USA concluded that vaccinating 80% of pregnant women with a vaccine that prevents 80% of cases among infants born at or after 34 weeks of gestation would prevent approximately 4100 neonatal cases annually with a net savings of 131 million USD.[105] A study in South Africa also concluded that GBS maternal vaccination would be very cost-effective by WHO guidelines.[106] This study reported that, assuming that vaccine efficacy varies from 50% to 90% with a 75% coverage, GBS immunisation alone, without IAP prevention, would prevent 30–54% of infant GBS cases compared to doing nothing. In contrast, risk factor based-IAP alone prevents 10% of infant GBS cases compared to doing nothing. Furthermore, at a vaccination cost between 10 and 30 USD, and mid-range efficacy, vaccine introduction costs range from 676 to 2390 USD per disability-adjusted life-year (DALY) averted, compared to doing nothing.[106] A modeling study of different sub-Saharan African countries showed that maternal GBS immunisation could be a cost-effective intervention, with cost-effectiveness ratios similar to other recently introduced vaccines.[107] 37 African countries were clustered in four different groups according to their economic and health resources and public health outcomes. One country of each cluster was chosen as representative: Guinea-Bissau, Uganda, Nigeria and Ghana. At equal coverage to that of pregnant women that attend four or more antenatal visits and with vaccine efficacy of 70%, maternal vaccination would prevent one-third of GBS cases in Uganda and Nigeria, 42–43% in Guinea-Bissau and 55–57% in Ghana. For a vaccine price of 7 USD per dose, maternal vaccination would cost from 320 to 350 USD per DALY averted in Guinea-Bissau, Nigeria and Ghana, as well as 573 USD in Uganda. The vaccine would be less cost-effective in Uganda as neonatal mortality seems to be lower.[107] A recent study by our group of cost-effectiveness of a potential hexavalent vaccine in the Gambia indicated that disease incidence was the key factor in determining cost-effectiveness in a low income setting as the cost of doing nothing is very inexpensive as infants would classically die at home without receiving treatment.[108] These studies, together with more epidemiological data in LMIC, might raise the impact resulting from a vaccine prevention strategy.

Data provided in this review demonstrate that obtaining a vaccine for pregnant women is a promising strategy to prevent neonatal and infant GBS disease. Consensus among public health institutions and sponsors is now a priority to allow this breakthrough that will help reduce neonatal and infant mortality, especially in the most vulnerable populations.

Disclosure

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