Review

Considerations for a phase-III trial to evaluate a group B *Streptococcus* polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young-infants

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ABSTRACT

In 2010, an estimated 393,000 infection-related neonatal deaths occurred worldwide with Group B streptococcus (GBS) being a leading cause. Prevention of early-onset disease (0–6 days; EOD) is currently focused on intra-partum antibiotic prophylaxis to mothers identified as being at risk; such strategies reduce EOD by 75–80% but are resource-intensive and logistically-difficult to implement in developing countries. Vaccination of pregnant women is an alternate strategy for preventing both EOD and late-onset disease (7–89 days; LOD). A trivalent GBS polysaccharide-protein conjugate vaccine (GBS-CV) composed of capsular epitopes from serotypes Ia, Ib and III is undergoing phase-II evaluation among pregnant women in Europe, North America and Africa. These serotypes cause 70–80% of all invasive GBS disease in early-infancy. Maternal anti-GBS antibodies are associated with protection from EOD, however, since a correlate of efficacy has not been defined, a phase III efficacy trial may be required for licensure. Criteria for selecting appropriate sites include sufficiently high GBS incidence in large birth cohorts, as well as adequate clinical and microbiological diagnostic skills and capacities. Alternate pathways to licensure should be explored, e.g. identification of serological correlates of protection with subsequent phase IV studies establishing vaccine-effectiveness against invasive GBS disease. Conducting a randomized, placebo-controlled efficacy trial, however, has the additional advantage of also being able to evaluate the role of GBS contributing to neonatal culture-negative sepsis, stillbirths, prematurity and low-birth weight.

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Contents

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1. Introduction

Significant progress has been made in reducing under-5 childhood mortality between 2000 and 2010, [1] including prevention of approximately 2.5 million deaths through vaccination alone. There have, however, been minimal advances in reducing mortality rates occurring during the neonatal period. [1] Globally in 2010, approximately 40% of all under-5 childhood deaths occurred during the neonatal period. Of the 3.07 million neonatal deaths, approximately 0.393 million (95%Confidence Interval: 0.252–0.552) were due to sepsis and meningitis. Although the role of Group B streptococcus (*Streptococcus agalactiae;* GBS) as a cause of neonatal death has not been conclusively quantified and may vary even between industrializing countries [2,3] there are recent African studies confirming it as a leading cause of neonatal sepsis [4–6]. The current incidence in some African countries is not dissimilar to rates in developed countries during the 1980–90s, prior to implementation of intra-partum antibiotic prophylaxis (IAP) as a strategy for preventing early-onset disease (within 6 days of birth, EOD) [7,8]. Risk factors for developing invasive GBS include maternal GBS vaginal-colonization, prematurity, prolonged rupture of membranes (>18 h), chorioamnionitis, young maternal age, black race and having a previous infant with invasive GBS disease [9].

There have been substantial advances in prevention of GBS-EOD in industrialized countries, whilst limited progress has been made in low-middle income countries [3]. The use of universal screening for GBS vaginal-colonization during pregnancy and intra-partum antibiotic prophylaxis (IAP) was associated with a significant reduction in incidence of EOD in the US from 1.7/1000 in the early 1990s to 0.34/1000 in recent years, an incidence comparable to disease rates occurring between 7 and 90 days of age (i.e. late-onset disease; LOD) [9]. Progress has also been observed in other developed countries [10]. Challenges with the universal screening and IAP approach as an intervention strategy include needing to identify vaginal-colonization during the last trimester, changes in vaginal-colonization status post-screening and ensuring receipt of IAP at least 4 hours prior to delivery [9,11,12]. In addition to the resource-intensive nature of this intervention, the high proportion of deliveries (40–70%) outside of health care settings in low-income countries limits the feasibility of adopting this strategy in such settings [13]. Additionally, IAP has not reduced the incidence of LOD, an important issue as this is the age group where the majority of meningitis occurs [7,8].

The protection of neonates and young-infants against infections by vaccination of pregnant women occurs mainly by trans-placental antibody transfer to the fetus. This is exemplified by the success of improved tetanus-toxoid immunization coverage in pregnant women resulting in >80% reduction in neonatal-tetanus infection globally between 1999 and 2011 [14]. Also, recently influenza vaccine immunization of pregnant women has been shown to reduce the risk of confirmed-influenza illness by 63% in their babies up to 6-months of age, [15] as well as being associated with lower rates of premature delivery and higher birth weights of newborns [16–18].

The potential of GBS vaccination of pregnant women to reduce the risk of newborn invasive disease is supported by studies which demonstrate that higher maternal anti-capsular serotype-specific antibody concentrations are associated with a lower risk of neonatal-GBS disease. Investigational studies on GBS polysaccharide-protein conjugate vaccine (GBS-CV) have been underway since the 1990s, [19,20] and have established the immunogenicity of mono-valent vaccines in pregnant women [19–21]. Further clinical development of GBS-CV during pregnancy has, however, been impeded because of the success of IAP in reducing the risk of EOD in industrialized countries and concerns around potential liability-issues. More recently, a tri-valent polysaccharide-protein conjugate vaccine has advanced to phase II clinical trials among pregnant women in Europe, Canada and Africa. This vaccine includes the polysaccharides of serotypes Ia, Ib and III, which together cause 78.8% of invasive disease during early-infancy [3]. Studies currently underway with this vaccine include evaluation of its safety in healthy pregnant women (Clinical Trials Gov: NCT01193920), determining optimal formulation and dosing schedules (Clinical Trials Gov: NCT01150123), kinetics of antibody transfer to the newborns and persistence of antibody during early infancy (Clinical Trials Gov: NCT01446289) and the effect of maternal HIV and malaria co-infection on immune responses and kinetics of antibody transfer to newborns (Clinical Trials Gov: NCT01412801).

In July 2012, Novartis, sponsored a scientific meeting to discuss the further clinical evaluation of this trivalent GBS-CV, geared toward future licensure of this vaccine. This included a workshop on planning a Phase III study to evaluate the safety and efficacy of maternal GBS-CV immunization during pregnancy to prevent GBS disease in their infants. This manuscript summarizes key discussion points and corroborating evidence aimed at planning such a study.

2. Site selection considerations

2.1. GBS epidemiology

The success of IAP in reducing EOD in Europe and North America is a relative impediment to undertaking a GBS-CV efficacy trial in such settings. With an estimated current incidence of invasive GBS during early-infancy of 0.57 to 0.67 per 1000 live-births [3], an efficacy trial in such settings would probably require >150,000 women to detect a 75% reduction in EOD and LOD. This sample size is driven not just by the lower overall disease incidence but also relative contribution of vaccine-serotypes (70–80% of the total incidence) and the approximate 15–20% of invasive disease that occurs among premature births (<34 weeks gestation) [8,22], who may be less likely to acquire trans-placental antibody [23].

A phase III study evaluating protection against early-infancy confirmed invasive GBS disease will thus only be feasible in settings with an established high disease burden (i.e., ≥1–2 per 1000 live births). In a recent review of epidemiologic studies undertaken since the late 1990s, an incidence of invasive GBS disease of ≥1.0 per 1000 live-births was only identifiable in six countries in studies undertaken since the late-1990s. Of these, IAP has since been implemented in Norway, Slovakia and USA [3]. Accordingly, the only other countries with a current established incidence of invasive GBS ≥1.0 per 1000 live births and where IAP has not been implemented are located in Africa, and include Kenya, Malawi, Tunisia and South Africa [3]. In South Africa, the incidence of invasive GBS disease has remained unchanged (2.97–3.06 per 1000 live-births) between 1997 and 2007, despite standard-of-care being IAP during labor for women with identifiable risk-factors for neonatal GBS disease

Table 1
Timing of onset of invasive Group B Streptococcus (GBS) invasive disease in infants aged less than three months in Soweto, South Africa between 2005 and 2008.

Year	Early onset GBS (within 7 days of birth)								Late onset disease
	0 days	1 day	2 day	3 day	4 day	5 day	6 day	Total	7–90 days
2005	23	14	0	0	3	2	3	45	27
2006	26	7	3	0	1	1	1	39	29
2007	35	3	1	0	0	0	1	40	24
2008	46	4	0	0	0	1	1	52	34
Total	130	28	4	0	4	4	6	176	115

[4,24]. Further robust epidemiological studies are needed, as these figures are most likely an underestimate of the true incidence of neonatal GBS disease, especially in Africa and Asia due to diagnostic challenges [3]. More recently, hospital-based studies in the Dominican Republic and Hong Kong revealed an incidence of invasive GBS disease of 2.52 and 1.14 per 1000 live births, respectively [25]. This initiative has contributed toward identifying settings with a high incidence of invasive GBS which could be involved in future phase III trials. Assuming a mean incidence of 2.0 per 1000 live births of the composite of EOD and LOD of invasive GBS among newborns at the sites that would be involved in the GBS phase III efficacy trial, and adjusting for approximately 75–85% of these cases being due to vaccine-serotypes of which 70–80% are eligible per protocol for inclusion as outcome cases, the likely incidence of eligible cases among controls would be approximately 1.05–1.36 per 1000 live births. The sample size calculation to detect a 75% reduction with the lower limit of the 95% confidence interval for efficacy of >20%, with the above incidence is a range of 40–60,000 overall.

Additional features of trial sites include the identification of experienced clinical-trialist and institutions with well-established and accredited Ethics Review Committees and Regulatory Authorities, to ensure the highest compliance with Good Clinical Practice standards. Although there are other vaccines which are now recommended during pregnancy, including tetanus toxoid, inactivated influenza vaccine and diphtheria-acellular pertussis-tetanus toxoid (dTaP) vaccines, these vaccines have only been recommended for pregnant women following decades of use and accumulated safety data in other populations, at times following inadvertent vaccination of pregnant women and more recently with additional safety studies [26,27]. The GBS-CV is currently the most advanced vaccine under clinical-development, which is being designed specifically for vaccination during pregnancy to confer protection to the newborn infant. This represents a shift in the evaluation of investigational-vaccine products, where pregnancy is frequently an exclusion criterion for participation in the early clinical-evaluation phase. Another novel concept for the development of this vaccine is that the risk-benefit of the vaccine will need to be assessed in two separate populations. Consequently, stringent criteria regarding sufficient medical care and infrastructure to enable adequate identification of adverse events in both vaccinated pregnant women and their newborn infants need to guide the selection of clinical-sites for the phase III study.

2.2. Case detection and diagnostic methods

In addition to the pre-requisite of there being an established burden of disease among neonates, it would also be necessary that the selected sites have the necessary laboratory-infrastructure for optimal identification of causes of neonatal sepsis, including GBS. Differences in laboratory methods, where the yield of GBS and reported incidence of invasive disease are higher in settings where automated rather than manual methods of culture have been used, may explain in part the differences in incidence of invasive GBS disease between low and middle-income countries [2]. Adequate microbiological GBS diagnosis will further depend on the ability to

selected sites to provide the necessary medical infrastructure that allows for early availability of specimens within 24 h of onset of GBS disease [3].

2.3. Local health care considerations

As the majority of EOD occurs within 24 h, and frequently at birth, ensuring that deliveries are likely to occur at a health-center where newborns identified with early onset sepsis can be timeously investigated would be essential. Over a five-year period in South Africa, overall 60.9% of invasive GBS in infants <3 months was EOD, of which 73.9% was diagnosed on samples collected within 24 h (frequently at birth) and 89.8% within 48 h of birth (Table 1). Similarly, the majority of EOD presented within 24 h of birth in USA and the UK [28,29].

A major bias of studies investigating the etiology and pathogen-specific incidence of neonatal sepsis in developing countries, is the exclusion of newborns with sepsis or pneumonia that presents soon after delivery in those born outside of health care facilities. Many such newborns, especially where there are limited readily-accessible health-care facilities, may succumb to invasive GBS disease without having been investigated. Consequently, pathogens identified in such settings, particularly in relation to EOD, may provide a biased representation of community-acquired pathogens acquired from the surrounding environment rather than due to infections occurring in-utero or during delivery [30].

In summary, the number and types of sites to be involved in a phase III study would largely be determined by the realities of identifying sites which demonstrate a high burden of invasive GBS disease during early-infancy, which should be coupled with the availability of qualified and experienced clinical-trialists, adequate microbiologic diagnostic capacity and expertise, clinical trial management skills, internal quality control, GCP compliance as well as availability of regulatory and institutional safety monitoring infrastructure. Such sites should be able to enroll sufficient number of women that would contribute to clinical endpoints given that only 1–2 confirmed cases of GBS among neonates would be identified for every 1000 women enrolled.

2.4. Study design issues and ethical considerations

The extent to which a clinical-study should intervene in protecting individuals from developing disease for which interventions already exist, even if not standard-of-care in the local context, has previously generated controversy with HIV-prevention studies. It has been argued that placebo-controlled trials in any setting, irrespective of the resource and logistical issues which prohibit its use as part of local standard-of-care, are not justified [31]. Conversely, it has also been argued that varying standard-of-care is determined by the realities and resource-availability in different settings; and represents an opportunity for evaluation of new clinical interventions that may have long-term and sustainable benefits in those settings [32]. The presence of IAP based on screening for GBS colonization during pregnancy for the prevention of EOD represents a similar issue in the context of evaluating GBS-CV. Although this

does not directly impact on whether GBS-CV can be compared to a placebo, as all eligible women could still receive IAP, the use of IAP based on the GBS colonization status of the mother would result in a limited residual burden of GBS disease that would preclude the ability to conduct an efficacy trial. The decision on whether women should be screened for GBS-colonization coupled with IAP being provided, in settings where this strategy is not standard-of-care, needs to be contextualized within the code of the Declaration of Helsinki for conduct of clinical trials in humans, which highlights the obligation to provide the best available local standard-of-care. Implementation of a sustainable IAP program, based on screening for vaginal-GBS colonization during pregnancy in low and middle-income countries, is unlikely to succeed due to factors such as limited-resources for laboratory testing, high proportions of births occurring outside of health facilities and limited staffing even within health care facilities. Indeed even in high-income countries (e.g., the United Kingdom), universal screening to guide IAP has been evaluated but not implemented as part of routine obstetrical care. Consequently, it was considered justifiable that screening for GBS-colonization and provision of IAP not be undertaken as a study-specific procedure in settings where it was not standard-of-care. Potential study-participants should, however, be made aware of the availability of such preventative strategies, which may be available to them outside of the study and health-care program. The sample size of the study may need to be adjusted upward in anticipation of lower attack rate of neonatal GBS disease should many women choose to exercise this option. Although risk of EOD may be substantially reduced, as the newborns of such mothers will still be at risk of developing LOD, their participation in the study remains justified. Study-sites should be encouraged to ensure compliance with existing standard-of-care procedures, which may include targeted IAP of women with risk factors for GBS-EOD, e.g. as currently exist in South Africa.

In lieu of IAP not being implemented as a study procedure, the merits of having a control group who could potentially derive some benefit from another vaccine rather than a placebo-control arm was discussed. In addition to the recommendation for tetanus-toxoid vaccination during pregnancy, recently the WHO recommended that pregnant women be considered as a priority target-group for influenza vaccine immunization, [33] as well as dTaP being recommended for pregnant women in the US and in the UK [27]. Whilst there are safety data for the use of most of these vaccines now recommended in pregnant women, [27] the uptake of these recommendations are limited. Randomization of pregnant women to selectively receive one of the currently recommended vaccines as a control-group, in lieu of placebo, was not considered to be a feasible option. It was, however, agreed that all women should receive any country-specific recommended vaccines as standard-of-care if indicated and that administration of the study-vaccine could occur concurrently in a phase III trial. Furthermore, randomization which included a placebo-control group was considered to be important to establish a robust safety database to supplement the safety data on the mother, fetus and neonate which will have been derived from the small number of participants involved in the current Phase I-II GBS-CV trials.

Current phase I-II GBS-CV studies will also assist in informing the inclusion and exclusion criteria to be used for a large phase III efficacy trial. It was decided that the gestational-age at which randomization and receipt of study-vaccine occur should be delayed at least until the latter part of the second-trimester, to avoid any (theoretical) effect of maternal-vaccine on embryogenesis. Given the disparate methods for estimating gestational age, it is important to evaluate those methods (ultrasound, LMP, fundal height) and implement a single standardized method across study sites. The timing of vaccination will also be influenced by the current immunogenicity studies with particular consideration of the

magnitude of antibody responses induced by vaccination and the subsequent kinetics, including waning of antibody.

2.5. Study endpoints–disease prevention

Although not exclusively, licensure of new, novel vaccines, has generally been based on establishing efficacy against the disease in question. In the case of GBS-CV, the natural primary efficacy end-point would be to establish protection against the composite of EOD and LOD vaccine-serotype specific GBS invasive disease. The extent of this protection may however, be influenced by a number of important factors including when maternal vaccination occurs in relation to the birth of the child (allowing sufficient time for a maternal antibody response), the gestational age at birth (placental transfer will be less in those born prematurely) and the chronological age of the infant (antibody levels will wane over the first 2–3 months of life). Although these factors need to be considered in the analysis plan, narrowing down the spectrum of disease to be included in the primary endpoint of the phase III study may diminish the generalizability of the study findings, as well as the number of outcome cases that would be observed in the cohort. Accordingly, it was proposed that efficacy be measured against prevention of vaccine-serotype specific invasive GBS disease occurring in infants aged 0–90 days and who were born at least four-weeks after vaccination of the mother. Further end-points may include limiting efficacy estimates limited to only those infants who had been born at term, should the kinetics of antibody transfer to the fetus be impaired in premature born newborns; as well as stratified analysis for vaccine-serotype EOD and LOD independently. Another secondary efficacy objective, would be to determine efficacy against invasive GBS disease within 90 days of birth irrespective of serotype.

2.6. Study endpoints–immune correlate of protection

An alternate pathway to licensure of some new-vaccines is based on immunologic endpoints for those diseases for which immunological correlates of protection have been established from previous vaccine-studies or through sero-epidemiological studies. In such instances, new vaccines to be licensed, need to demonstrate non-inferiority for immunogenicity measures of either sero-protection or sero-conversion compared to other comparator licensed formulations [34]. This has been the approach to the initial licensure of most meningococcal vaccines where the presence of bactericidal antibody activity has been accepted for licensure as a surrogate marker for disease protection [35]. A compelling case can be similarly made for protection against GBS disease as well.

Antibodies to GBS antigens are transferred trans-placentally to fetuses mainly after 34 weeks of gestational age [36,37]. These antibodies are of IgG isotype [38] and include serotype specific anti-capsular antibody and surface-protein antibodies [39,40]. Numerous studies have demonstrated an association between low maternal anti-capsular antibody levels and the risk of developing invasive GBS disease in the newborn. In an early study by Baker et al., using a radioactive antigen binding assay, [41] median levels of anti-capsular antibody to serotype III in infants with GBS sepsis and meningitis were lower than among controls, [41] similar to a larger subsequent study which also identified lower median anti-capsular serotype III antibody levels in both mothers and infants with GBS disease among cases compared to control mother-infant dyads [42]. Using an enzyme linked immunosorbent assay (ELISA), Suara et al. also reported that serotype-specific higher antibody levels to serotype III and serotype Ia was possibly associated with protection against invasive disease in The Gambia [43]. Additional insight was provided by a case control study conducted in the US,

[44,45] in which maternal-blood and/or cord-blood was obtained from a birth cohort of 138 740. This cohort included sera from 50 cases of EOD due to serotype Ia, 26 cases of type III and 479 matched-controls, lower anti-capsular bodies levels to serotypes Ia and III were again observed among cases compared to controls. Other in vitro (serotype III) and mouse model studies (serotype Ia) support the link between serotype-specific capsular antibody (>1 μg/ml) and phagocytosis and protection (90% protected against a lethal challenge of homotypic-serotype GBS) [46,47]. Direct comparability between these various reported anticapsular antibody levels protection against invasive disease is hindered by variation between the assay methods, as well as the absence of any standardized reference sera being used in these studies.

Use of a serological endpoint offers a resource- and cost-efficient pathway to licensure of a vaccine; despite the available data it remains unclear whether the current epidemiological and animal-model studies would permit licensure of a GBS-CV through immunogenicity studies alone. Augmenting antibody studies with functional assays (e.g., opsonophagocytic analyses) may further support such an approach. Licensure by antibody threshold would require engagement with the various licensing regulatory authorities and could be supplemented with phase-IV studies in which vaccine effectiveness can be evaluated by time-series ecological studies or by case-control studies. Establishing an immunologic correlate of protection against invasive GBS disease could also be important to licensing future GBS-CV formulations such as those with additional serotypes or which use different protein-conjugates. Also, establishing an antibody threshold correlating with protection, could fulfill potential regulatory requirement for clinical-trial data from populations similar to where the vaccine is being submitted for licensure.

In addition to evaluating the efficacy of maternal vaccination with GBS-CV against early-infancy clinically-confirmed invasive disease, an adjunct measure may include the efficacy of the vaccine in reducing the risk of subsequent acquisition of vaginal-colonization and/or clearance of vaccine-serotype colonization between the time of vaccination and delivery. This is premised on GBS vaginal-colonization being the major risk factor and dominant pre-requisite for acquisition of GBS by the fetus or newborn. Recto-vaginal colonization by GBS is common (10–37%) during the reproductive-years of women and 30–70% of babies born to colonized women develop mucosal or skin-surface colonization when born. Approximately 1–3% of such-colonized newborns develop EOD [2,3]. These estimates were corroborated in a recent cohort study of 8129 pregnant women and their newborns in South Africa. The prevalence of vaginal GBS colonization was 20.9% among the pregnant women during labor and 57% of their newborns had mucosal/skin surface colonization by the homotypic serotype at birth [4,48,49]. Based on the vaginal-colonization rates in mothers and acquisition rates in the newborns, the expected number of cases of EOD based on 1–3% of colonized newborns developing disease, ranged between 10 and 30 cases of EOD, with a resultant incidence of 1–3 per 1000 live births. The actual observed incidence of EOD among neonates in this cohort was 2.0 per 1000 live births [4].

These data support the strong association between maternal-GBS colonization and the risk of developing EOD. Consequently, if vaccination could be shown to reduce or eradicate vaginal GBS colonization by the time of delivery of targeted invasive serotypes, the risk of developing EOD due to those serotypes would be diminished. Further ecological data supporting this include epidemiological studies which report on geographic variation in incidence of EOD in different regions and communities across the world. Although the reasons for variation in incidence of EOD may be multi-factorial, there remains an association with a lower prevalence of vaginal-colonization by GBS among pregnant women is such settings, especially in Asia [2]. The immune mediators which are associated with reduced risk of vaginal GBS colonization in pregnant women are yet to be established.

GBS has been associated with still-births, premature deliveries and birth-asphyxia [3]. The causes of these adverse fetal and early-newborn outcomes are multi-factorial, and frequently as in the case of still-births, any association with GBS disease may be under-recognized, particularly in high-burden settings with limited laboratory capacity and where post-mortems are seldom undertaken. The availability of a highly efficacious GBS-CV in protecting against invasive-disease may provide an opportunity to probe the role of GBS in contributing to still-births, birth-asphyxia and premature labor. Although abnormal fetal-outcomes would be collected as part of safety-data, they should also be analyzed in the context of vaccine-efficacy, especially in the absence of any alternate biological explanations. Also, a highly efficacious GBS-CV evaluated in a randomized-controlled trial could probe the contribution of GBS to all-cause early-infant sepsis and pneumonia, which in the majority (>90%) of neonates is culture-negative [4]. Although many of these outcomes are non-specific to GBS, even a small change in the proportion of such outcomes in newborns of mothers who received GBS-CV could potentially have far greater public-health implications than simply establishing efficacy against vaccine-serotype, invasive-disease.

2.7. Vaccine safety

As in any new vaccine development, vaccine safety is a key consideration. Unique to a vaccine for which pregnant women are the recipients, safety assessment will be focused on both the mother and the fetus/infant. Current phase II studies include neuro-developmental assessments up until one-year of age in the infants born to vaccinated mothers. The duration of safety follow-up would require agreement with regulators but if a large phase III efficacy study is conducted, adverse events which occur with lower frequency could be evaluated during the pre-licensure phase of development.

3. Conclusion

Successes of maternal immunization with tetanus-toxoid and influenza-vaccine to protect neonates up until six months of age from the targeted diseases, coupled with immuno-epidemiological studies support the potential of GBS-CV immunization during pregnancy for the prevention of early-infancy invasive-disease. The feasibility of conducting a Phase III efficacy study requires the collaborative and dedicated effort of highly committed stakeholders to clinically develop the most advanced GBS vaccine through licensure. The clearest path toward licensure is through a traditional vaccine efficacy study with an endpoint of disease prevention in young infants, although further explorations of licensure through an immune correlate are warranted. Regardless of the agreed path, establishing an immune correlate of protection against invasive GBS in young infants, either through epidemiological studies or within the context of the study, is an important additional step to provide confidence in the applicability of the data beyond the population evaluated in the Phase III efficacy study.

4. Conflict of interest

5. Authors' contribution

The first draft was written by SAM. All the authors subsequently critically reviewed the manuscript and approved the final version.

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