FDA Briefing Document

Vaccines and Related Biological Products Advisory Committee Meeting

May 17, 2018

Evaluation of the Effectiveness of Vaccines Intended to Prevent Group B Streptococcal Disease in Infants

Table of Contents

1.0 Introduction

Group B *Streptococcus* (GBS, also known as *Streptococcus agalactiae*) causes substantial infant morbidity and mortality globally, and investment in vaccine development to address this unmet medical need has been widely supported. The development, licensure, and distribution of an effective vaccine that protects against invasive GBS disease in the newborn and young infant would be expected to significantly reduce disease, especially in low and middle income countries (LMIC). In 2015, the WHO Product Development for Vaccines Advisory Committee identified GBS as a high priority for vaccine development.[1] Given that the disease onset is often within the first few hours of life and may even affect the fetus prior to delivery, a strategy of immunizing pregnant women (maternal immunization) is expected to have the greatest impact on protecting infants from GBS.

On November 13, 2015, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met to discuss the topic, "Considerations for evaluation of the safety and effectiveness of vaccines administered to pregnant women to protect the infant." The Advisory Committee was asked to address the use of serological endpoints for maternal immunization vaccines. The outcome of that advisory committee meeting was that "serological markers may be acceptable to infer vaccine effectiveness to protect the infant from disease. However, the adequacy of using serological endpoints as markers of passive protection in the infant will depend on the vaccine used in maternal immunization programs."[2] For GBS vaccine development in countries where the disease incidence is low, such as in the U.S. and other high income countries (HIC), potential ways to demonstrate vaccine effectiveness and appropriate endpoints for evaluation, including clinical disease and immunologic endpoints, are under discussion.

Purpose of the VRBPAC

The primary focus of the session will be to discuss approaches for evaluating the effectiveness of GBS vaccines in preventing infant disease in the context of maternal immunization.

2.0 Background

GBS is an encapsulated, gram-positive bacterium that is part of the normal vaginal and gut microbiome. GBS can be classified into serotypes by the structure of the capsular polysaccharide (CPS). Ten GBS serotypes have been identified: Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX. Globally, as well as in the U.S., serotypes Ia, Ib, II, III, and V account for up to 97% of invasive disease in young infants.[3, 4]

Research on GBS vaccines has mainly focused on the development of antigens that induce serotype-specific antibodies, although work has also been done towards antibody production against GBS-specific surface proteins. Natural protection from GBS disease is thought to be serotype-specific and vaccines with polysaccharide-protein conjugates are expected to provide protective immune responses. The polysaccharide-protein conjugate approach used for GBS vaccine development parallels that used in the successful development and U.S. licensure of *Haemophilus influenzae* type B, pneumococcal, and quadrivalent meningococcal vaccines.

3.0 GBS Clinical Disease

GBS can cause serious disease in infants and is categorized by the age of the infant at disease onset. Early-onset disease (EOD) occurs within the first six days after birth. It is usually noted within the first 24 hours (72%) and presents as bacteremia/sepsis without a focus (83%), pneumonia (9%), or meningitis (7%) (U.S. data).[4] Late-onset disease (LOD) occurs from days 7 to 89 after birth (median 37 days) and most commonly presents as bacteremia/sepsis without a focus (65%) and meningitis (27%), but can also present as cellulitis (3%), pneumonia (3%), septic arthritis, osteomyelitis, and other rare focal infections (U.S. data).[4] Globally, meningitis may be a more common presentation of EOD (16%) and LOD (43%).[3] Late, late onset disease is very rare, occurring in infants older than 3 months of age, primarily in those born at < 28 weeks gestation or who have immunodeficiency. In the U.S., EOD is most often caused by serotype Ia (30%) and serotype III (28%) and LOD is most often caused by serotype III (51%).[4] Globally, serotype III is the most common cause of EOD (47%) and LOD (73%).[3] Serotype III is associated with an increased risk of meningitis.[4]

GBS is a significant cause of early infant morbidity and mortality in the U.S. and globally. Centers for Disease Control and Prevention (CDC) estimated the mortality rate due to GBS disease in active bacterial core surveillance areas in the U.S. to be 4.5 per 100,000 infants younger than 1 year of age in 2015. In the U.S., approximately 7% of EOD and 5 – 6% of LOD cases result in death,[3, 4, 5] with preterm infants with EOD and LOD having approximately eight and four times the risk of death compared to term infants, respectively.[4] A recent meta-analysis of infant GBS disease showed a case fatality risk of 8.4% globally (95% confidence interval [CI], 6.6 – 10.2%); the case fatality risk for EOD ranged from 5% (95% CI, 4.0 – 7.0%) in developed countries to 27% (95% CI 17.0 – 37.0%) in Africa. The case fatality risk for LOD ranged from 4% (95% CI 3.0 – 6.0%) in developed countries to 12% (95% CI 5.0% - 19.0%) in Africa. GBS meningitis, a common presentation for LOD, results in moderate to severe long-term neurodevelopmental impairment in a substantial proportion of survivors (18% in a recent global meta-analysis).[6]

In EOD, neonatal GBS infection is acquired through vertical transmission from ascending spread of GBS that can occur *in utero* prior to or following the onset of labor and rupture of membranes, or during passage through the vagina.[7, 8, 9] The greatest risk factor for EOD is maternal GBS colonization (colonization at delivery odds ratio 204, 95% CI 100 – 419).[10] Other risk factors for EOD are preterm delivery, premature or prolonged rupture of membranes, chorioamnionitis, maternal intrapartum fever, prior delivery of an infant with GBS disease, heavy colonization, GBS bacteriuria, and deficient maternal anti-CPS immunoglobulin (Ig) G.[10, 11, 12, 13, 14] The same pathologic mechanism, ascending GBS infection in a colonized pregnant woman, may lead to GBS-related stillbirth.[15, 16] For LOD, young infants may acquire GBS via vertical transmission or via horizontal transmission from colonized household contacts or the community.[17, 18, 19] Risk factors for LOD are not as well-characterized as for EOD. Maternal colonization, preterm birth, and HIV are risk factors for LOD.[20, 21]

GBS disease can also occur in pregnant women, causing urinary tract infections, chorioamnionitis, postpartum endometritis, bacteremia, and puerperal sepsis. Few studies reporting the rate of maternal GBS disease are available, even in HIC, and definitions and units of reporting differ in the studies. A recent meta-analysis found a pooled incidence of invasive maternal GBS disease (GBS isolated from a sterile site, such as blood, in a pregnant or post-partum woman) in developed countries of 0.23 (95% CI,

.09–.37) per 1,000 maternities (pregnancies resulting in live or stillbirth) based on three studies, which included one hospital-based study from the U.S. that found a rate of 0.10 per 1,000 maternities.[22] The total burden of maternal disease may be greater, even in HICs, due to underreporting or low case ascertainment. In that analysis, the case fatality risk of maternal disease in HICs was 0.2%. However, the risk to the fetus was greater, with 7% of pregnancies ending in miscarriage or stillbirth and 2% of infants born to mothers with invasive GBS disease dying within the first month of life. The serotype distribution of invasive disease in pregnant women with disease is similar to that of EOD.[3, 22] Based on U.S. data, in contrast to some other infections, pregnant women with invasive GBS disease do not appear to have greater severity of disease than non-pregnant women.[23]

Intrapartum antibiotic prophylaxis (IAP) can be used to reduce transmission of GBS from mother to infant during labor and delivery. Initial clinical trials suggested 100% efficacy of IAP administered to colonized women for prevention of EOD, but later observational studies found effectiveness to be 86 – 89% among infants born to women who received IAP.[7, 11, 24, 25, 26, 27] Two major strategies have been used to identify candidates for IAP: risk-based and culture-based screening. The risk-based strategy identifies women based on the presence of known risk factors for EOD, which may include maternal fever, prolonged rupture of membranes, preterm delivery, previous birth of an infant with invasive GBS disease, and detection of GBS bacteriuria during the current pregnancy. Countries employing the risk-based approach vary in the specific risk factors considered. Culture-based screening uses rectovaginal culture late in pregnancy to identify women with GBS colonization, indicating they are at risk of having an infant with invasive disease.

Since 1996, in the U.S., CDC, American College of Obstetricians and Gynecologists (ACOG), and American Academy of Pediatrics (AAP) have recommended IAP for women at risk of transmitting GBS to their infants. In 2002, the guidelines endorsing either risk- or culture-based screening were revised to recommend universal screening of pregnant women by culture for rectovaginal GBS colonization at 35 – 37 weeks' gestation and the use of IAP for GBS carriers.[15] Implementation of this recommendation has reduced incidence of early-onset, but not late-onset, GBS. The incidence of EOD in the U.S. has decreased approximately 85% from 1.44 per 1,000 live births in 1990[28] to 0.21 cases per 1,000 live births in 2015.[29] The estimated national incidence of LOD has remained relatively steady and was 0.32 cases per 1,000 live births in 2015. There is a racial disparity in the U.S. in the incidence of EOD, which is estimated to be 0.57 and 0.15 per 1,000 live births in black and white infants, respectively, and LOD, which is estimated to be 0.68 and 0.25 per 1,000 live births in black and white infants, respectively.[29]

Rates of early infant GBS disease in many regions are generally higher than in the United States, particularly in LMICs and areas where women are not universally screened by culture for IAP. Globally, a meta-analysis found the incidence of infant GBS disease was 0.49 per 1000 live births (95% CI 0.43 – 0.56) overall, ranging from 0.30 in Asia to 1.12 in Africa. The incidence of EOD worldwide was 0.41 per 1,000 live births (95% CI 0.36 – 0.47), ranging from 0.32 in Asia to 0.71 in Africa. Incidence of LOD worldwide was 0.26 per 1,000 live births (95% CI 0.21 – 0.30), ranging from 0.04 in Asia to 0.65 in Africa.[3] In Soweto, South Africa, an area with high maternal HIV prevalence, an overall infant GBS disease incidence of 2.72 per 1,000 live births (95% CI 2.46 – 3.01) has been reported.[30]

Currently, no vaccine to prevent GBS disease is licensed in any country. However, several factors have led to an emphasis on development of a vaccine that can be administered to pregnant women to prevent

infant disease. Even the most aggressive prevention methods of universal culture-based screening and administration of IAP to mothers with GBS carriage have failed to eliminate EOD or to affect LOD incidence. This approach can also be costly and logistically difficult to implement. In addition, IAP has potential adverse effects, such as allergic reactions, and there are concerns about the emergence of antibiotic-resistant GBS and non-GBS bacteria. EOD usually occurs within the first hours of life, too early for an infant vaccine to generate a protective immune response. Because maternal IgG can be transferred to the fetus across the placenta, particularly late in the third trimester, maternal immunization could be a viable approach to passively immunizing the infant and potentially providing protection from disease for infants during the remainder of gestation through the high-risk period of early life.

4.0 Considerations for Demonstration of GBS Vaccine Effectiveness

4.1 General considerations

U. S. licensure of a vaccine requires that the vaccine is demonstrated to be safe and effective. Vaccine effectiveness can be demonstrated in several ways. A clinical efficacy trial with a disease endpoint, whether the disease of interest or a well-established precursor, is the gold standard for demonstrating vaccine effectiveness. For some vaccines, a biomarker may be used to support vaccine effectiveness. For GBS, discussion around possible primary and supportive endpoints for clinical trials to demonstrate effectiveness have focused on clinical disease endpoints, immune markers, such as immunoglobulin (Ig) G titer and measurement of functional antibodies, and colonization.

4.2 Demonstrating effectiveness based on studies using clinical disease endpoints

Because invasive neonatal and early infant GBS disease are rare, particularly in the U.S. where universal culture-based GBS screening and IAP is recommended for women with GBS colonization, a clinical endpoint efficacy study would require a large number of subjects. Estimates of sample size are found in the literature and can vary based on different estimates for EOD and LOD incidence by location, proportion of disease caused by serotypes contained in the vaccine, expected vaccine efficacy, lower bound of vaccine efficacy, power, proportion of subjects eligible for evaluation, and sensitivity of accurately identifying cases (for example, blood culture collection and factors that affect culture positivity).[31, 32] A study size of at least 200,000 subjects has been estimated based on an endpoint of EOD in the U.S. (0.25 per 1,000 live births in 2014) and 75 – 85% of disease being caused by vaccine serotypes.[31] Inclusion of LOD as part of the clinical primary endpoint for a study in the U.S. would be expected to reduce the sample size, but still require over 100,000 subjects.[31, 32] A candidate vaccine that includes serotypes that cover a greater proportion of invasive disease would also be expected to reduce the sample size. However, a clinical disease endpoint efficacy trial in the U.S. will likely be difficult to conduct.

A clinical study with disease endpoint(s) in a population outside of the U.S. with a higher burden of GBS disease may be possible and may be the most direct way to demonstrate vaccine effectiveness. South

Africa has been suggested as a location with a relatively high burden of GBS disease where a clinical efficacy study may be conducted. A study size of 25,000 – 33,000 has been proposed based on an estimated incidence of early infant GBS disease (EOD and LOD) of 2.7 per 1,000 live births in South Africa.[31] Other countries may have a substantial burden of disease and may be considered as locations in which to conduct an efficacy trial. A study sample size of 34,000 – 60,000 has been proposed based upon an overall disease incidence of 2.0 per 1,000 live births.[31, 32]

A critical question for the design of an efficacy study for GBS is selection of study endpoints. Invasive infant GBS disease is the most obvious candidate for an efficacy endpoint. One proposed case definition is isolation of GBS by culture from a sterile site in an infant with possible or probable severe bacterial infection.[31] As both early and late onset disease would likely represent relevant clinical outcomes, an endpoint of young infant invasive GBS disease, capturing disease from 0 – 89 days of age, would likely also be acceptable and allow for a reduced sample size compared to either early or late onset disease alone. If this early infant endpoint is used, vaccine effectiveness stratified by early- and late-onset disease, or by gestational age, might also be considered clinically relevant. Serotype-specific vaccine effectiveness could also be analyzed.[32]

GBS-related stillbirth is a clinical outcome affecting the fetus that could be considered as part of a composite endpoint. A systematic review found that definitions of stillbirth and diagnostic assessment for GBS varied significantly, but identified eight studies reporting GBS-related stillbirth rates of 0.04–0.9 per 1,000 births.[33] Another systematic review and meta-analysis estimated that, based on studies including data since 2000, 1% (95% CI 0 – 2%) of all stillbirths in developed countries and 4% (95% CI 2% – 6%) in Africa were associated with GBS.[16] Given the potential for contamination of the placenta and fetus during labor and delivery in colonized women, a case definition used in a clinical trial would need to be carefully defined and may require confirmation by autopsy or by culture of GBS from a normally sterile site, such as infant cerebrospinal fluid or internal organs.[31, 34] Challenges to inclusion of this outcome as part of a composite endpoint include cultural acceptability of autopsy and the ability of sites to perform the necessary evaluations.[31] However, if including GBS-related stillbirths in a composite endpoint is feasible, it could reduce the study sample size.

Additional possible disease endpoints with varying specificity to GBS have been proposed. GBS is known or suspected to contribute to several adverse pregnancy and infant outcomes, but a causative agent may not be identified or assessed in each case. Probable or possible GBS sepsis (sepsis plus surface colonization and no other identified cause), clinical sepsis/probable severe bacterial infection, or all-cause early infant sepsis or pneumonia, including culture-negative sepsis,[31, 32, 35] have all been proposed as potentially clinically relevant endpoints or outcomes of interest. Stillbirth (not specific to GBS relationship) has been suggested as a possible endpoint to consider, particularly if obtaining relationship to GBS is infeasible.[31] However, GBS only accounts for a limited proportion of stillbirths.[16, 33] GBS has also been associated with preterm birth, which has been proposed as a possible endpoint.[31] A global meta-analysis estimated the risk ratio for preterm birth with maternal GBS colonization to be 1.21 (95% CI 0.99 – 1.48; P = .061) in cohort and cross-sectional studies, and the odds ratio to be 1.85 (95% CI 1.24 – 2.77; P = .003) in case-control studies. In this analysis, preterm birth was associated with GBS bacteriuria in cohort studies (RR 1.98, 95% CI 1.45 – 2.69, P < 0.001).[36] However, the authors also suggested the results may be due to confounding and advocated for an assessment of the effects of a GBS vaccine on preterm birth. While GBS disease may contribute to each of these outcomes, a trial using a clinical

endpoint with low disease specificity may underestimate vaccine efficacy. Identification of appropriate endpoints will likely depend upon selection of clinical study sites. An analysis of vaccine effect on these endpoints or in combination with other endpoints would contribute to understanding GBS disease and may be able to provide additional support for licensure.

As described above, GBS can cause disease in pregnant women, including urinary tract infections, upper genital tract infections, and bloodstream infections. Data on maternal invasive GBS disease is lacking even in HICs. Based on limited data in HICs, maternal invasive GBS infection may be less frequent and less severe than infant disease.[22] Given that the timing of maternal GBS disease is usually during labor and delivery or post-partum, a GBS vaccine may prevent maternal disease. Prevention of invasive GBS disease in pregnant women may be considered a clinically relevant outcome to evaluate and may support vaccine licensure.[35] Discussion would be required on appropriate case definitions, background rate estimates given the limited data, and the importance of maternal outcomes in the context of infant disease.

4.3 Demonstrating effectiveness based on studies using immunologic markers of protection

Immunologic markers have been used to measure vaccine effectiveness in support of vaccine licensure as they are intended to predict the outcome of interest, protection from disease. Determination that a specific immune endpoint can be considered as a marker to predict efficacy relies upon scientific evidence, an understanding of the disease process, and an understanding of the vaccine's mechanism of protection. Depending upon the strength of the evidence supporting the ability of a marker to predict clinical benefit, additional regulatory considerations may apply (see section 5.0). An immunologic endpoint, as with any endpoint, should also be reliably measured using validated assays.

Anti-CPS IgG to GBS as a potential immune marker to infer effectiveness

Anti-CPS antibodies measured in ligand binding assays have been used successfully to evaluate vaccines against *Haemophilus influenzae* type B and pneumococci. Multiple observational studies have examined the relationship between serum serotype-specific anti-CPS IgG and infant GBS disease.[37, 38, 39, 40, 41, 42] In these case-control studies, infant and/or maternal serum IgG levels of EOD or early infant cases were compared to controls born to mothers colonized with the same serotype, but who did not develop disease. These studies show an inverse association between naturally-acquired serum anti-CPS IgG titers (assessed by ELISA or Luminex) and the odds of EOD or early infant invasive disease for serotypes Ia, III, and V. Based on this association, as well as pre-clinical data,[43, 44] for a CPS-based vaccine, a serotype-specific anti-CPS IgG threshold is a potential immunologic marker to serve as clinical endpoint in a pivotal trial. Associations between maternal antibody levels to GBS surface protein and infant invasive disease have also been investigated.

In these studies (cited above) thresholds are suggested by the authors which provide similar estimates of protection from invasive disease. These levels vary by serotype and by study and thresholds for some serotypes have yet to be proposed. Different assay techniques utilized and lack of standardized reference

sera make comparability between these studies difficult. Thresholds of protection may also vary by study population. Furthermore, protection from LOD may require higher maternal antibody levels to protect infants through the LOD risk period compared to the EOD risk period due to antibody decay, potentially contributing to differences in suggested thresholds. Despite the inverse association observed between serotype-specific anti-CPS IgG and infant disease in the above studies, some infants in these studies developed disease despite high maternal or infant serum concentrations of anti-CPS antibody, suggesting additional factors play a role in protection from infection. In addition, the possibility of differences between a vaccine-induced and a naturally-acquired immune response must be carefully considered when evaluating the utility and limitations of an immune marker as a potential endpoint for a pivotal study.

Functional antibodies as a potential immune marker to infer effectiveness

Some established immunologic biomarkers use measurements of functional antibody, such as the meningococcal bactericidal assays and pneumococcal opsonophagocytosis assays. Opsonophagocytosis *in vitro* killing assays (OPKA) for the GBS serotypes have been developed to measure functional antibody and may mimic the *in vivo* process of bacterial killing. The host defense mechanism for opsonophagocytosis occurs via complement-mediated killing of the bacteria, proceeding from antibody and complement deposition on the capsular polysaccharide of the bacterial surface (opsonization) to phagocytosis and intracellular killing of bacteria by polymorphonuclear leukocytes.

In one of the sero-epidemiologic studies referenced above and conducted in Europe, 28 of 31 mothers of infants with invasive disease (serotypes Ia and III) had OPKA titers that were not measurable, suggesting lack of antibodies as measured by OPKA may be associated with susceptibility to disease. In a subset of mothers colonized with GBS serotype Ia, Ib, or III who delivered infants without invasive GBS disease, maternal OPKA titer was found to positively correlate with IgG concentration such that a doubling in IgG concentration corresponded to expected OPKA increases between 70 – 80%, and IgG concentrations at the lower limit of quantitation corresponded to OPKA titers below the detection limit.[42]

Other functional assays have been developed, including antibody-mediated complement C3b/iC3b deposition assay and avidity assays, but the data on the utility of those assays are limited.

4.4 Demonstrating effectiveness based on studies using colonization as a possible marker of clinical disease

Colonization, as a precursor of disease, is sometimes discussed as a potential outcome of interest for evaluation in vaccine trials. A recent systematic review and meta-analysis provided an adjusted estimate of worldwide maternal GBS colonization of 18% (95% CI 17% – 19%), with regional variation of 11%–35%. Serotype distribution also varied regionally.[45] Approximately 50% of infants born to colonized women become colonized themselves and without IAP approximately 1-3% of these infants develop EOD.[32, 46, 47, 48] As colonization of the young infant or exposure via a colonized mother is a prerequisite for invasive disease, an evaluation of maternal clearance of colonization, lack of acquisition of maternal

colonization, maternal asymptomatic bacteriuria (a marker of heavy colonization), or prevention of infant colonization has been proposed to be considered as supportive evidence for vaccine effectiveness. [31, 32, 35]

While GBS colonization may be a possible endpoint for clinical trials, several factors should be considered. Colonization with GBS is not a disease itself, but provides an indirect measure of the potential for disease. Only a small proportion of colonized neonates develop invasive disease. An effective vaccine might eliminate, reduce, or have no effect on maternal and infant colonization. Interactions between the colonizing bacteria and the host's immune system that may work to confer protection to the host are complex. The impact of colonization on immune responses of both the mother and the infant should be well characterized if considering colonization as a supportive predictor of invasive GBS disease in infants born to women administered GBS vaccine during pregnancy. The potential for false negative or positive results and transient episodes of loss or acquisition would also need to be addressed.

5.0 Regulatory pathways under consideration for licensure for GBS vaccines

Vaccines are licensed based on data derived from adequate clinical trials demonstrating that the products are safe and effective. Although all approaches to vaccine licensure require that quality and safety are shown, licensure does not necessarily require demonstration of efficacy in a clinical trial using a clinical disease endpoint.

Under the U.S. Food and Drug Administration's (FDA's) "traditional approval" pathway demonstration of GBS vaccine effectiveness could be based either on a clinical disease endpoint or alternatively, a scientifically well-established biomarker demonstrated to be predictive of vaccine effectiveness. Confidence that a proposed marker(s), as induced by the vaccine, can predict protection against disease is the critical question in determining whether a marker can be used for traditional approval. If vaccine effectiveness is based on a clinical disease endpoint efficacy trial, foreign efficacy trials may be necessary because the low disease incidence in the U.S. would make efficacy trials difficult. Independent of which endpoints are chosen, clinical disease or biomarker, an acceptable means of bridging efficacy data obtained outside of the U.S. to the U.S. population will require further discussion. Any bridging method would need to take into account differences between the U.S. and the country in which the study is conducted, including in ethnicity, disease incidence, and prevention strategies.

Products for serious or life-threatening illnesses providing meaningful benefit over existing treatments can be approved using the FDA's accelerated approval provisions. Approval of a GBS vaccine by this pathway would rely on adequate and well controlled clinical trials establishing an effect of the product on a surrogate endpoint (for example, immune response) that is "reasonably likely" to predict clinical benefit.[49] In contrast to the traditional approval pathway, there remains some uncertainty as to the surrogate endpoint's ability to predict effectiveness. Data showing that human immunological responses to a GBS vaccine (for example, cord blood antibody titer) that reach a level that is deemed reasonably likely to be associated with clinical benefit could support vaccine efficacy. An accelerated approval would require adequate and well-controlled studies designed to verify clinical benefit to be underway at

the time of approval or conducted post-licensure. As confirmatory efficacy trials of GBS may be difficult to conduct, particularly in a location where the vaccine has been approved, the acceptability of using alternative study designs, such as an observational study, to confirm efficacy could be considered.

6.0 Summary

Globally, invasive GBS disease is a leading cause of neonatal morbidity and mortality. A vaccine administered to pregnant women could offer an effective option for prevention of invasive early infant disease. CBER solicits the Advisory Committee's consideration and discussion of approaches to demonstrate effectiveness of a GBS vaccine for maternal immunization. Discussion should focus on the possible endpoints to demonstrate vaccine effectiveness, including the merits, challenges, and additional information that is needed to consider for each endpoint.

References

[1] Giersing BK, Modjarrad K, Kaslow DC, Moorthy VS. Report from the World Health Organization's Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 7–9th Sep 2015. Vaccine. 2016;34(26):2865 – 2869.

[2] U.S. Food and Drug Administration (FDA), Center for Biologics Evaluation and Research. "Summary Minutes, 140th Vaccines and Related Biological Products Advisory Committee Meeting." FDA White Oak Campus, 13 Nov 2015. Available at: http://wayback.archive-it.org/7993/20170405194032/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM481319.pdf

[3] Madrid L, Seale AC, Kohli-Lynch M, et al. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017;65(Suppl 2):S160–72.

[4] Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008;299(17):2056 - 65.

[5] Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatric Infectious Disease Journal. 2011;30(11):937 – 941.

[6] Kohli-Lynch M, Russell NJ, Seale AC. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017;65(Suppl 2):S190 – S199.

[7] Verani JR, McGee L, Schrag SJ: Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. Morbidity and Mortality Weekly Report Recommendations and Reports. 2010;59(RR-10):1–36.

[8] Desa DJ, Trevenen CL. Intrauterine infections with group B beta-haemolytic streptococci. British Journal of Obstetrics and Gynaecology. 1984;91(3):237-9.

[9] Katz V, Bowes WA Jr. Perinatal group B streptococcal infections across intact amniotic membranes. Journal Reproductive Medicine. 1988 May;33(5):445-9.

[10] Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics. 1999;103(6):e77.

[11] Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. New England Journal of Medicine 2002;347:233 – 239.

[12] Regan JA, Klebanoff MA, Nugent RP, et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. American Journal of Obstetrics and Gynecology. 1996;174:1354 - 1360.

[13] Heath PT, Balfour GF, Tighe H, et al. Group B streptococcal disease in infants: a case control study. Archives of Disease in Childhood. 2009;94:674 – 680.

[14] Baker CJ, Edwards MS, Kasper DL. Role of antibody to native type III polysaccharide of group B *Streptococcus* in infant infection. Pediatrics. 1981;68:544 – 549.

[15] Schrag S, Gorwitz R, Fultz-Butts K, et al. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. Morbidity and Mortality Weekly Report. 2002;51(RR11):1-22.

[16] Seale AC, Blencowe H, Bianchi-Jassir F, et al. Stillbirth with group B *Streptococcus* disease worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017; 65(Suppl 2): S125 – S132.

[17] Dillon HC Jr., Khare S, Gray BM. Group B streptococcal carriage and disease: a 6-year prospective study. Journal of Pediatrics. 1987;110(1):31 – 36.

[18] Kim HJ, Kim SY, Seo WH, et al. Outbreak of late-onset group B streptococcal infections in healthy newborn infants after discharge from a maternity hospital: a case report. Journal of Korean Medical Science. 2006;21(2):347–350.

[19] MacFarquhar JK, Jones TF, Woron AM, et al. Outbreak of late-onset group B Streptococcus in a neonatal intensive care unit. American Journal of Infection Control. 2010;38(4):283–288.

[20] Lin FY, Weisman LE, Troendle J, et al. Prematurity is the major risk factor for late-onset group B Streptococcus disease. Journal of Infectious Diseases. 2003;188(2):267–271.

[21] Dangor Z, Lala SG, Cutland CL, et al. Burden of invasive group B *Streptococcus* disease and early neurological sequelae in South African infants. PLoS One. 2015;10(4):e0123014.

[22] Hall J, Adams NH, Bartlett L, et al. Maternal disease with group B *Streptococcus* and serotype distribution worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017;65(Suppl 2):S112 – S124.

[23] Deutscher M, Lewis M, Zell ER, et al. Incidence and severity of invasive *Streptococcus pneumoniae*, group A *Streptococcus*, and group B *Streptococcus* infections among pregnant and postpartum women. Clinical Infectious Diseases. 2011;53(2):114 – 123.

[24] Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. New England Journal of Medicine. 1986;314(26):1665 – 1669.

[25] Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. Journal of Clinical Microbiology. 1986;23(3):489 – 492.

[26] Matorras R, Garca-Perea A, Omeaca F, et al. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1991;40:57 – 62.

[27] Lin FY, Brenner RA, Johnson YR, et al. The effectiveness of risk-based intrapartum chemoprophylaxis for the prevention of early-onset neonatal group B streptococcal disease. American Journal of Obstetrics and Gynecology. 2001;184(6):1204 – 1210.

[28] Zangwill KM, Schuchat A, Wenger JD. Group B streptococcal disease in the United States, 1990: report from a multistate active surveillance system. CDC Surveillance Summaries, Morbidity and Mortality Weekly Report. 1992;41(SS-6):25-32.

[29] Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Group B *Streptococcus*, 2015.

[30] Cutland CL, Schrag SJ, Thigpen MC. Increased risk for group B *Streptococcus* sepsis in young infants exposed to HIV, Soweto, South Africa, 2004 – 2008. Emerging Infectious Diseases. 2015;21(4):638 – 645.

[31] Kobayashi M, Vekemans J, Baker CJ, et al. Group B *Streptococcus* vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries. *F1000Research*. 2016;5:2355 (doi: 10.12688/f1000research.9363.1).

[32] Madhi SA, Dangor Z, Heath PT, et al. 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. Vaccine. 2013;31S:D52– D57.

[33] Nan C, Dangor Z, Cutland CL, et al. Maternal group B *Streptococcus*-related stillbirth: a systematic review. British Journal of Obstetrics and Gynaecology. 2015;122(11):1437 – 1445.

[34] Gibbs RS, Roberts DJ. Case 27-2007 – A 30-year-old pregnant woman with intrauterine fetal death. New England Journal of Medicine. 2007;357(9):918 – 925.

[35] Heath PT. Status of vaccine research and development of vaccines for GBS. Vaccine. 2016;34(26):2876 – 2879.

[36] Bianchi-Jassir F, Seale AC, Kohli-Lynch M, et al. Preterm birth associated with group B *Streptococcus* maternal colonization worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017;65(Suppl 2):S133 – S142.

[37] Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. New England Journal of Medicine. 1976;294(14):753 – 756.

[38] Lin FYC, Phillips JB III, Azimi PH, et al. Level of maternal antibody required to protect neonates against early-onset disease caused by group B Streptococcus type Ia: a multicenter, seroepidemiology study. Journal of Infectious Diseases. 2001;184(8):1022 – 1028.

[39] Lin FY, Weisman LE, Azimi PH, et al.: Level of maternal IgG anti-group B Streptococcus type III antibody correlated with protection of neonates against early-onset disease caused by this pathogen. Journal of Infectious Diseases. 2004;190(5):928 – 934.

[40] Baker CJ, Carey VJ, Rench MA, et al. Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. Journal of Infectious Diseases. 2014;209(5):781 – 788.

[41] Dangor Z, Kwatra G, Izu A, et al. Correlates of protection of serotype-specific capsular antibody and invasive group B *Streptococcus* disease in South African infants. Vaccine. 2015;33(48):6793 – 6799.

[42] Fabbrini M, Rigat F, Rinaudo CD, et al. The protective value of maternal group B *Streptococcus* antibodies: quantitative and functional analysis of naturally acquired responses to capsular polysaccharides and pilus proteins in European maternal sera. Clinical Infectious Diseases. 2016;63(6):746 – 753.

[43] Madoff LC, Paoletti LC, Tai JY, et al. Maternal immunization of mice with group B streptococcal type III polysaccharide-beta C protein conjugate elicits protective antibody to multiple serotypes. Journal of Clinical Investigation. 1994;94(1):286 – 292.

[44] Paoletti LC, Wessels MR, Rodewald AK, et al. Neonatal mouse protection against infection with multiple group B streptococcal (GBS) serotypes by maternal immunization with a tetravalent GBS polysaccharide-tetanus toxoid conjugate vaccine. Infection and Immunity. 1994;62(8):3236 – 3243.

[45] Russell NJ, Seale AC, O'Driscoll M, et al. Maternal colonization with group B *Streptococcus* and serotype distribution worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017;65(Suppl 2):S100 – S111.

[46] Yow MD, Leeds LJ, Thompson PK, et al. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. I. Colonization studies. American Journal of Obstetrics and Gynecology. 1980;137(1):34 – 38.

[47] Cutland CL, Madhi SA, Zell ER, et al. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial. Lancet. 2009;374(9705):1909 – 1916.

[48] Russell NJ, Seale AC, O'Sullivan C, et al. Risk of early-onset neonatal group B streptococcal disease with maternal colonization worldwide: systematic review and meta-analyses. Clinical Infectious Diseases. 2017;65(Suppl 2):S152 – S159.

[49] 21 CFR 601 Subpart E