Workshop Report

Group B Streptococcus Correlate of Protection Methodology Workshop

10 and 11 February 2021

Executive Summary

On 10 and 11 February 2021, the Bill & Melinda Gates Foundation hosted a virtual workshop discussing the considerations and potential statistical methodologies for establishing a correlate of protection (CoP) for invasive Group B *Streptococcus* (GBS) disease. The workshop brought together experts across a variety of disciplines including statisticians, vaccine developers, vaccinologists, investigators, regulatory, and academia to discuss the following objectives:

1. To review and evaluate the statistical approaches which support the establishment of a CoP which may be used as the basis of licensure for hexavalent GBS glycoconjugate vaccines
2. To describe next steps towards defining the evidence needed for an immunological basis of vaccine licensure

Day 1 of the meeting focused on background on GBS vaccine development, the use of CoPs in development of other vaccines, the regulatory perspective on potential use of CoP in licensure of GBS vaccines, and an introduction to three GBS seroepidemiology studies being performed in the South Africa, the UK, and the US.

The key points from Day 1 were:

- VRBPAC-supported expert agreement that maternal IgG may reasonably predict protection in the neonate
- In general, an immune biomarker to support accelerated approval of a GBS vaccine would be acceptable to CBER, with data details and analysis required to support licensure dependent on the manufacturer's clinical development plans
- Manufacturers would be obliged to conduct post-approval RWE to confirm clinical benefit
- A single global correlate across regions would be advantageous to vaccine development from multiple manufacturers, and would support a licensure application
- Binding Ab likely to serve as primary basis of CoP used in licensure application and further supported by data on functional Ab response
- Minimum number of covariates to be evaluated: gestational age, maternal age, maternal infection

Additional considerations were:

- Need for more data before the discussion on potential need for serotype-specific CoPs is closed
- Identification of optimal functional assay to be used
- Characterization of neonatal Ab response (functionality, affinity, isotype mix, kinetics, glycosylation pattern, persistence)
- Association between maternal Ab at time of delivery in protection against colonization, cord blood levels in protection against LOD
- Mucosal immunity: characterization of memory B cell response in gut and genital tract
- Role of differences in pathogenesis between EOD and LOD regarding amount of Ab needed to confer protection
- Evaluation of timing and characteristics of protective Ab response in preterm infants
- Validation of protective antibody threshold via post-approval real-world evidence

Day 2 of the workshop focused on statistical analysis methodologies, including a review of pros and cons of a variety of published methodologies, a potential statistical analysis pathway for estimating a CoP in GBS, and the benefits and pitfalls of pooling data across the seroepidemiology studies.

The key points from Day 2 included:

- Statistical analysis performed separately for each of the three seroepidemiology studies will allow more robust conclusions than pooling of data, given the fundamental differences in study designs and populations
- Pooling can be performed for exploratory analysis in rarer subgroups e.g. pre-term infants
- Consensus to select a few statistical methods for common analysis across the three studies, including ADR- and RRR-based methodologies
- Consensus that it is not feasible to estimate separate thresholds for each serotype and that either a single threshold should be used, or have thresholds for the major serotypes (e.g. serotype III and Ia) and a pooled estimate for the rarer serotypes
- Consensus to develop a single CoP estimate across all regions
- Statistical analysis for antibody threshold estimation should build in some margin for uncertainty, which may include robustness to: (1) imperfect causal mediation (vaccine immunity $\neq$ natural immunity), (2) potential unmeasured confounding, (3) selection bias in transporting results to populations of interest, (4) minimum level of predicted vaccine efficacy, and (5) variability in point and confidence interval estimates across studies/regions and serotypes.
- In addition to studying Ab thresholds, it is useful to apply methods that use the entire distribution of IgG concentration
- Assessment of the relationship, such as a ratio, between the binding and functional antibody levels would help in the support of licensure of a GBS vaccine
- A set of targeted sensitivity analyses should be pre-specified as part of the common set of methods that are selected, and too many sensitivity analyses should be avoided
- Common analyses across studies should be pre-specified rather than multiple post-hoc analyses
- Consensus for simplicity and avoid over-focusing on trying to control for a large number of confounders.
- Agreement to show results with no covariate adjustment as well as using one or two ways to adjust for covariates, focusing on a small number of variables with the most knowledge that they should be confounders.
- Agreement to not adjust for variables that are expected to be in the causal pathway between vaccination and GBS disease – these variables will need to be identified
- Antibody kinetics studies can provide important information on natural immunity vs vaccine-induced immunity
- Data from the UK and South African studies can be used to build a model predicting cord blood IgG concentration from disease-onset IgG concentration. Augmented inverse probability weighting, targeted minimum loss-based estimation, or multiple imputation could be used
- Many statistical analyses are designed to make inference for a study population based on a direct or biased sample from a study population, therefore representativeness could be an issue. However, these seroepidemiology studies themselves are reflecting populations of interest, including broader sets of individuals than would be included in randomized trials

- Post-approval effectiveness studies are likely to be required as part of a conditional licensure agreement. A large simple trial design may be helpful

Agenda

DAY 1: FEBRUARY 10 2021

Agenda	Presenter	Time
Welcome and introduction	*Keith Klugman*	5 mins
GBS vaccine development strategy and workshop objectives	*Ajoke Sobanjo-ter Meulen*	15 min
Context of use for GBS CoP	*David Goldblatt*	20 min
Use of biomarkers for regulatory decision-making in vaccine development and licensure application review	*Jeff Roberts*	15 min
Overview of GBS seroepidemiology studies:		
US GBS newborn blood spot study	*Stephanie Schrag*	15 min
UK	*Paul Heath (TBC)*	15 min
South Africa - Wits	*Shabir Madhi* *Alane Izu*	15 min 15 min
Break		10 min
Q&A on Seroepi studies	*George Siber*	20 min
Roundtable Discussion and Q/A <u>Discussants:</u> George Siber Larry Moulton David Goldblatt 1. What are the most important and impactful objectives from these seroepidemiology studies? 2. Is it important to have a single estimate that would be globally acceptable? 3. What data are needed to translate correlates based on natural immunity to vaccine-derived immunity? 4. How many covariates should be considered / influence the outcome of the studies? 5. Should correlates be based on cord-blood or maternal levels? 6. Is it acceptable to base correlates on data that includes antibody levels measured in cases at the time of disease rather than at birth?	*Richard Isbrucker* *Ajoke Sobanjo-ter Meulen*	40 mins
Closing Remarks	*Ajoke Sobanjo-ter Meulen*	15 min

Welcome

Dr Keith Klugman, Director of the Pneumonia Program at the Bill & Melinda Gates Foundation welcomed everyone to the workshop and provided an overview of the burden of Group B *Streptococcus* (GBS) disease and the rationale for GBS vaccine development. Invasive GBS disease occurs from time of birth (early onset disease; EOD [0–6 days after birth]) up to 90 days after birth (late onset disease; LOD [7–90 days after birth]), with the vast majority of EOD occurring on the first day of life and LOD occurring within a few weeks of birth. Worldwide, childhood mortality is shifting earlier, with improvements in hygiene and vaccinations against common childhood illnesses.[1] GBS is therefore now a significant contributor to childhood mortality, and is the leading cause of meningitis in infants.[2] Dr Klugman mentioned the long history of attempts to develop a GBS vaccine, and focused on the use of a correlate of protection (CoP) as a measure of vaccine success, given the large number of pregnant women who would need to be included in an efficacy study. Licensing a GBS vaccine based on CoP would be ideal, and would then allow us to further investigate factors such as the role of GBS in stillbirth and preterm birth using vaccine probe studies. As the burden of GBS varies worldwide, it would be easiest to do initial investigations in countries with a high burden (e.g. GAVI-eligible countries in Africa), followed by vaccine probe studies in South Asia and elsewhere.

References

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Workshop objectives and background to GBS vaccines

Dr Ajoke Sobanjo ter-Meulen, Head of the Maternal Immunization Initiative at the Bill & Melinda Gates Foundation outlined the objectives for the workshop:

3. To review and evaluate the statistical approaches which support the establishment of a CoP which may be used as the basis of licensure for hexavalent GBS glycoconjugate vaccines
4. To describe next steps towards defining the evidence needed for an immunological basis of vaccine licensure

Dr Sobanjo-ter Meulen highlighted the slow progress to date in reducing neonatal mortality, compared with infant and under-five mortality rates.[1] In 2016, 46% (2.6 million) of deaths in children under five occurred during the neonatal period. Additionally, approximately 2.6 million babies were estimated to be stillborn in 2015, 98% of whom were in low- and middle-income countries (LMICs).[1,2] She then explained that GBS colonization of women varies geographically and can be up to 40% in women in some regions.[3] The majority of GBS disease occurs within the first 72 hours of life, and may also be associated with up to 3% of stillbirths. The rapid onset of disease after birth complicates diagnosis and may lead to underestimation of prevalence, especially in resource-limited settings. Nearly all GBS disease is caused by five of the 10 serotypes (serotypes Ia, Ib, II, III, and V), with serotype III currently the predominant causative serotype for both EOD and LOD. Transmission can occur vertically or horizontally. Higher incidence of both EOD and LOD has been reported in black vs white infants, and in pre-term vs full-term.[4] While universal screening and the use of intrapartum antibiotic prophylaxis (IAP) in the US has reduced the incidence of EOD by about 90%, there has been no impact LOD.[5] A risk-based approach to IAP, such as is used in the UK, has resulted in

increased GBS rates over recent years,[6] therefore a vaccine against GBS remains an unmet clinical need.

The potential benefits of a GBS vaccine were outlined, including prevention of up to 90,000 infants deaths and 57,000 stillbirths. A GBS vaccine has the benefits of potential higher coverage in challenging settings where antibiotics may not be readily available, as well as reducting antibiotic usage. Many years of research have demonstrated the potential for maternal vaccination against GBS to confer protection to the infant. Currently three glycoconjugate vaccines and one protein vaccine are in development, with the Pfizer hexavalent CRM_{197} glycoconjugate vaccine (GBS6) in Phase 2 studies. In a Phase 1 trial in healthy men and non-pregnant women, all tested dosing regimens were immunogenic against all six serotypes and the vaccine had an acceptable safety profile.[7]

Given the incidence of EOD disease, any clinical vaccine efficacy study would need at least 40,000 to 60,000 participants,[8] therefore vaccine licensure based on CoP would be the preferred route, with post-licensure trials to demonstrate the impact on reduction of disease burden. Maternal antibodies against the GBS capsule have demonstrated protection of neonates against invasive GBS,[9,10] however a CoP remains to be established. One key element has been a need for standardization of immunological assays, to allow comparison between studies and serotypes. Other key elements which could enable licensure by CoP are improved estimates of disease burden and a demonstrated immune response of a single dose vaccine administered during pregnancy. Seroepidemiology studies are currently ongoing to assess disease burden in the US, UK, and South Africa, and were presented in detail later in the workshop, and a Phase 2 study of Pfizer GBS6 vaccine is currently ongoing in pregnant women in South Africa.

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Context of Use for GBS Correlates of Protection

Professor David Goldblatt, Professor of Vaccinology and Immunology at Great Ormond Street Institute of Child Health, University College London provided an introduction on the background of CoP use for other vaccines, including seminal studies performed for meningitis C, *Hemophilus influenzae* B (Hib), and pneumococcal conjugate vaccines (see below). Prof Goldblatt outlined the role of the capsule as virulence factor in GBS, preventing deposition of complement. However, the capsule is also the target for antibody, which can kill the bacteria directly or can bind to phagocytic cells which then ingests the bacteria. While binding antibody is the easiest to measure (ELISA or Luminex), it may not directly relate to functional antibody levels. Additionally, opsonophagocytic killing assay (OPKA) can be used to measure level of phagocytic activity against the capsule in diseases like GBS. Measurement of functional antibody activity is more labor intensive and not conducive to high-throughput, hence is more challenging to measure than binding antibody. Therefore understanding the relationship between binding and functional antibodies will be critical to establishing a meaningful correlate.

Prof Goldblatt briefly explained that conjugate vaccines have been shown to stimulate effective B and T cell responses, including generation of memory B cells and plasma cells. He then outlined the epidemiological methods that have been used to estimate the level of antibody that is protective, for both natural and vaccine-induced immunity, including data from seroepidemiology studies, observation in efficacy studies, and passive infusion of antibody in humans or animals. Firstly, Prof Goldblatt discussed the assessment of a CoP for the Hib vaccine, based on data from a large scale study in the 1970s and 1980s in Finland.[1] In this efficacy study, the vaccine showed good protective efficacy in children 18 months of age and above but was not very immunogenic in younger children. In non-vaccinated children, an antibody titer of 0.15µg/mL showed a good inverse correlation with incidence of disease and was a suitable CoP in a non-vaccinated population (considered short-term protection).[2] However, in the vaccinated population, 80% of children had this antibody level by 12 months of age but the vaccine did not provide protection in these young children. Therefore they estimated a CoP of 1µg/mL for the vaccine (considered long-term protection). Interestingly in a separate trial of a conjugate vaccine at 7 months of age, only 40% of the infants had an anti-Hib titer of >1.0µg/mL, however, the vaccine efficacy was 90% without the need for a booster.[3] This indicated that CoP which had been predicted based on natural immunity or polysaccharide vaccines was not entirely representative of immunity produced by the conjugate vaccines, possibly due to the memory cells generated by the conjugate vaccine.

For meningococcal serotype C, studies of natural immunity in army camps estimated a CoP from serum bactericidal activity using human complement (hSBA) of ≥1 in 4. These data were utilized to support the development of polysaccharide vaccines.[4] For conjugate vaccines, a substantial amount of bridging had to be performed, as data was based on hSBA, responses in adults, and polysaccharide immunogenicity, whereas the conjugate vaccine efficacy studies had used rabbit SBA (rSBA), and were performed in infants and toddlers. rSBA titers ≥8 or 16 correlated closely with observed efficacy data.[5,6] This bridging is potentially very relevant to GBS. Additionally, efficacy of the meningococcal vaccine waned after the first year,[7] which may also be relevant to consider for GBS as while conjugate vaccines induce memory, circulating antibody levels may be key, as this is a rapidly multiplying pathogen.

Prof Goldblatt then presented the pneumococcal vaccine studies used to establish a CoP, based on a very simple model between vaccine efficacy for invasive disease and distribution of serum antibody concentrations in the vaccinated populations (reverse cumulative distribution curves [RCDCs]).[8,9] An aggregate CoP across serotypes was used as there was only one case in the vaccinated groups, so couldn't be assessed by serotype. The CoPs based on antibody data from the three studies, performed in different geographic regions, varied from 0.2 to 0.99 µg/mL.[8] The data was therefore pooled and weighted, giving a pooled CoP of 0.35µg/mL which was set as the CoP for pneumococcal vaccines. However, the threshold of antibody needed varies by serotype (0.14 to 2.83 µg/mL)[10] but nevertheless the overall CoP of 0.35 is still used, mainly because vaccine-induced antibody titers have been considerably above this level.

Finally, Prof Goldblatt briefly discussed the relevance to carriage. From analysis of Hib IgG concentrations, a CoP was estimated as 5 µg/mL, considerably higher than that needed to protect against invasive disease.[11] Studies on pneumococcus have also demonstrated that the risk of carriage decreases as serotype-specific IgG increases.[12,13] However, it is not known if circulating antibody is what is needed for protection against colonization, and some studies have shown that carriage is not prevented by circulating antibodies.[14]

For GBS, there is a threshold amount of antibody needed at three months of age for protection against invasive disease. Given antibody waning and the efficiency of transplacental antibody transfer, the level of antibody that needs to be induced by the vaccine to provide protection across the first three months of life will need to be established.

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Use of biomarkers for regulatory decision-making in vaccine development and licensure application review

Dr Jeffrey Roberts, Associate Director for Scientific Affairs at the Office of Vaccines Research and Review at Center for Biologics Evaluation and Research (CBER) at the US Food and Drug Administration (FDA) presented the use of biomarkers from an FDA regulatory perspective. Biomarkers are currently used for many regulatory purposes including as the basis for approval of new vaccines, for bridging effectiveness, for assessment of interference with concomitant administration, to support applications to quality for expedited programs, and for bridging manufacturing changes. The strength of evidence and data source required varies based on the regulatory objective, with some requiring much stronger evidence than others (e.g. a new first-in-class vaccine). Mechanisms by which vaccine-associated biomarkers are developed and established include under an investigational new drug application (IND), via peer-reviewed literature, and using the FDA's biomarker qualification program. The regulatory use case scenario most appropriate to Group B Streptococcus vaccines is to support an application for licensure under the accelerated approval pathway. Dr Roberts then explained the criteria for the accelerated approval pathway, including that approval can be granted based on demonstration that the biological product "has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit". Dr Roberts briefly reviewed the discussion at the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting "Evaluation of the Effectiveness of Vaccine intended to Prevent Group B Streptococcal Disease in Infants" on May 17th, 2018. In that VRBPAC, committee members agreed that anti-capsular GBS IgG antibody is reasonably likely to predict clinical benefit.[1] While this is a positive statement for the potential for licensing a GBS vaccine through and immune biomarker, the link between binding and functional antibody, particularly in the context of vaccine immune response, not just from seroepidemiological studies, will also need to be established.[2]

Dr Roberts discussed the use of real-world evidence (RWE) in FDA assessments, including supporting approval of a new indication or satisfying post-approval study requirements.[3] The FDA has a long history of using RWE for safety evaluations, however, effectiveness evaluation has been much more limited. There is a wide spectrum of potential sources of RWE, and if these are used as supporting evidence for effectiveness they should be well documented, with methodological rigor, replication, consistency with randomized clinical trial results, registration, and locked datasets increasing confidence in the quality of the data collected.

Dr Roberts summarized that from a conceptual perspective, CBER accepts the concept of use of an immune biomarker to support accelerated approval of a GBS vaccine. However further discussion is needed on the details of supporting data and analyses, and post-licensure RWE studies will be required to confirm clinical benefit.

References

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Seroepidemiology Studies

1. US GBS Newborn Blood Spot Study

Dr Stephanie Schrag, Lead of the Epidemiology Team at the Respiratory Diseases Branch, Centers for Disease Control and Prevention (CDC) presented the first of three seroepidemiology studies being performed to estimate titers corresponding to GBS natural immunity in mothers and infants. As the US has a low incidence of GBS due to IAP, this study will be an unmatched case-control study built onto the US CDC's Active Bacterial Core surveillance (ABC's) platform. Controls will be mother/infant dyads in which the mother was detected as being colonized during the current pregnancy but where their infants did not have invasive GBS during the first 90 days of life. The primary objective of the study, revised following FDA feedback is: to describe serotype-specific GBS invasive disease (<90 days of age, and stratified by early and late-onset) probabilities associated with a range of antibody concentrations at birth. The study is using newborn dried blood spot data collected from multiple locations across eight US states, with the background of widespread implementation of screening-based IAP. The study population will include multiple races/ethnicities, multiple socioeconomic status, and a range of gestational ages (including infants <34 weeks gestation) and delivery modes. Study endpoints are the disease probability by serotype-specific antibody distributions for the overall study population and by gestation age (<34 and ≥34 weeks) and time of disease onset (EOD and LOD). The study will use GBS Assay Standardization Consortium assays and Luminex-based ELISA for the main correlate analyses. OPKA will also be performed if the blood sample is large enough. Some of the challenges for this study are that there will be no matched controls, no maternal blood samples, limited sample volume, obtaining consent is very laborious, laws about accessing spots vary by state, and recruitment of a control population. The statistical analysis plan (SAP) is yet to be finalized, but at this stage they intend to use a covariate adjusted scaled logit model (as presented by Nong Shang on Day 2 of this workshop).

2. UK GBS seroepidemiology study

Professor Paul Heath, Professor of Paediatric Infectious Disease at St George's, University of London provided an overview of the iGBS3 study (Development of a serocorrelate of protection against invasive Group B *Streptococcus* disease), which is being performed as part of an existing cluster randomized controlled GBS trial (GBS3) evaluating risk versus swab-based screening for prevention of early onset GBS disease. They intend to collect cord blood from approximately 180,000 women with the aim of capturing 100 cases of serotype III invasive GBS disease. The primary objective of the study is to quantify the relationship between antibody and disease risk by estimating the odds ratio of GBS disease for antibody levels above various thresholds. Phase 1 of the study will also include determining whether antibody levels obtained at the time of iGBS disease (acute disease sample)

can be used to predict cord blood antibody levels. Phase 2 in the second year of the study will complete data collection for assessment of the primary objective. The study will be performed across all regions of the UK and will reflect the diversity of the UK population and obstetric practices. Case control matching will be based on the same GBS serotype; maternal age, ethnicity, gestation, and infant sex will also be captured and will enable adjustment as potential confounders. Antibody concentrations will be measured using multiplex Luminex for IgG and functional responses will be assessed by OPKA. Controls will include infants exposed to the same GBS serotype at delivery as the case but do not go on to develop invasive GBS. Exclusion criteria for the primary endpoint include gestational age <34 weeks, born via caesarean section with intact membranes, receipt of adequate IAP, and receipt of a blood transfusion in the previous month. Logistic regression will be used to estimate the odds of being a case at different threshold concentrations, starting from a defined lower threshold of c1=0.01 µg/mL, with comparisons of (≥c1 v <c1), (≥c2 v <c2), (≥c3 v <c3) etc being the preferred model. For the kinetics objective, geometric mean slope will be calculated using individual slopes and used to estimate birth concentrations.

3. South Africa seroepidemiology study

Professor Shabir Madhi, Professor of Vaccinology at the University of Witwatersrand presented details of a recently published South Africa GBS seroepidemiology study (28OB) for establishing a serotype-specific threshold for reduction of risk of invasive GBS disease.[1] Briefly, blood samples were collected from 38,233 pregnant women and their infants, who were followed up to 90 days post-delivery for assessment of development of invasive early and late GBS. A total of 53 cases were identified (cohort cases) and there was surveillance in the hospital to identify non-cohort cases, where maternal and infant blood samples were collected within 48 hours of culture confirmation of disease. Professor Madhi presented data on serotype-specific GMCs in infants >34 gestational age from cord blood and maternal blood, which showed higher point estimate thresholds for EOD vs LOD. GMCs in maternal blood associated with 90% reduction in disease were approximately 2.2-fold higher than cord blood, which is consistent with what we know about the efficiency of trans-placental antibody transfer. Non-cohort data was harder to interpret and it remained inconclusive whether later samples could be taken as a proxy for birth samples.

Prof Madhi then moved on to another GBS seroepidemiology study that was co-funded by the Bill & Melinda Gates Foundation and Pfizer (GBS-CoP). The primary study objective is to determine the infant GBS serotype Ia and III-specific capsular serum IgG antibody level associated with 80% reduced odds of invasive GBS disease between 0-89 days of age for the combined “cohort” and “retrospectively enrolled” cases in 18,243 pregnant women and their infants. Cases included 109 infants born at ≥34 gestational age and with culture confirmed invasive GBS diseases. Controls included 791 infants born at ≥34 gestational age to women with rectal or vaginal colonization by serotypes Ia or III. Cohort enrolment is at two sites in Johannesburg, with non-cohort enrolment over a much larger geographical area. He outlined the study design and timing of procedures and presented the data available so far. To date, the majority of EOD in both the cohort and non-cohort cases occurred on Day 0 after birth. Approximately 50% of cases were EOD, with 109 cases enrolled to date. GBS colonization was found in 25% of rectal or vaginal swabs. Currently serology testing is underway, and the correlation of anti-capsular antibody concentration in paired cord blood and immediate post-invasive disease samples will be formed to confirm the utility of the later sample.

Dr Alane Izu, Statistician at the University of Witwatersrand then presented the statistical approaches to analyzing the ongoing South Africa seroepidemiology study. She explained that published parametric and non-parametric models don’t allow for clusters within the same disease status and therefore they are assessing the suitability of alternative models for analyzing case-

control serological studies. The aims of the current analysis were to examine the accuracy of unsupervised mixture models using a pre-specified maximum number of components, and to assess the use of mixture model averaging (MMA) to account for uncertainty in the functional form of the IgG distributions. To validate the analysis, they performed some simulations and re-analyzed published data from the DEVANI and SA GBS seroepidemiology studies.[1,2] They used RCDCs and relative risk reduction or absolute disease risk. The mixture model included two clusters of cases, with the majority of cases having low IgG concentrations and the other cluster having high IgG concentrations. MMA was estimated as a weighted sum of different models which used different distributions (e.g. lognormal, Weibull). Dr Izu presented examples of mixture models estimates of RRR and ADR, based on differing proportions of cases coming from each cluster (high or low IgG). The team also performed 10,000 simulations varying the proportion of cases from the high IgG component to assess the accuracy of the model against the non-parametric and MMA. Both were found to be quite precise, although the precision was less for relative risk reduction (RRR) than absolute disease risk (ADR). When the infant and maternal antibody data from the 28OB study was reanalyzed using the MMA, the model performed well for RRR but for ADR there was a rise at higher concentrations, whereas the original Weibull model went down to zero. She presented a figure showing all the different models, which all behaved reasonably similarly. They also looked at the thresholds between different models and the MMA was more precise compared with the Weibull and Kapler-Meier curves. She concluded that MMA provides accurate and robust estimates of RRR and ADR, with similar estimates for distributions in exponential family. ADR is more sensitive that the RRR but this can be fixed with prior calibration.

References

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Q&A Session

The following questions were discussed during the Q&A session

1. *What is the current status of the CDC US seroepidemiology study?*
   The CDC US study has currently enrolled approximately 1300 controls (original target enrolment was 2400). They also estimate to have access to blood spots for 560 cases, although most have not yet been actively enrolled.
2. *How is the role of bias and confounding being addressed in the seroepidemiology studies?*
   The CDC US study is not matching cases and controls to give more flexibility but they are collecting a large number of covariates. Optimal methods to adjust for potential confounders will be discussed in Day 2 of the workshop. The UK study is matching based on serotype and also aims to adjust for multiple confounders. The South Africa study matches cases and controls, but discussion of which variables are potential confounders and the best methods of analyzing the data will be the focus of Day 2 of the workshop
3. *Is there a biological difference that would impact CoP estimates for infants infected at birth versus those infected after birth?*

The pathogenesis of EOD and LOD is quite different. EOD is acquired from the mother, and is dose-dependent (depending on the duration of exposure) and serotype dependent. It may be that antibody levels have to be higher to protect against EOD. Additionally, the gestational age of the baby is important. Neonates are biologically very different to older infants. In contrast, LOD is contracted horizontally from the mother or family members. Serotype III has been seen to be predominant as it is more likely to persist at mucosal sites. By the peak age of onset for LOD (5–6 weeks) maternal antibody levels are waning but phagocytic activity is increasing. Therefore the situation is very complex and it would not be expected that the CoP will be the same for both EOD and LOD.

4. Do we need a CoP that covers LOD rather than just EOD?
   Given the data already observed in Phase 1 and 2 studies with conjugate vaccines, it may not be an issue. A CoP that includes LOD would be an important target as there is higher risk of meningitis with LOD

Discussion

There then followed a panel discussion which focused on the following questions:

1. What are the most important and impactful objectives from these seroepidemiology studies?
2. Is it important to have a single CoP estimate that would be globally acceptable?
3. What data are needed to translate correlates based on natural immunity to vaccine-derived immunity?
4. How many covariates should be considered / influence the outcome of the studies?
5. Should correlates be based on cord-blood or maternal levels?
6. Is it acceptable to base correlates on data that includes antibody levels measured in cases at the time of disease rather than at birth?

Key points from the discussion included:

- From a general vaccine development point of view, maternal antibody titers post-vaccination would be the key measure as infant antibody titers cannot be controlled by vaccine design and are dependent on multiple factors such as gestational age, interval between vaccination and birth, time of colonization of the mother, and how much maternal antibody is transferred.
- Major questions to be addressed include the optimal timing of vaccination during pregnancy to obtain the highest titers at birth; antibody profiles in the infant in the first three months after birth, and the level of cord blood antibodies achieved by maternal immunization. An antibody level of ~1µg/mL is thought to be effective against GBS, but one of the major questions would be to assess waning of bactericidal antibodies to maintain protection through to three months of age
- Given that a CoP predictive of infant disease should preferably be measured in the population to be protected, seroepidemiology studies, as well as prior expert and regulatory consultations have determined that cord blood titers may serve as the primary measure.
- Assessment of the levels of functional vs binding antibodies is a key consideration and bridging analysis should be performed to assess the correlations between binding and functional antibody titers. Currently correlations between functional antibody and IgG ELISA levels vary by assay. There is also a serotype-dependent element as serotypes Ia and Ib, for

example, are structurally very similar so that antibody binds to both serotypes but functional capacity varies. It may be worthwhile performing animal models of how predictive binding antibody is of functional levels.

- Assay standardization is currently also being performed for OPKA by the GBS assay consortium.
- Consensus to have a single estimate of CoP across geographical regions and age of onset as this is important for comparing vaccines. As with the pneumococcal vaccine, a single CoP was used with the understanding that protective thresholds varied geographically.
- When considering the potential for CoPs for individual serotypes, it may not be possible or desired to estimate values for each serotype individually, particularly for the rarer serotypes. It may be that one CoP can be applied to all serotypes, or there is a CoP for the most common serotype and a different CoP from pooled data across the other serotypes. With the pneumococcal vaccine, one CoP was applied across all serotypes, even though there was a 20-fold difference in protective titer between some serotypes. There was consensus to leave this open until data from the ongoing seroepidemiology studies had been analyzed to see the magnitude of differences
- Important consideration to collect data on many potential confounding covariates, which includes reduction in antibody titers post-birth (as this is particularly important for LOD); IAP, chorioamnionitis; maternal age (older more likely to have antibody); gestational age. Consensus that it would be best to have as few covariates as possible in the analysis but this need to be identified and standardized across studies.
- Analysis of when the best timing for vaccination of the mother needs to be performed in order to obtain the highest titers at birth
- Cord blood should be used to estimate antibody levels in the infant, as blood taken after disease onset is that antibody levels may already have been influenced by the infection in LOD (although any increase from the infection itself is unlikely due to the rapid onset of disease). Studies of serotype III show that immune complexes have already formed within 24 hours. However, as LOD doesn't present until a later point, cord blood may no longer be available. Therefore assays comparing kinetics in cord blood and post-disease onset samples are needed, and can be performed on data from the ongoing seroepidemiology studies.
- Functional assays comparing antibodies from natural and vaccine-induced antibodies should be performed to compare natural vs vaccine-induced immunity. Animal models may be useful for this. Should assess affinity and IgG isotype mix, as well as the kinetics of antibody transfer (e.g. differences in glycosylation) and antibody persistence, as these may differ between natural and vaccine-induced antibodies

Summary of Key Outputs from Day 1

The key points from the first day of the meeting were:

- VRBPAC-supported expert agreement that maternal IgG may reasonably predict protection in the neonate
- In general, an immune biomarker to support accelerated approval of a GBS vaccine would be acceptable to CBER, with data details and analysis required to support licensure dependent on the manufacturer's clinical development plans
- Manufacturers would be obliged to conduct post-approval RWE to confirm clinical benefit
- A single global correlate across regions would be advantageous to vaccine development from multiple manufacturers, and would support a licensure application
- Binding Ab likely to serve as primary basis of CoP used in licensure application and further supported by data on functional Ab response
- Minimum number of covariates to be evaluated: gestational age, maternal age, maternal infection

Additional considerations were:

- Need for more data before the discussion on potential need for serotype-specific CoPs is closed
- Identification of optimal functional assay to be used
- Characterization of neonatal Ab response (functionality, affinity, isotype mix, kinetics, glycosylation pattern, persistence)
- Association between maternal Ab at time of delivery in protection against colonization, cord blood levels in protection against LOD
- Mucosal immunity: characterization of memory B cell response in gut and genital tract
- Role of differences in pathogenesis between EOD and LOD regarding amount of Ab needed to confer protection
- Evaluation of timing and characteristics of protective Ab response in preterm infants
- Validation of protective antibody threshold via post-approval real-world evidence

DAY 2: FEBRUARY 11, 2020

Agenda	Presenter	Time
Welcome back and summary of Day 1	*Ajoke Sobanjo-ter Meulen*	10 min
Review of existing methods for establishing correlate protection threshold with adjustment of covariate effects	*Nong Shang*	25 min
Experience with Designating CoPs and Statistical Approaches for the GBS Sero-Epi Studies	*Peter Gilbert*	25 min
What I Would Want to See if I Were Sitting on VRBPAC: Haphazard Comments	*Larry Moulton*	15 min
Harmonization of data or pooling of data across studies	*Nick Andrews*	20 min
Break		10 min
Q&A session	*Chairs:* *Larry Moulton* *Peter Gilbert*	30 min
Discussion 2) For the proposed study-specific statistical analysis methods presented: a) *Are there any modifications of the methods, or additional methods, that should be considered?* b) *Within a study should multiple methods be used? If so, does it matter which is used as the primary method? What are the risks/benefits?* c) Is there a single method that should be applied to all studies? 3) What are the most critical next steps towards finalizing statistical method plans for the seroepi studies and is additional in person convening required?	*Moderators:* *Larry Moulton* *Peter Gilbert*	35 min
Closing	*Keith Klugman* *Ajoke Sobanjo-ter Meulen*	10 min

Welcome and objectives for Day 2

Dr Sobanjo ter-Meulen opened Day 2 of the workshop with a reminder of the main points from Day 1 and the key questions to be discussed on the second day of the meeting:

1) For the proposed study-specific statistical analysis methods presented:
    a) Are there any modifications of the methods, or additional methods, that should be considered?
    b) Within a study should multiple methods be used? If so, does it matter which is used as the primary method? What are the risks/benefits?
    c) Is there a single method that should be applied to all studies?
2) What are the most critical next steps towards finalizing statistical method plans for the seroepidemiology studies and is additional in-person convening required?

Review of existing methods for establishing a CoP threshold with adjustment of covariate effects

Dr Nong Shang, Chief of Biostatistics Office at the Division of Bacterial Diseases at CDC presented a summary of existing models available for establishing a CoP. He highlighted the main challenge for all methods was appropriate adjustments for covariates. If there were no covariates, then most methods can be applied successfully, however it is highly likely that covariates affect factors such as antibody level distribution, baseline disease probabilities, and effect of antibody level on disease probability. Possible confounders for analysis of GBS CoP include gestational age, race/ethnicity, maternal age, and maternal immunocompromised state. Dr Shang outlined the primary methods under consideration:

- Method 1: ADR based on RCDCs
- Method 2: Odds ratio curve
- Method 3: ADRs based on separate antibody distributions for cases and controls (non-parametric, or parametric with Bayesian modelling)
- Method 4: Logistic regression
- Method 5: Local odds ratio curves

The first two methods are the most frequently used. Method 1 is based on RCDCs and assumes a high disease rate at low titers which then decreases, with a titer threshold estimable based on a pre-specified probability threshold. It is a simple model but has good accuracy and robustness.[1] The ADR is specific to the study population, and inverse probability weighting is possible through comparing the distributions of the covariates between study population and the sample. However, adjustment for covariates is not straightforward if the study population is not fully characterized, data are from a case-control study with no knowledge of the population case rate, multiple covariates, there is a need to pool or compare across studies (e.g. with different covariate structure), and if the covariates are not well defined. Method 2, the odds ratio curves, work by for each titer value (t0), the odds ratio is calculated by comparing subjects with titer values larger than t0 to subjects with titer values smaller than t0 to generate a curve. The method has the advantages of being applicable to both cohort and case-control studies, and providing an ad-hoc connection to vaccine efficacy (VE).[2] Covariates can be adjusted for by using logistic regression to obtain and adjusted odds ratio for each titer value t0. However, this is generally not very successful and the results from simulation experiments showed different thresholds based on different covariates.

Method 3 was based on separate estimates for antibody levels in cases and controls to construct ADR curves. This can be implemented either parametrically[3] or non-parametrically,[4] and can be applied to both cohort or case-control designs. The model requires knowledge of disease rate and adjustment for covariates is possible but is complex, therefore adjustments often take place at the study design phase by using matched case-controls and using a heuristic approach for adjustments. Dr Shang provided the example of a study by Carey but there was an assumption that the covariates don't affect antibody levels in the cases or controls, which may not be the case. Therefore the model resulted in a regular case-control analysis with no adjustments for covariates.

Method 4, a logistic regression approach, is a commonly used method to adjust for covariates,[5] and has the advantage of the relative relationship not depending on antibody distribution levels, so can be applied to different study populations (e.g. across studies or pooled data). While logistic regression is good at adjusting the effect of confounders on the slope of the curve, it does not take any effects on the intercept into account. Therefore the approach does not generate a transportable relationship between antibody level and the disease probability. The center of the curve could be defined to allow adjustment of the intercept, but this is somewhat arbitrary and results in the curve becoming population-specific.

Method 5, a local odds ratio curve, divides titer values into small bins to compare disease risk between each bin with the bin with the smallest titer value. It has the advantage of baseline disease probability at the lowest bin will be canceled out during calculation. Hence, the covariate effects on the baseline probability will be removed. Logistic regression can then be used to adjust for covariates.

Dr Shang ended the talk by describing that for estimating a CoP for GBS antibody level distributions, disease probabilities, and the relationships between the two have to be taken into account, which is much more complicated than routine consideration of effects of confounders. His team have developed a potential model which could potentially be used, based on the scaled logistic regression model[5] (details available in powerpoint slides).

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Experience with Designating CoPs and Statistical Approaches for the GBS Sero-Epi Studies

Dr Peter Gilbert, Professor at the Fred Hutchinson Cancer Research Center and Department of Biostatistics, University of Washington then introduced a potential statistical pathway for the data collected in seroepidemiology studies to provide enough evidence to support use of an immune marker for provisional vaccine approval. While there will be caveats in the statistical results given

these are observational studies susceptible to confounding and selection biases, building conservative margins into threshold estimates together with replication of strong and consistent correlates across the 3 studies may be sufficient to achieve this goal. Dr Gilbert started by outlining a general statistical approach to estimating CoPs and then provided further details of estimating thresholds based on prospective cohort studies and case-control studies. The aim of the analysis is to establish how a surrogate endpoint (e.g. IgG from infant cord blood samples) can be used to predict VE against invasive GBS. Dr Gilbert outlined the main ways in which immunologic surrogate endpoints are validated including natural history studies, randomized VE trials, and studies to gain knowledge on the mechanisms of interrelating vaccination, clinical endpoints, and the surrogate endpoint. When considering how we can establish a surrogate that is "reasonably likely to predict VE", it is likely that in the absence of randomized VE data that demonstration of a strong and approximately consistent correlate of risk across different settings is needed. As IgG is an accepted natural immunity mechanism of protection against GBS, arguments from analogy with diseases with vaccines with validated IgG surrogate endpoints are critical (e.g. Hib, pneumococcus).

Dr Gilbert then provided a detailed description of methods which could be used to estimate thresholds for a prospective cohort seroepidemiology study for both absolute and relative risk parameters. Potential approaches for an absolute risk parameter with no covariate adjustments included Carey et al.,[1] Fabbrini et al.,[2] Donovan et al.[3] whereas an extension of Carey's Bayesian model or a flexible frequentist targeted maximum likelihood estimation (TMLE) model[4] could be used for covariate adjustment. Potential approaches for relative association parameters include logistic regression, covariate-adjusted scaled logit model (as outlined by Nong Shang in the previous presentation), or TMLE for matched or unmatched studies.[5] Dr Gilbert then explained that it would be more straightforward to develop a formula for predicting VE based on an absolute risk parameter than on a relative association parameter. He then provided some example formulas for predicting VE based on three assumptions (vaccine immunity is the same as natural immunity, no unmeasured confounders of the effect of the surrogate endpoint on the clinical endpoint, and positivity) and accounting for GBS colonization.

Dr Gilbert then repeated the exercise for estimating a threshold based on case-control studies (UK and US seroepidemiology studies, and part of the South Africa study). The case-control study can directly estimate relative association parameters such as covariate-adjusted odds ratios and two approaches could be used, either based on relative parameters only, or absolute risk parameters with sensitivity analysis. He outlined that one potential solution for a common approach across all three seroepidemiology studies is the TMLE method,[5] as this could provide a covariate-adjusted estimate of causal relative risk for both individually-matched and unmatched studies.

Finally, Dr Gilbert concluded with a brief discussion of the need for an analysis that allows representativeness, and that by building conservative margins into an estimate and having comparable results across studies may be key. He concluded with the critical next steps towards finalizing statistical method plans for the sero-epidemiology studies including commonality of at least some of the statistical methods and development of a harmonized statistical plan across studies.

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What would I want to see if I were sitting on VRBPAC: haphazard comments

Professor Larry Moulton, Professor at the Departments of International Health and Biostatistics at Johns Hopkins Bloomberg School of Public Health presented his thoughts on important considerations for assessment of the methodologies used for establishing a CoP. He explained that there should be results for at least one serotype (probably serotype III), which show that vaccine-induced antibody in the infants is at least nearly as high as naturally-induced antibody, and it does not decay faster.[1] There would need to be data from several studies in different populations, and at least two statistical methods used to analyze the data. He emphasized that consistency of results across studies was a big strength, and separate analysis of studies, rather than pooling or a meta-analysis, would be preferred, with appropriate bridging analysis. He did, however, state that estimates across studies would also be useful for subgroup analysis (e.g. looking at pre-term birth, estimates for a specific serotype). Regarding a statistical method, it would be preferable to use a method that had been previously published, or was adapted from a peer-reviewed method. Both unadjusted, and adjusted analyses that include a relatively small number of covariates across the three data sets from the sero-epidemiology studies, would be desirable. The nature of the problem and the design of these studies are such that only variables related to antibody distribution need be considered for adjustment. Regarding the CoP itself, you ideally want to see a high probability of an important risk reduction (e.g. if 1.0 μg/mL corresponds to 95% probability of having a >25% risk reduction). Prof Moulton concluded the presentation by discussing post-approval research, including having a suitable package of phase 4 studies already planned or recruiting. He suggested that ABC sites would be ideal for these kinds of investigations.

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Harmonization of data or pooling of data across studies

Dr Nick Andrews, Senior Statistician at Public Health England concluded the presentations for Day 2 of the workshop with a discussion of pooling and harmonizing data collection and analysis across the three seroepidemiology studies. He presented the potential benefits of pooling the data, including making the CoP more generalizable across different populations, adding precision where there are small sample sizes (e.g. sub-population analysis, or less common serotypes), and to provide greater insight into potential confounders. He also noted that if we don't perform analysis across all three

studies, a third party may try to do it as a meta-analysis. Additionally, pooling across studies would be useful if a CoP is required based on a different assay than that used in the studies (e.g. OPKA). Dr Andrews outlined three different levels of pooling which could be applied based on the types of study. Firstly, different studies may give broadly the same interpretation such that it at least makes sense to look at the results together and come to an overall conclusion. In this case, meta-analysis may not be possible due to differences in the population studied or other important characteristics which are deemed to affect the exact correlate. Secondly, different studies may measure the same thing, although potentially with different designs, such that it is possible to do a meta-analysis on results to produce more precise results. To perform a meta-analysis, the data would need to be reported with the same cut-offs and stratifications, and populations should have similar inclusion/exclusion criteria or adjustments for confounders. Finally, the different studies may measure the same thing and use similar designs and covariates, such that individual level data can be combined to obtain pooled results. The latter is more difficult in practice, as it will require agreements to share data, very similar methodologies, and the same covariates collected in the same way, so may not be possible with these three seroepidemiology studies. For any pooling, the studies would all have to use assays that have the same interpretation across the quantitative range and that are stable over time (including standardization of storage, transport and processing) and the sample used to define the correlate needs to be the same (e.g. cord blood).

Q&A and discussion sessions

Is there any more information on the plans for Pfizer's pivotal GBS vaccine study?

As yet there are no detailed plans. Within the phase 3 program Pfizer are planning pivotal studies in pregnant women which will include collection of cord blood to align antibody levels at birth with data from the seroepidemiology studies, and collection of maternal responses. It was noted that a large-scale effectiveness trial would be very useful, especially if it is as near to randomized as possible (for example, as were performed for COVID-19 vaccines)

What are the major variables affecting IgG concentration?

Maternal age and prematurity were two of the key variables discussed. Older mothers are more likely to have been colonized by GBS and therefore have antibody. Babies born before 32 or 34 weeks are unlikely to be protected due to the timing of transplacental antibody transfer

The key points from the panel discussion were:

Seroepidemiology studies

- Pooled data analysis across the three seroepidemiology studies is not warranted given the fundamental differences in study cohorts. It is more useful to view the results as replication of findings across three diverse contexts. An exception may be pooled exploratory analysis across studies/regions for generating hypotheses for rare subgroups such as pre-term babies.
- Consensus to select a few methods for common analysis across the three studies. Specifically, a preference stated for the 'simple threshold method 3 in the UK SAP' and the CALM method. These two methods are very similar and one task would be to define a harmonized version of this method.

- Wits Vaccines and Infectious Diseases Analytics and Pfizer have developed extensions of the Carey approach that also may be appropriate, given the field's familiarity with the basic method.
- A compelling case for using IgG for provisional approval would include robust results from the three studies, showing strong and consistent inverse correlations of infant cord blood IgG concentration with invasive GBS disease across all studies and by at least two statistical methods (for individual major serotypes and pooled over serotypes)
- The seroepidemiology studies have the advantage of not having major concerns with typical pitfalls of case-control studies (differential exposure cases vs. controls and systematic missing diagnoses of cases). The studies capture most all GBS cases, and the exposure is well controlled for. These thoughts support that validity of results are unlikely to be majorly compromised by confounding or selection bias.

CoP estimates

- There was consensus that it is not feasible to define/estimate separate thresholds for each serotype. Consensus for the analyses to pool all serotypes except the most prevalent one (e.g. serotype Ia or III). In addition, comparisons and modeling may be done to inform if a single threshold is reasonable.
- There was consensus to target development of a single IgG concentration threshold estimate across regions.
- A fundamental issue is how to translate IgG as a natural immunity CoP to a vaccine immunity CoP. Antibody kinetic studies comparing curves of IgG concentration across the placenta from natural infection vs. vaccination are informative, as well as comparing the relationship of IgG with functional immunological readouts natural infection vs. vaccination

Statistical methodology

- Consensus that statistical analyses for antibody threshold estimation should build in some margin for uncertainty, which may include robustness to: (1) imperfect causal mediation (vaccine immunity $\neq$ natural immunity), (2) potential unmeasured confounding, (3) selection bias in transporting results to populations of interest, (4) minimum level of predicted vaccine efficacy, and (5) variability in point and confidence interval estimates across studies/regions and serotypes. One technique would be a threshold on an xx% credible interval from the adjusted ADR curve, where discussion may be needed to define xx.
- In addition to studying Ab thresholds, it is useful to apply methods that use the entire distribution of IgG concentration. For example, a simple analysis could compare RCDF curves for non-cases vs. cases vs. ~peak Ab time point for vaccine recipients in a phase 1 or 2 trial. Via direct standardization/G-computation, these RCDF curves could be estimated for a given reference cohort such as the phase 1 or 2 vaccine trial cohort or any one of the seroepidemiology study cohorts (creating standardization on the distribution of baseline prognostic factors).
- Related to RCDF curves, the Siber et al. (Vaccine 2007;25(19):3816-26)/Andrews et al. (Clin Diagn Lab Immunol. 2003 Sep;10(5):780-6)/Chang-Kohberger simple CoP threshold method may be a good fit given that IgG has been accepted as a natural immunity correlate of protection. Results from this analysis would be interpreted under the supposition natural immunity = vaccine immunity (complete causal mediation of the vaccine effect on GBS through IgG concentration).

- Knowledge from antibody kinetic studies can be inputted into models that predict vaccine efficacy from an IgG distribution in vaccine recipients and from data results in the seroepidemiology studies. Part of the uncertainty in the full mediation assumption vaccine immunity = natural immunity stems from biological expectations that vaccine-induced antibody tends to be more functional than naturally-induced antibody, yet only if there is enough time post vaccination for affinity maturation.
- Data from the UK and South African studies can be used to build a model predicting cord blood IgG concentration from disease-onset IgG concentration (and perhaps other participant variables). Statistical methods for assessing cord blood IgG as a correlate of GBS disease can include all the cases in the analysis and use the model in the validation set. A variety of such validation set missing data methods could be used, such as augmented inverse probability weighting and targeted minimum loss-based estimation. There are existing methods and software for such validation set estimation. Another option would be multiple imputation, which is less robust, but very easy to implement and to add on to an existing method. Inverse probability complete case weighting is less appealing because it would ignore information in the cases without cord blood IgG.
- Consensus to include both an ADR-based method and a relative association-based method in the small common set of methods. More discussion is needed to define the ADR-based method.
- A set of targeted sensitivity analyses should be pre-specified as part of the common set of methods that are selected, and too many sensitivity analyses should be avoided
- Common analyses across studies should be pre-specified rather than multiple post-hoc analyses
- 'Representativeness' is a key issue that needs resolution. Many statistical analyses are designed to make inference for a study population based on a direct or biased sample from a study population. These seroepidemiology studies themselves are reflecting populations of interest, including broader sets of individuals than would be included in randomized trials. Thus, it may be worth considering defining IgG thresholds and prediction of VE for the seroepidemiology study participants themselves (akin to finite-sample inference that survey samplers consider).

Covariates

- Consensus for simplicity and avoid over-focusing on trying to control for a large number of confounders.
- Agreement to show results with no covariate adjustment as well as using one or two ways to adjust for covariates, focusing on a small number of variables with the most knowledge that they should be confounders.
- Agreement to not adjust for variables that are expected to be in the causal pathway between vaccination and GBS disease. These variables will need to be defined but should include maternal age and gestational age. One challenge includes that while corrected gestational age will be correlated with the amount of antibody in infant cord blood, this amount is also affected by the magnitude of antibody in the mother. A set of known prognostic factors could be studied for their correlation with infant cord blood IgG concentration, and only those variables with correlation would then be included.

Additional studies

- Given that provisional approval is the sought-after pathway for a GBS vaccine, designing post-approval effectiveness studies is important. Consideration of a large simple trial may be helpful.

The following next steps were identified:

- Development of a joint publication on CoP methodology approach
- WHO stakeholder meeting on GBS CoP

Summary and meeting close

Drs Klugman and Sobanjo ter-Meulen thanked all the speakers and attendees for a very insightful discussion and closed the meeting.