Serocorrelates of protection against infant group B streptococcus disease

Kirsty Le Doare, Beate Kampmann, Johan Vekemans, Paul T Heath, David Goldblatt, Moon H Nahm, Carol Baker, Morven S Edwards, Gaurav Kwatra, Nick Andrews, Shabir A Madhi, Ajoke Sobanjo ter Meulen, Annaliesa S Anderson, Bart Corsaro, Per Fischer, Andrew Gorringe

Group B streptococcus (GBS) is a leading cause of young infant mortality and morbidity globally, with vaccines being developed for over four decades but none licensed to date. A serocorrelate of protection against invasive disease in young infants is being considered to facilitate vaccine early licensure, followed by demonstration of efficacy assessed postlicensure. In this Review, we synthesise the available scientific evidence to define an immune correlate associated with GBS disease risk reduction on the basis of studies of natural infection. We summarise studies that have investigated GBS serum anticapsular or anti-protein antibodies, and studies measuring the association between antibody function and disease risk reduction. We highlight how knowledge on the development of correlates of protection from existing vaccines could be harnessed to facilitate GBS vaccine development. These lessons include aggregation of serocorrelates of protection for individual serotypes, understanding the relationship between immunity derived from natural exposure of adults and vaccine-induced immunity, or using extrapolation of protection from in-vitro immunoassay results. We also highlight key considerations for the assessment of the role of antibodies to derive a serocorrelate of risk reduction in future seroepidemiological studies of GBS disease.

Lancet Infect Dis 2019; 19: e162–71

Published Online January 22, 2019 http://dx.doi.org/10.1016/S1473-3099(18)30659-5

Paediatric Infectious Diseases Research Group and Vaccine Institute (K Le Doare PhD, Prof P T Heath FRCPCH) **and Institute of Infection and Immunity** (K Le Doare, Prof P T Heath), **St George's University of London and St George's University Hospitals National Health Service Trust, London, UK; The Vaccine Centre, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK** (Prof B Kampmann PhD); **Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland** (J Vekemans PhD); **Great Ormond Street Institute of Child Health, University College London, London, UK** (Prof D Goldblatt PhD); **University of Alabama at Birmingham, Birmingham, AL, USA** (Prof M H Nahm MD); **Feigin Center, Baylor College of Medicine Hospitals, Houston, TX, USA** (Prof C Baker MD, Prof M S Edwards MD); **Medical Research Council Respiratory and Meningeal Pathogens Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa** (G Kwatra PhD, Prof S A Madhi PhD); **Department of Statistics, Public Health England, London** (N Andrews PhD), **and Pathogen Immunology Group, Salisbury** (Prof A Gorringe PhD), **UK; Bill & Melinda Gates Foundation, Seattle, USA** (A S ter Meulen PhD); **Vaccine Research and Development, Pfizer, New York, NY, USA** (A S Anderson PhD); **GlaxoSmithKline, Rockville, MD, USA** (B Corsaro PhD); **Minervax, Copenhagen, Denmark** (P Fischer PhD)

Introduction

Group B streptococcus (GBS) remains a leading cause of neonatal and infant sepsis globally.[1–3] Ten GBS serotypes are known (Ia, Ib, and II–IX), with Ia, III, and V being the most prevalent serotypes in neonates (younger than 28 days) and infants (28 days or older).[4] One in five GBS meningitis survivors have long-term adverse neurodevelopmental outcomes.[5,6] Several strategies exist to reduce the early-onset (first 6 days of life) GBS disease burden globally. In the USA, universal screening for rectovaginal GBS carriage of pregnant women between 35 and 37 weeks of gestation has been in place since 2002; for women with GBS carriage, intrapartum antibiotic prophylaxis (IAP) is offered.[7] By contrast, other countries offer IAP to pregnant women only if specific risk factors (such as maternal fever or having had a previous child with GBS disease) are present. In these countries, the cases of early-onset disease have not decreased to the same extent as in the USA. For example, in the UK, GBS cases have increased 19% from 2000–01 (0·48/1000 livebirths) to 2014–15 (0·57/1000 livebirths) and, in 2015, were double those found in the USA (0·21/1000 livebirths in 2015).[1,8] In South Africa, GBS incidence has remained consistently over 1·4/1000 livebirths since 2005, despite risk factor-based IAP strategies.[9] Importantly, although international and local guidelines exist for the management of neonatal and infant infection risk, these policies and guidelines are poorly implemented, making IAP administration suboptimal in most low-income and middle-income settings.[10]

Despite the reduction of early-onset disease in countries implementing universal screening,[8] GBS late-onset disease (7–90 days of life) has remained static over the past 10 years worldwide.[1,8,9,11] GBS is now the most important cause of bacterial meningitis in infants under 3 months of age in countries reporting late-onset disease incidence.[12,13] Therefore, a GBS vaccine could be a cost-effective method to reduce the burden of all forms of infant disease worldwide.[14]

Clinical evaluation of GBS vaccines with prevention of invasive neonatal and infant disease as a primary endpoint requires large studies, which are, therefore, best done in regions with relatively high GBS disease incidence. It is estimated that a vaccine efficacy study of approximately 60 000 pregnant women would be required to detect a 75% reduction in early-onset and late-onset disease in countries with a disease incidence of more than 1/1000 livebirths, assuming the vaccine protects against 90% of circulating serotypes.[14–16]

Seroprotective thresholds (usually an antibody titre or concentration above which no person has disease, or above which the risk or disease is substantially reduced) have been derived for several vaccines and have been useful in regulatory pathways for meningococcal serogroup W and Y polysaccharide vaccines, meningococcal serogroup B vaccines, and higher-valency formulations of pneumococcal polysaccharide-conjugate vaccines. Although important differences need to be considered between a GBS vaccine and these vaccines, serocorrelates of protection could have a role in the pathway to GBS vaccine registration, policy decisions, and implementation.

Several retrospective case control studies provide data that indicate that serocorrelates of protection against infant GBS disease might be determined.[17–20] The size of the cohorts in these studies ranged from 150 to 140 000 pregnant women and identified between 19 and 109 cases of neonatal and infant GBS serotype Ia and III disease, determined by a variety of microbiological methods, such as latex agglutination, PCR, or other tests. Each study showed that greater maternal anticapsular antibody concentration was associated with reduced GBS disease risk. However, no study was sufficiently statistically powered to provide a definitive answer, and

Correspondence to:
Kirsty Le Doare, Paediatric Infectious Diseases Research Group and Vaccine Institute, St George's Hospital, University of London, London SW17 0QT, UK
k.ledoare@nhs.net

because of the use of different assays, the comparison and pooling of these results was not possible. Therefore, the need to establish consensus around the data analyses used to identify serocorrelates of risk reduction in seroepidemiological studies and their role in the regulatory pathway.

Better defining a serocorrelate of risk reduction for neonatal and infant invasive GBS disease might prove useful to facilitate more rapid licensure and availability of a GBS vaccine for prevention of early-onset and late-onset disease. However, when applying a serocorrelate of risk reduction with a defined risk period, following maternal vaccination, additional factors (eg, placental IgG transfer, maternal comorbidity, and antibody decay) must be considered.[21] These factors are important, since a serocorrelate will need to show that vaccines can generate maternal antibodies that can be effectively transferred to her infant, and then persist so that they are protected not only against early-onset but also late-onset disease.

For the purposes of this Review, we use the term serocorrelates of protection when referring to a specific antibody response to a vaccine, or risk reduction when referring to a natural infection that is closely related to protection against infection, disease, or other defined endpoint (eg, prevention of stillbirth or premature birth).[22] We define natural antibody as an antibody developed from exposure to bacterial challenge, either from invasive disease or carriage. Publications from the non-GBS literature were selected to illustrate key insights from other vaccine-preventable diseases and are not intended to be an exhaustive review, because serocorrelates of protection in vaccination have been described in detail elsewhere.[22]

In this Review we aim to describe the evidence that antibodies are involved in invasive GBS disease or maternal and infant carriage risk reduction, and we review all targets that might be relevant for future vaccine evaluation. We also highlight key insights from existing vaccines against other pathogens, for which serological correlates have been applied, that could be used for the benefit of the GBS field and to identify the main considerations for the assessment of antibody mediating protection in future seroepidemiological studies.

Serotype-specific anticapsular antibodies

The importance of maternally-derived anti-GBS-IgG in preventing GBS invasive disease was first shown by Baker and colleagues[17] in the 1970s who showed that infants who developed GBS serotype III disease had significantly lower serotype III-specific IgG in maternal serum than infants without disease also born to women recto-vaginally colonised by that serotype.[17,23] Subsequent studies have shown similar results for serotypes Ia, Ib, and V in maternal serum.[24,25]

Determining a protective antibody concentration or titre is not easily achieved, since it can vary by serotype and the assessment of immunogenicity varies by the assay methods used. Originally, the radioantigen binding assay (RABA) was the gold standard for the quantification of anti-GBS antibodies because it measures antibody in its native state.[17] However, RABA quantifies all isotypes of antibody (including IgM) and so offers an incomplete picture of placentally transferred immunity because it does not distinguish between isotypes. Sub-sequently, antibody-binding assays have been used to measure antibody concentrations relative to a standard reference serum. More recently, Luminex or Bioplex platforms have been used to improve both the sensitivity and the throughput of the assays by measuring antibody against several GBS serotypes simultaneously.

A standardised immunoassay (with standardised reagents) will be a crucial step forward in the assessment of serocorrelates of protection against invasive GBS disease. Such assays would allow comparison of antibody data from studies in diverse geographies and between different vaccine products. The antigen used to detect the target antibodies needs to be in a native capsular polysaccharide (CPS) conformation that matches that on the surface of the GBS bacteria. The use of conjugated CPS to detect IgG raises concerns, as conjugation might alter efficiency of surface binding to the CPS, the ELISA plate, or both.[26]

Serotype-specific anticapsular antibodies in maternal serum

Several different values of invasive (eg, sepsis, pneumonia, and meningitis) neonatal and infant disease risk reduction have been proposed over the past 20 years, ranging from 0·5–10 µg/mL of serotype-specific IgG, depending on GBS serotype and country of study. In total, estimates for a serocorrelate of protection against serotype Ia are based on 119 infant disease cases and against serotype III GBS infant disease on 179 cases. Studies have been too small to determine corresponding information for remaining, less prevalent, GBS serotypes.

The first studies to describe a correlation between GBS disease risk reduction and anti-CPS IgG were undertaken by Lin and colleagues (table 1).[18,27] These case-control studies compared GBS CPS-specific IgG (measured by ELISA) from maternal and cord serum samples in infants born to GBS-colonised women who went on to develop early-onset disease compared with those of infants who remained healthy but were GBS-colonised at birth. Logistic regression analysis was used to compare the relative risk of disease at different antibody thresholds in 1 µg/mL increments to a reference value of less than 0·5 µg/mL for serotype Ia and less than 2 µg/mL for serotype III. With these reference values, they identified that thresholds of 5 µg/mL or more for serotype Ia and of 10 µg/mL or more for serotype III in maternal serum resulted in relative risk reduction of 85% or more for disease caused by these serotypes.[18,27]

An alternative modelling approach in three studies published between 2014 and 2016, involved Bayesian data

	Cases	Controls	Sampling methods	Method of IgG determination	Data analysis method	Proposed protective IgG concentration	Risk of disease protection
Baker et al (2014)[24]	26 cases of EOD; 17 cases of serotype Ia and 9 of serotype III	99 healthy infants born from colonised mothers	Maternal serum	Monoplex ELISA using in-house CPS and CB reference sera	Bayesian model with 1% background risk, antibody concentration compared with a reference value of 0·1 μg/mL	Serotype Ia and III ≥0·5 μg/mL; combined serotypes Ia and III >1 μg/mL	OR if antibody ≥0·5 μg/mL: 0·11 (95% CI 0·01–0·74) for serotype Ia; 0·09 (0·00–0·72) for serotype III; and 0·29 (0·01–3·10) for serotype V
Lin et al (2001)[27]	50 cases of EOD, serotype Ia	336 colonised infants without disease	Maternal and cord serum	ELISA using NABI reference sera, with known quantity of IgG (66 mg/mL of serotype Ia), and commercially available CPS	Logistical regression at fixed antibody concentration of 1 μg/mL compared with a reference value of <0·5 μg/mL	Maternal serotype Ia ≥5 μg/mL; cord serotype Ia ≥4 μg/mL	Maternal serum OR=0·12 (95%CI 0·02–0·93); cord serum relative risk reduction=91% (28–99)
Lin et al (2004)[18]	26 cases of EOD serotype III	143 colonised infants without disease	Maternal and cord serum	ELISA using NABI reference sera with known quantity of IgG (143 ng/mL for serotype III) and commercially available CPS	Logistical regression at fixed antibody concentration of 1 μg/mL compared with a reference value of <2 μg/mL	Maternal serotype III ≥10 μg/mL; cord serotype III ≥7 μg/mL	Maternal serum OR=0·09 (95% CI 0·01– 0·78); cord serum relative risk reduction=85% (29–97)
Fabbrini et al (2014)[28]	55 cases of EOD (14 cases of serotype Ia and 41 of serotype III); 66 cases of LOD (11 cases of serotype Ia and 55 of serotype III)	984 GBS colonised pregnant women and 473 non-colonised pregnant women	Maternal serum	ELISA using CB standard reference sera and OPkA using HL60 cells and rabbit complement, and commercially developed CPS	Bayesian modelling with 3% background risk	Serotype Ia and III ≥1 mg/mL	OR=0·19 (95%CI 0·0–0·6) for serotype Ia; OR=0·22 (0·0–0·55) for serotype III
Dangor et al (2015)[19]	22 cases of EOD (15 cases of serotype Ia and 7 of serotype III); 34 cases of LOD (12 cases of serotype Ia and 22 of serotype III)	135 colonised women and 352 non-colonised women	Maternal and infant serum	Fluorescence-based microbead immunosorbent assay using human immunoglobulin and commercially available CPS	Bayesian modelling with 1% background risk	Maternal serotype Ia ≥6 μg/mL and serotype III≥3 μg/mL; cord serotypes Ia and III ≥0·5 μg/mL	Maternal serum: RR= 6·5% (50% credible interval 1·4–21·9) for serotype Ia; RR=1·3% (0·1–9·9) for serotype III. Infant serum: RR=0·18 (0·04–0·85) for serotype Ia; RR=0·14 (0·02–1·38) for serotype III

In total, these studies analysed 179 infants with early-onset disease (EOD), 96 with serotype Ia and 83 with serotype III; 100 infants with late-onset disease (LOD), 23 with serotype Ia and 77 with serotype III; 479 healthy, group B streptococcus (GBS)-colonised infants; 1218 healthy infants born from GBS-colonised women; and 825 healthy infants born from non-colonised women. CPS=capsular polysaccharide. OPkA=opsonophagocytosis killing assay. CB=Carol Baker. NABI=Nabi pharmaceuticals. OR=odds ratio. RR=relative risk.

Table 1: **Studies proposing protective antibody concentrations for group B streptococcus serotype Ia and III**

analysis to estimate both absolute and relative risk reduction at different anti-GBS CPS IgG concentration cutoff values in case-control studies.[19,24,28] The Bayesian model uses data on the background disease risk in the population and the antibody distribution in the cases and controls to calculate the probability of disease above different antibody thresholds. The antibody distributions in cases and controls can either be modelled using parametric functions[29] or based on the empirical distributions.[28] The relative reduction in risk when antibody concentrations are above a threshold compared with the overall population risk can then be calculated using the Bayesian model with the advantage of not needing to define a reference comparator antibody concentration as in the studies by Lin and colleagues.[18,27]

Baker and colleagues[24] compared maternal serum from colonised women who had healthy infants with women who had infants with early-onset disease in a case control study using Bayesian modelling. They found a 90% relative risk reduction of early-onset disease for serotypes Ia (95% CI 26–99) and III (28–100) with antibody concentrations (measured with ELISA) of 0·5 μg/mL or more in maternal serum compared with a reference value of less than 0·1 μg/mL.[24] Combining data for serotypes Ia, III, and V provided an estimated 70% risk reduction for disease due to these three serotypes with antibody concentrations in maternal serum of more than 1 μg/mL.[24]

Antibody thresholds were similar for serotypes Ia and III in the Fabbrini and colleagues'[28] study based on cases and controls of European maternal sera from GBS colonised and non-colonised women. This study used a positive reference serum developed by Carol Baker in a multiplex ELISA assay and Bayesian modelling.[28] Fabbrini and colleagues[28] predicted a 75% absolute early-onset disease risk reduction with anti-CPS IgG concentrations of 1 μg/mL or more for serotypes Ia and III. They also predicted a 76% risk reduction (95% prediction interval 21–100) in late-onset disease caused by serotype III with antibody concentrations of 1 μg/mL or more.

Dangor and colleagues[19] used the Bayesian model in a South African population to determine the relative and absolute risk of a mother giving birth to an infant with GBS disease (early-onset or late-onset) at different antibody thresholds, with both colonised and non-colonised mothers with healthy infants as controls. In this analysis, maternal anti-CPS IgG concentrations of 6 µg/mL or more for GBS serotype Ia and 3 µg/mL or more for GBS serotype III were associated with a combined relative risk of GBS disease in infants of less than 10% (6·5% for serotype III [50% credible interval 1·4–21·9] and 1·3% for serotype Ia [0·1–9·9]).[19]

Comparison between these four studies is difficult for several reasons. Comparison between the Lin and colleagues studies[18,27] and any of the Bayesian modelling studies is not possible because of differences in data analysis methods and the selected endpoints (relative risk reduction at threshold cutoffs versus absolute or relative risk reduction using continuous antibody thresholds). Even for those studies using the Bayesian model direct comparison is problematic. Baker and colleagues[24] and Dangor and colleagues[19] used the same disease risk assumption (1% risk), whereas the Fabbrini and colleagues study[28] used a 3% background risk. Assay parameters and CPS and reference sera used are additional issues, which lead to the appearance of variation in specific antibody concentration thresholds of risk reduction for individual strains and for different GBS serotypes. Lin and colleagues[18,27] used vaccinee sera from Nabi pharmaceuticals from an adult vaccinated with a quadravalent vaccine and commercially available CPS (Dynatech Laboratories), whereas Baker and colleagues[24] and Fabbrini and colleagues[28] used reference serum from monovalent vaccine studies done in the USA with CPS from in-house (Baker and colleagues)[24] or commercially developed (GlaxoSmithKlein [GSK])[28] stocks, and Dangor and colleagues[19] used human gammaglobulin standards (calibrated to Carol Baker reference standards) and CPS supplied by GSK.[19] Assay methods also differ in each study. The studies by Baker and colleagues and Lin and colleagues[18,27] used different monoplex ELISA and CPS-conjugation methods, the study by Fabbrini and colleagues[28] used a multiplex ELISA, and the study by Dangor and colleagues[19] used the Luminex platform, all with different data analysis. Finally, control populations varied between studies, with Baker and colleagues and Lin and colleagues using colonised women with healthy infants as controls, and Fabbrini and colleagues[28] and Dangor and colleagues[19] selecting both colonised and non-colonised women as controls (but with considerable variations in control selection in both studies).

Serotype-specific anti-capsular antibodies in infant serum

All studies[18,19,24,27,28] have measured maternal serum to estimate protective antibody concentrations against early-onset disease. However, as placental antibody transfer of anti-CPS antibodies is less than 100%,[30] antibody concentration in cord or infant sera is also important to consider. Lin and colleagues[18,27] also measured antibodies from cord serum, and found that thresholds of 4 µg/mL or more for serotype Ia and of 7 µg/mL or more for serotype III were associated with a 91% (95% CI 28–99) relative risk reduction for serotype Ia and 85% (29–97) for serotype III disease.[18,27] Dangor and colleagues[19] also collected paired mother and infant sera and determined adjusted odds ratios for disease with antibody concentrations of more than 0·5 µg/mL in infant serum for serotype Ia were 0·18 (0·04–0·85) and 0·14 (0·02–1·38) for serotype III.[19] However, these data were not used in the Bayesian model.[19] At present, estimation of serocorrelates of GBS disease risk reduction from studies reporting antibody concentrations in infant sera is not possible.

Anti-protein IgG antibodies and neonatal and infant disease risk reduction

Proteins on the surface of GBS are also potential targets for antibodies. Several case-control studies have shown an association between high anti-Rib protein antibodies and GBS disease risk reduction. A significant association was noted between high concentrations of naturally occurring antibody against Rib and reduced invasive GBS disease risk (adjusted odds ratio 0·002 [95%CI 0·00 to 0·57]; p=0·03).[31] However, this was a small study (30 infants with disease and 60 healthy controls) and thus was unable to fully assess a correlation between anti-Rib protein antibody and disease. In addition to anti-CPS IgG, Fabbrini and colleagues[28] used the Bayesian model to investigate antipilus protein BP-1, API-2a, and BP-2b antibodies (pilus-island [PI] PI-1, PI-2a, and PI-2, respectively) against early-onset disease isolates expressing these proteins.[28] They found that, compared with infants who remained healthy during the 7-day follow up period, sera of mothers delivering infants who developed early-onset disease had significantly lower antibody titres against BP-1 and API-2a but not BP-2b (table 2).[28] However, no association between fibrinogen-binding protein A or PI-1, PI-2a, and PI-2 antibodies and disease was observed in a similar study of all-cause GBS invasive disease in South Africa.[32] This study used Bayesian modelling to predict antibody thresholds associated with a relative risk of less than 10% for invasive disease but was unable to predict anti-protein antibody concentrations associated with protection for any of the proteins tested.

These conflicting data highlight some of the outstanding issues in determining the role of protein targets and serological protection against invasive disease. Difficulties in comparing these three studies also arise from variations in assay methods, source of proteins, and lack of a common reference serum, in addition to study design differences (table 2).

	Cases	Controls	Sampling methods	Method of IgG determination	Method of data analysis	Proposed protective IgG concentration	Risk of disease protection
Larsson et al (2006)[31]	30 cases for Rib in infants with disease	Infants admitted to the neonatal unit without signs of infection	Maternal and infant serum	ELISA against Rib and α proteins using in-house protein preparations and immunoglobulin reference sera	Logistical regression	Not stated	AOR=0·002 (95% CI 0–0·57)
Fabbrini et al (2014)[28]	35 cases for Pili 1, 25 for Pili 2a, and 18 for Pili 3 in infants with disease	428 Pili 1 GBS colonised pregnant women, 568 Pili 2a GBS colonised pregnant women, 107 Pili 2b GBS colonised pregnant women	Maternal serum	ELISA against Pili 1, 2a, and 2b proteins using in-house protein preparations and high protein titre reference sera	Logistical regression	Not stated	BP-1 (antibody against Pili1) 13·5 EU/mL for disease (LLOQ of 555 EU/mL) *vs* 21·3 EU/mL for controls (LLOQ of 1083 EU/mL, 37% lower in disease); API-2a (antibody against Pili 2a) 28·8 EU/mL for disease (LLOQ of 160 EU/mL) *vs* 37·3 EU/mL for controls (LLOQ of 523 EU/mL, 23% lower in disease); no association between antibody against Pili 2b and disease
Dangor et al (2015)[32]	FbsA or BibA proteins, 34 cases of EOD and 35 cases of LOD	Healthy infants without disease, 75 infants under 6 days old and 53 between 7 and 89 days old	Maternal and infant serum	ELISA against BibA, FbsA, Pili 1, Pili 2a, and Pili 2b proteins using in-house protein preparations and high protein titre reference sera	Bayesian modelling	None found	No associations found

EOD=early-onset GBS disease. LOD=late-onset GBS disease. FbSA=fibrinogen-binding protein. BiBA=group B streptococcus immunogenic bacterial adhesin. GBS=group B streptococcus. EU=endotoxin units. LLOQ=lower limit of quantification. AOR=adjusted odds ratio. OR=odds ratio. RR=relative risk.

***Table 2*: Studies proposing protective antibody concentrations for group B streptococcus surface proteins**

The role of antibody-mediated killing in disease risk reduction

Fewer studies have considered the role of antibody in GBS disease risk reduction using opsonophagocytosis assays (OPkAs).[29,33–35] Two in-vitro GBS OPkAs that use different approaches are available. One approach, which was also used for pneumococcal vaccine studies and licensure, determines the dilution of antiserum that kills at least half of the target bacteria in the presence of exogenous complement.[28] The other approach, which has been used in the majority of GBS studies, determines the degree of bacterial killing over a fixed incubation period by a human serum sample with endogenous complement.[34]

Studies in both animals and humans indicate that functional activity of OPkA appears to correlate well with GBS-serotype specific anti-CPS antibody concen-tration.[28,34] Baker and colleagues[35] have shown that adult sera containing high concentrations of anti-GBS CPS antibodies are capable of promoting efficient opsonisation and phagocytosis of GBS in vitro. Studies in non-pregnant adults also indicate that higher vaccine-induced antibody concentrations generate greater opsonophagocytic killing against serotypes Ia, Ib,[36] II,[37] and V.[38]

Opsonophagocytosis-mediated by antibodies in maternal serum

Only one study has compared maternal antibody concentration with opsonophagocytosis from natural antibodies.[28] This study found significant correlations between maternal IgG against serotypes Ia, Ib, and III (measured by multiplex ELISA) and opsonophagocytosis (percentage killing with exogenous complement), when IgG antibody concentrations were higher than 1 µg/mL (R=0·8 for serotype Ia, R=0·8 for serotype Ib, R=0·85 for serotype III).[28] Extrapolation using the correlation coefficients from this study suggests that doubling the IgG concentration might increase the OPkA titre by 70–80% and also adds evidence that a serocorrelate of protection might be established at around 1 µg/mL and OPkA titres of 1/64–1/128 for serotypes Ia and III.[28]

Opsonophagocytosis mediated by antibodies in infant serum

It might be important to consider the effect of antibody function in neonatal or infant serum, since differences in their immune function might alter the response to GBS challenge compared with adult sera. No studies

***Panel 1*: Lessons learned from vaccines**

- Mechanisms of natural immune protection are similar to vaccine-derived protection (eg, serum bactericidal antibody for *Haemophilus influenzae* type b and *Neisseria meningitidis*, or opsonophagocytosis for pneumococcus)
- Protection depends on functional antibodies in infant studies (eg, bactericidal antibodies from *H influenzae* type b and meningococcus, and opsonophagocytic antibodies for pneumococcus)
- Thresholds defined for one serogroup or serotype have been used as evidence to inform a putative threshold for rarer serogroups or serotypes (eg, pneumococcal 13-valent vaccines that were licensed for additional serotypes without additional efficacy data to that available for seven-valent vaccines); aggregate thresholds were used temporarily for rarer pneumococcal serotypes before it was possible to establish individual serotype-specific thresholds

have investigated the association between antibody function in neonatal and infant serum at the time of disease and disease risk reduction. Only one small study investigated antibody function in convalescent sera of ten infants with GBS disease and their mothers using endogenous complement.[35] This study showed that when antibody concentrations measured by RABA were more than 2 µg/mL, killing was uniformly more than 1 log reduction in colony forming units (five infants) while bactericidal activity was highly variable with antibody concentrations of less than 2 µg/mL.[35]

Although opsonophagocytic killing is important in studies of infant vaccination, in the case when a maternal vaccine producing IgG antibody that crosses the placenta is the sole mechanism of protection against invasive neonatal and infant GBS disease, it might suffice to measure the non-functional IgG antibody that correlates with opsonophagocytic killing activity. If the clinical endpoints for vaccine efficacy include endpoints other than invasive GBS disease, such as maternal carriage or puerperal sepsis, when IgM could also contribute to protection,[39] determination of functional activity might become more important.

The role of antibody in reduction of maternal, neonate, and infant carriage risk

Maternal carriage is a prerequisite for early-onset disease; therefore, several studies of vaccine and natural immune sera have investigated whether GBS carriage could be used as a clinical endpoint in trials of vaccine efficacy. Although cross-sectional studies show higher concentrations of naturally acquired GBS IgG antibody in colonised compared with non-colonised women,[40] in a longitudinal study of pregnant women tested for carriage at 6 weekly intervals, between 20–25 weeks of pregnancy and delivery, Kwatra and colleagues[41] found that IgG antibody of 1 µg/mL or more for serotype V (odds ratio of 0·23 [95% CI 0·05–1·02]), and 3 µg/mL or more for serotypes Ia (0·37 [0·14–0·98]) and III (0·11 [0·01–1·75]) were associated with absence of carriage by these serotypes throughout pregnancy. Furthermore, absent carriage was associated with OPkA titres of more than 1/14 [1/14 *vs* 1/5; p<0·001) for serotype Ia and of more than 1/132 (1/132 *vs* 1/20; p<0·001) for serotype III.[41]

A study of 750 pregnant women from The Gambia also indicated that antibody-mediated complement deposition onto the surface of whole GBS bacteria, measured by flow cytometry above the 95th centile of the GMC (equivalent to an OPkA titre of 1/3000), was associated with absent neonatal and infant carriage for serotype V at birth and on day 60–89 of life (p<0·001).[42]

These results are not directly comparable because of major methodological differences in study design and antibody analysis. In addition, whereas the role of maternal GBS carriage in the development of early-onset disease is well established, transmission of GBS from a source other than the mother can also cause late-onset disease. Therefore, using reduction of maternal carriage as a clinical endpoint might be less predictive of prevention against late-onset than against early-onset disease. This consideration is particularly important given that an advantage of vaccination over IAP is its expected protection against late-onset disease.

Lessons learned from vaccines against other bacterial pathogens

The experience gained from defining serocorrelates of protection against the encapsulated bacterium *Haemophilus influenzae* type b (Hib) might provide important lessons in defining serocorrelates of risk reduction from seroepidemiological studies (panel 1). In 1933, an inverse relationship between disease occurrence and serum Hib bactericidal activity was noted.[43] The same inverse relationship was later shown for specific anticapsular antibodies.[44] However, since protection was required against infant Hib disease (especially meningitis), for which antibody concentrations required for protection might differ, Smith and colleagues[45] determined that IgG concentrations of more than 0·2 µg/mL were protective. Further evidence for antibody-mediated protection against invasive Hib disease came from phase 2 and 3 vaccine trials in over 30 000 children in Finland. Hib vaccine was rolled out during this trial, therefore, age-specific Hib disease incidence declined significantly when antibody concentrations were more than 0·15 µg/mL (aggregate concentration), with long-term protection associated with concentrations of more than 1 µg/mL.[46] Although the correct threshold[47] and assay to use[48] were debated, the consensus of the scientific community was that an anti-Hib antibody concentration of 0·15 µg/mL was likely to be associated with protection against infant bacteraemia.[44]

In addition to Hib, seroepidemiology studies were used to show the importance of complement-dependent, antibody-mediated bactericidal activity for protection from invasive meningococcal disease in two seminal seroepidemiological studies.[49,50] The first study was in infants through to young adults (up to 26 years of age) and showed an inverse relationship between the age-specific prevalence of serum bactericidal activity and the incidence of meningococcal disease caused by serogroups A, B, and C. In infants, these antibodies were maternally derived and declined after birth. The second study, done in military recruits, was able to define the serocorrelate of protection on the basis of serum bactericidal titre. This work was validated by showing the efficacy of serogroup C polysaccharide vaccines[51] and led to the licensure of subsequent meningococcal vaccines based on serocorrelates of protection. For example, for the meningococcus C conjugate vaccine, early discussions between manufacturers and the UK Medicines Control Agency indicated that licensure on the basis of immunogenicity data alone, without direct evidence of protective efficacy, might be considered.[52] The basis for this decision in the UK was, firstly, that plain serogroup C polysaccharide vaccines were already licensed for children aged 2 years and older and earlier trials provided direct evidence of efficacy.[52] Secondly, serum bactericidal activity was accepted as a serological correlate of protection, which could be extrapolated to infants in whom the unconjugated meningococcus C polysaccharide was neither immunogenic nor efficacious.[53] This approach established an important precedent for other meningococcal conjugate polysaccharide vaccines.[52]

Efficacy of meningococcus B outer membrane vesicle vaccines was shown in Cuba[54] and Norway[55] and was associated with induction of serum bactericidal activity.[56] For new protein-based meningococcus B vaccines, protection against disease was extrapolated from the in-vitro ability of vaccinee sera to kill bacteria with vaccine-matched antigens in the presence of human complement.[57] The efficacy of the 4CMenB vaccine is being evaluated following implementation in the UK infant immunisation schedule.[58]

Initial pneumococcal IgG antibody serocorrelates of protection against invasive disease were developed after vaccines had been licensed using efficacy studies, on the basis of an aggregate IgG value of three common serotypes from three clinical trials and agreed by consensus opinion to be more than 0·35 µg/mL.[59] As more data became available from subsequent trials, serocorrelates of protection against other (but not all) serotypes were identified. A UK postlicensure study[60] indicated that pneumococcus serotype-specific correlates of protection were higher than 0·35 µg/mL for serotypes 1, 3, 7F, 19A, and 19F, and lower for 6A, 6B, 18C, and 23F. Correlation between post-vaccination opsonophagocytic pneumococcal antibody titre and IgG as measured by ELISA has also been reported (0·2 µg/mL IgG corresponds to an opsonophagocytic killing titre of 1/8).[61] Extensive consultations, facilitated by WHO, were undertaken to standardise both binding and functional assays for the assessment of pneumococcal antibody to aid prediction of serocorrelates. This approach has paved the way for collaborative working for other pathogens such as GBS. Efforts are underway within a large scientific, industrial, and technical consortium (GASTON) to standardise assays in order to define serocorrelates of risk reduction for neonatal and infant GBS disease.[21]

***Panel 2:* Next steps and future research for seroepidemiological studies of group B streptococcus disease**

- Standardise the assays to assess antibody quantity and function against group B streptococcus and establish the correlation between them
- Use the immunity derived from natural exposure to GBS from large prospective case control studies in diverse populations to predict serocorrelates of disease risk reduction
- Study factors influencing antibody transfer from mother to infant (including malaria, HIV, and gestation) and antibody decline between birth and 3 months of life

Further considerations for prediction of serocorrelates of risk reduction

In considering a serocorrelate of risk reduction for invasive neonatal or infant disease provided by maternal anti-GBS CPS IgG, either from immunity derived from natural exposure or from a vaccine study, additional consideration should be given to the site of measurement (maternal or infant serum), the passage of the IgG across the placenta at different gestations and, thus, the effect of prematurity or maternal comorbidity or infection on the correlate, and the longevity of the antibody to protect for the duration of the at risk period for GBS (panel 2).

Antibody persistence following vaccination in pregnancy

Both IgG concentration and opsonophagocytosis have been measured in a small study of 30 vaccinated women and their infants up to day 90 post partum with IgG decline of 50–75% in infants.[62]

In pregnant women, post-vaccination IgG responses to GBS serotypes Ia, Ib, II, III, and V peak at 4–8 weeks and then remain detectable for 26–52 weeks after delivery.[36,37,63,64] Healthy South African vaccinated pregnant women had maternal antibody concentrations post-vaccination of more than 1 µg/mL for serotypes Ia, Ib, and III at day 91 post partum.[65] The most recent multicentre study, published in 2016, of a variety of doses of a trivalent vaccine reported measurable antibody concentrations post-vaccination at 361 days post partum in South African, Belgian, and Canadian women

Search strategy and selection criteria

We searched PubMed for "group B streptococcus" OR "streptococcus agalactiae" (MeSH terms) AND "antibody" OR "vaccination" OR "immunisation" OR "vaccine" OR "pregnancy", for papers published until May 5, 2018. Multiple spellings, truncated nomenclature, and abbreviations were also used as search terms. Articles and their references lists were reviewed without language restrictions. Articles were included if they reported on antibodies against group B streptococcus (GBS) in studies comparing infants with GBS disease with infants without the disease; antibodies against GBS in vaccine trials comparing vaccinated and unvaccinated populations; or on antibodies measured in studies in which the primary endpoint was either protection against invasive GBS disease or protection against infant or maternal carriage.

(1·97–2·78 μg/mL for serotype Ia and 0·51– 0·69 μg/mL for serotype III),[65] with an antibody half-life of 42 days in infants without HIV infection.[66]

In infants, results from phase 1 and 2 trials of GBS-CPS conjugate vaccines show that IgG antibody decreases to around 25% of maternal concentrations by 3 months of age.[62,66,67] For example, in a small study of women vaccinated during pregnancy with a GBS serotype III conjugate vaccine, infants were found to have 50% of birth anti-GBS-CPS antibody concentrations at 1 month of age and 30% at 2 months of age, although opsonophagocytosis was observed up to 2 months of age in all infants with detectable anti-CPS antibody.[62] In this vaccine study, antibody levels remained higher than 1 μg/mL in 95% of infant sera at 2 months of age.[62] A second small study reported antibody decay of 22–25% of birth concentrations 91 days after birth in vaccinated infants, but with antibody concentrations at least five times higher than in the unvaccinated control group.[67]

Placental antibody transfer and the effect of comorbidities

Placental antibody transfer with CPS vaccines is often less than that for protein vaccines because of the antibody isotype generated (ie, preferential placental transfer of IgG1 over IgG2 subclasses). In the case of the investigational GBS CPS-protein conjugate vaccines, placental transfer ratios of less than one have been reported for all serotypes tested, despite conjugation with tetanus toxoid or CRM_{197}. Thus, measuring antibody in mother cord or infant sera is important, since variations in placental transfer will affect antibody concentrations that are used to predict any serocorrelate.

The first small study of 30 pregnant women vaccinated with a CPS-tetanus toxoid conjugate vaccine showed a post-vaccination serotype-specific IgG concentration of 10 μg/mL and a median placental transfer ratio of 0·77.[62] Several studies have investigated the immunogenicity of the trivalent (serotypes Ia, Ib, and III) CRM_{197} conjugate vaccine. A small study from Belgium and Canada[67] enrolled 86 pregnant women and showed geometric mean placental antibody transfer ratios of 0·68–0·81, depending on serotype. A large vaccine study of 320 healthy HIV-negative women and 317 infants, in South Africa, showed placental antibody transfer ratios of 0·58 for serotype Ia, 0·65 for serotype Ib, and 0·72 for serotype III.[65] A second multicentre vaccine study from South Africa and Malawi of 270 HIV-infected and uninfected pregnant women and 266 infants showed similar placental transfer ratios between HIV-infected women with low and high CD4 counts and HIV-uninfected women but reduced immunogenicity associated with HIV infection.[66] To our knowledge, no studies to assess other conditions that might affect placental transfer of anti-CPS GBS antibody, such as prematurity or malaria, or to assess placental transfer of protein-based vaccines are available.

Conclusion

Data suggest that anti-GBS-CPS IgG concentrations between 1–10 μg/mL are protective for GBS serotypes Ia and III. These concentrations would be well within responses seen in phase 1 and 2 vaccine studies done to date, indicating that vaccination might provide protective antibody concentrations.[36,62,65,66] The most probable mechanism of action for a GBS-CPS protein conjugate vaccine is to induce antibodies that can facilitate GBS killing via opsonophagocytosis. No indicated protective opsonophagocytosis titre has been defined. Studies that measure antibody in maternal serum are complicated by the presence of IgM that, unlike IgG, is not transferred to the baby; therefore, it remains important to measure maternal and cord or infant serum antibodies.

Importantly, in higher disease-burden settings, antibody thresholds required for protection might need to be high because of co-infection leading to impaired GBS-specific placental antibody transfer, which should be considered when extrapolating efficacy data between populations.[68] A further consideration is that high antibody concentrations measured in some populations might be due to a high background GBS carriage, which could mean that thresholds for protection would need to be correspondingly higher in these settings.

Sponsors will need to agree on the approach and the assay to be used for serocorrelates to be the basis for licensure. In addition, for a vaccine to be implemented, consensus among public health bodies is needed to show that the vaccine adds benefit to existing IAP strategies. As vaccine development progresses, these decisions become imperative if the vaccine is to reach the people that need it most as quickly as possible.

Contributors

KLD devised and prepared the manuscript and did the literature search. DG, MHN, CB, and AG provided expert opinion on serocorrelates of

protection for inclusion in this manuscript and contributed to the editing of the manuscript. BK, JV, PTH, CB, MSE, GK, NA, SAM, AStM, ASA, BC, and PF provided expert input into the preparation of this manuscript and revised the final draft.

Declaration of interests

KLD has received an honorarium travel grant from Pfizer. BK directs IMmunising PRegnant women and INfants neTwork (IMPRINT), funded by the Global Challenges Research Fund Networks in Vaccines Research and Development that was co-funded by the UK Medical Research Council (MRC), the Biotechnology and Biological Sciences Research Council, and the National Vaccine Program Office; and is the theme leader at the MRC unit in The Gambia that has previously received funding for vaccine trials, including vaccines produced by Pfizer and GSK. PTH is an investigator for clinical trials done on behalf of St George's Hospital, St George's University of London, UK, sponsored by various vaccine manufacturers, including Novartis, Pfizer, and GSK, and has been a consultant to Novartis and Pfizer on GBS vaccines, but received no personal funding for these activities. DG participates in advisory boards and consultancies for vaccine manufacturers, including Merck, Sanofi Pasteur, and GSK. CB has been an adviser to GSK and Pfizer. MSE has received a research grant from Pfizer. GK has received funds from Pfizer to attend a meeting. AStM is an employee of the Bill & Melinda Gates Foundation, which funded this Review. ASA is employed by Pfizer and owns stock in the company. BC is employed by the GSK group of companies and owns stock of the GSK group of companies. The phase 2 studies investigating the trivalent CRM_{197} conjugate GBS vaccine were initially supported by Novartis Vaccines and Diagnostics, before the divestiture of its non-influenza vaccine business, which was acquired by GSK Biologicals in March, 2015. PF is an employee of Minervax and owns stock in the company. AG has received a grant for meeting travel from Pfizer. SAM, JV, MHN, and NA have nothing to declare.

Acknowledgments

This Review was funded by a grant (OPP1119788) from the Bill & Melinda Gates Foundation.

References

1 O'Sullivan CP, Lamagni T, Patel D, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study. *Lancet Infect Dis* 2018; **19:** 83–90.

2 Sigauque B, Kobayashi M, Vubil D, et al. Invasive bacterial disease trends and characterization of group B streptococcal isolates among young infants in southern Mozambique, 2001–2015. *PLoS One* 2018; **13:** e0191193.

3 Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the burden of group B streptococcal disease worldwide for pregnant women, stillbirths, and children. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S200–19.

4 Le Doare K, Heath PT. An overview of global GBS epidemiology. *Vaccine* 2013; **31** (suppl 4)**:** D7–12.

5 Kohli-Lynch M, Russell NJ, Seale AC, et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S190–99.

6 Bedford H, de Louvois J, Halket S, Peckham C, Hurley R, Harvey D. Meningitis in infancy in England and Wales: follow up at age 5 years. *BMJ* 2001; **323:** 533–36.

7 Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep* 2002; **51:** 1–22.

8 Active Bacterial Core Surveillance (ABCs) Report. Emerging infections program network group B streptococcus, 2016. https://www.cdc.gov/abcs/reports-findings/survreports/gbs16.html (accessed May 26, 2018).

9 Dangor Z, Cutland CL, Izu A, et al. Temporal changes in invasive group B streptococcus serotypes: implications for vaccine development. *PLoS One* 2016; **11:** e0169101.

10 Le Doare K, O'Driscoll M, Turner K, et al. Intrapartum antibiotic chemoprophylaxis policies for the prevention of group B streptococcal disease worldwide: systematic review. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S143–51.

11 Madrid L, Seale AC, Kohli-Lynch M, et al. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. *Clin Infect Dis* 2017; **65** (suppl 2)**:** S160–72.

12 Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med* 2011; **364:** 2016–25.

13 Sadarangani M, Willis L, Kadambari S, et al. Childhood meningitis in the conjugate vaccine era: a prospective cohort study. *Arch Dis Child* 2015; **100:** 292–94.

14 Kobayashi M, Vekemans J, Baker CJ, Ratner AJ, Le Doare K, Schrag SJ. Group B streptococcus vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries. *F1000Res* 2016; **5:** 2355.

15 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; **31** (suppl 4)**:** D52–57.

16 Kobayashi M, Schrag SJ, Alderson MR, et al. WHO consultation on group B streptococcus vaccine development: report from a meeting held on 27–28 April, 2016. *Vaccine* 2016; published online Dec 22. DOI:10.1016/j.vaccine.2016.12.029.

17 Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. *N Engl J Med* 1976; **294:** 753–56.

18 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. *J Infect Dis* 2004; **190:** 928–34.

19 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:** 6793–99.

20 Feldman RG, Ferrante A. Prevalence of anti-group B streptococcal type III capsular IgG antibodies in the United Kingdom and an analysis of their specific IgG subclasses. *J Infect Dis* 1990; **162:** 883–87.

21 Vekemans J, Moorthy V, Friede M, et al. Maternal immunization against group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. *Vaccine* 2018; published online Feb 2. DOI:10.1016/j.vaccine.2017.09.087.

22 Plotkin SA. Vaccines: correlates of vaccine-induced immunity. *Clin Infect Dis* 2008; **47:** 401–09.

23 Baker CJ, Kasper DL, Tager I, et al. Quantitative determination of antibody to capsular polysaccharide in infection with type III strains of group B streptococcus. *J Clin Invest* 1977; **59:** 810–18.

24 Baker CJ, Carey VJ, Rench MA, et al. Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. *J Infect Dis* 2014; **209:** 781–88.

25 Christensen KK, Christensen P, Dahlander K, Faxelius G, Jacobson B, Svenningsen N. Quantitation of serum antibodies to surface antigens of group B streptococci types Ia, Ib, and III: low antibody levels in mothers of neonatally infected infants. *Scand J Infect Dis* 1980; **12:** 105–10.

26 Kasper DL, Wessels MR, Guttormsen HK, Paoletti LC, Edwards MS, Baker CJ. Measurement of human antibodies to type III group B Streptococcus. *Infect Immun* 1999; **67:** 4303–05.

27 Lin FY, Philips JB 3rd, 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. *J Infect Dis* 2001; **184:** 1022–28.

28 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. *Clin Infect Dis* 2016; **63:** 746–53.

29 Carey VJ, Baker CJ, Platt R. Bayesian inference on protective antibody levels using case-control data. *Biometrics* 2001; **57:** 135–42.

30 Calvert A, Jones CE. Placental transfer of antibody and its relationship to vaccination in pregnancy. *Curr Opin Infect Dis* 2017; **30:** 268–73.

31 Larsson C, Lindroth M, Nordin P, Stalhammar-Carlemalm M, Lindahl G, Krantz I. Association between low concentrations of antibodies to protein alpha and Rib and invasive neonatal group B streptococcal infection. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F403–08.

32 Dangor Z, Kwatra G, Izu A, et al. Association between maternal group B streptococcus surface-protein antibody concentrations and invasive disease in their infants. *Expert Rev Vaccines* 2015; **14:** 1651–60.

33 Baltimore RS, Kasper DL, Baker CJ, Goroff DK. Antigenic specificity of opsonophagocytic antibodies in rabbit anti-sera to group B streptococci. *J Immunol* 1977; **118:** 673–78.

34 Edwards MS, Baker CJ, Kasper DL. Opsonic specificity of human antibody to the type III polysaccharide of group B streptococcus. *J Infect Dis* 1979; **140:** 1004–08.

35 Baker CJ, Edwards MS, Kasper DL. Role of antibody to native type III polysaccharide of group B streptococcus in infant infection. *Pediatrics* 1981; **68:** 544–49.

36 Baker CJ, Paoletti LC, Wessels MR, et al. Safety and immunogenicity of capsular polysaccharide-tetanus toxoid conjugate vaccines for group B streptococcal types Ia and Ib. *J Infect Dis* 1999; **179:** 142–50.

37 Baker CJ, Paoletti LC, Rench MA, et al. Use of capsular polysaccharide-tetanus toxoid conjugate vaccine for type II group B streptococcus in healthy women. *J Infect Dis* 2000; **182:** 1129–38.

38 Baker CJ, Rench MA, Paoletti LC, Edwards MS. Dose-response to type V group B streptococcal polysaccharide-tetanus toxoid conjugate vaccine in healthy adults. *Vaccine* 2007; **25:** 55–63.

39 Glynn AA. Immunity in acute bacterial infections. *Ann R Coll Surg Engl* 1975; **56:** 212–17.

40 Baker CJ, Webb BJ, Kasper DL, Yow MD, Beachler CW. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. II. Determination of serum antibody to capsular polysaccharide from type III, group B streptococcus. *Am J Obstet Gynecol* 1980; **137:** 39–42.

41 Kwatra G, Adrian PV, Shiri T, Buchmann EJ, Cutland CL, Madhi SA. Natural acquired humoral immunity against serotype-specific group B streptococcus rectovaginal colonization acquisition in pregnant women. *Clin Microbiol Infect* 2015; **21:** 568.e13–21.

42 Le Doare K, Faal A, Jaiteh M, et al. Association between functional antibody against group B streptococcus and maternal and infant colonization in a Gambian cohort. *Vaccine* 2017; **35:** 2970–78.

43 Le Roy D, Fothergill L, Wright J. Relation of age incidence to the bactericidal power of blood against the causal organism. *J Immunol* 1933; **24:** 273–84.

44 Kayhty H. Difficulties in establishing a serological correlate of protection after immunization with *Haemophilus influenzae* conjugate vaccines. *Biologicals* 1994; **22:** 397–402.

45 Smith DH, Peter G, Ingram DL, Harding AL, Anderson P. Responses of children immunized with the capsular polysaccharide of *Hemophilus influenzae*, type b. *Pediatrics* 1973; **52:** 637–44.

46 Kayhty H, Peltola H, Karanko V, Makela PH. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1983; **147:** 1100.

47 Makela PH, Peltola H, Kayhty H, et al. Polysaccharide vaccines of group A *Neisseria meningtitidis* and *Haemophilus influenzae* type b: a field trial in Finland. *J Infect Dis* 1977; **136** (suppl)**:** S43–50.

48 Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1984; **149:** 1034–35.

49 Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med* 1969; **129:** 1307–26.

50 Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. II. Development of natural immunity. *J Exp Med* 1969; **129:** 1327–48.

51 Gold R, Lepow ML, Goldschneider I, Draper TL, Gotschlich EC. Clinical evaluation of group A and group C meningococcal polysaccharide vaccines in infants. *J Clin Invest* 1975; **56:** 1536–47.

52 Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* 2001; **20** (suppl 1)**:** S58–67.

53 Rosenstein N, Levine O, Taylor JP, et al. Efficacy of meningococcal vaccine and barriers to vaccination. *JAMA* 1998; **279:** 435–39.

54 Sierra GV, Campa HC, Varcacel NM, et al. Vaccine against group B *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. *NIPH Ann* 1991; **14:** 195–207.

55 Bjune G, Høiby EA, Grønnesby JK, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 1991; **338:** 1093–96.

56 Holst J, Feiring B, Fuglesang JE, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. *Vaccine* 2003; **21:** 734–37.

57 Toneatto D, Pizza M, Masignani V, Rappuoli R. Emerging experience with meningococcal serogroup B protein vaccines. *Expert Rev Vaccines* 2017; **16:** 433–51.

58 Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *Lancet* 2016; **388:** 2775–82.

59 Siber GR, Chang I, Baker S, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* 2007; **25:** 3816–26.

60 Andrews NJ, Waight PA, Burbidge P, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. *Lancet Infect Dis* 2014; **14:** 839–46.

61 Goldblatt D, Southern J, Ashton L, et al. Immunogenicity of a reduced schedule of pneumococcal conjugate vaccine in healthy infants and correlates of protection for serotype 6B in the United Kingdom. *Pediatr Infect Dis J* 2010; **29**: 401–05.

62 Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. *Vaccine* 2003; **21:** 3468–72.

63 Baker CJ, Paoletti LC, Rench MA, Guttormsen HK, Edwards MS, Kasper DL. Immune response of healthy women to 2 different group B streptococcal type V capsular polysaccharide-protein conjugate vaccines. *J Infect Dis* 2004; **189:** 1103–12.

64 Baker CJ, Rench MA, Fernandez M, Paoletti LC, Kasper DL, Edwards MS. Safety and immunogenicity of a bivalent group B streptococcal conjugate vaccine for serotypes II and III. *J Infect Dis* 2003; **188:** 66–73.

65 Madhi SA, Cutland CL, Jose L, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. *Lancet Infect Dis* 2016; **16:** 923–34.

66 Heyderman RS, Madhi SA, French N, et al. Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a non-randomised phase 2, open-label, multicentre trial. *Lancet Infect Dis* 2016; **16:** 546–55.

67 Donders GG, Halperin SA, Devlieger R, et al. Maternal immunization with an investigational trivalent group B streptococcal vaccine: a randomized controlled trial. *Obstet Gynecol* 2016; **127:** 213–21.

68 Saaka M, Okoko BJ, Kohberger RC, et al. Immunogenicity and serotype-specific efficacy of a 9-valent pneumococcal conjugate vaccine (PCV-9) determined during an efficacy trial in The Gambia. *Vaccine* 2008; **26:** 3719–26.