**Group B Streptococcus and Respiratory Syncytial Virus immunization**

**during pregnancy: a landscape analysis**

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**Summary**

*Streptococcus agalactiae or group B Streptococcus (GBS) and Respiratory Syncytial Virus (RSV) are leading causes of infant morbidity and mortality worldwide. There are currently no licensed vaccines for either disease, but vaccines for both are under development. Severe RSV disease can be prevented by passively administered antibody. The presence of maternal RSV-specific IgG antibody is associated with reduced prevalence and severity of RSV disease in the first few weeks of life, while maternal serotype-specific anti-capsular antibody is associated with protection against both early onset (EO) and late onset (LO) GBS disease. Vaccination in pregnancy offers an attractive method of protecting infants against both diseases. This structured review identifies what is known about immune protection against both diseases and identifies knowledge gaps in the immunobiology, with the aim of prioritizing research directions in maternal immunization.*

**Introduction**

The transfer of antibodies from pregnant women to their infants is profoundly important for the health and survival of neonates and young infants. Actively immunizing women before or during pregnancy can enhance infant protection against specific infections, the near-elimination of neonatal tetanus being an outstanding example of successful application of this strategy 1. More recently, vaccination in pregnancy has been shown to be effective in preventing influenza 2 and pertussis 3 in infants, adding momentum to similar strategies to prevent group B *Streptococcus* (GBS) and Respiratory Syncytial Virus (RSV) infections.

The specific aim of this review is to identify the current knowledge gaps in the immunobiology of maternal immunization against GBS and RSV based on a comprehensive review of published literature and global consultation with leaders in the field. Awareness of the important knowledge gaps is expected to inform future research in this area.

**Search strategy and selection criteria**

The search strategy used to prepare this manuscript is described in detail in a companion manuscript entitled « Maternal Immunization: Collaborating with Mother Nature » by Arnaud Marchant et al.

**I. NATURAL INFECTION**

**a. Disease burden**

**GBS**

*Streptococcus agalactiae* (group B *Streptococcus*, GBS) is the leading cause of neonatal sepsis and meningitis in most countries. Where blood cultures are part of routine diagnostic evaluation and cases are consistently reported, it is also recognized as an important cause of disease in pregnant women, immunocompromised adults and the elderly 4. The highest incidence of disease is in the first 3 months of life, where it is traditionally divided into early-onset disease (EOD, defined as disease occurring <7 days of age) or late onset disease (LOD, defined as disease occurring 7-89 days of age).

Overall, EOD accounts for 70 to 80% of GBS disease in the first 3 months of life (the relative proportions of EOD and LOD vary depending on whether and to what extent intrapartum antibiotic prophylaxis (IAP) is used). Maternal carriage of GBS in the gastrointestinal and/or genital tracts is a pre-requisite for EOD, vertical transmission occurring during or just prior to birth. It has been estimated that 20–35% of pregnant women are colonized with GBS 5,6, vertical transmission is approximately 50% (and higher if the mother has “heavy” vaginal colonization) and 1% of neonates born to colonized women develop invasive disease (Figure 1). EOD may occur rapidly, with signs evident at birth or within 12 hours in the majority of cases, and presentation is typically with sepsis, pneumonia and/or meningitis 7.

Prematurity and low birth weight are major risk factors for EOD and, especially for LOD. For example, in England in 2001 the incidence of EOD and LOD was 11-fold and 48-fold higher in babies with birth weights < 1500g compared with those born > 2500g 8. Nevertheless it should be noted that the majority of babies with invasive GBS disease are born at term. Maternal HIV infection is another well described risk factor. In a population-based surveillance study (South Africa 9), the incidence of invasive GBS disease was 2.25-fold (95% CI 1.84–2.76) greater in HIV-exposed than HIV-unexposed neonates (4.46 cases /1,000 live births [95% CI 3.85-5.13] vs. 1.98/1,000 live births [95% CI 1.71-2.28]). The higher incidence of GBS disease amongst HIV-exposed infants was particularly evident for LOD (risk ratio 3.18, 95%CI 2.34-4.36). However, maternal HIV infection does not appear to be associated with a higher prevalence of maternal GBS colonisation 9,10.

In high-income countries (HIC) the burden is generally well established such that IAP policies in one form or another have been instituted in many countries. The incidence of EO GBS disease in the USA in the 1990s, prior to the introduction of IAP, was around 1.7/1000 live births 11. Other countries had lower baseline figures (around 0.5/1000 live births) but some, including the Netherlands 12 and the United Kingdom 13, have reported recent increases in both EOD and LOD.

In low and middle-income countries (LMIC), the disease burden is less certain, although in several countries in Southern Africa is comparable to or higher than that of HIC 14,15. EOD can be fulminant in onset and cases can be missed before appropriate diagnostic samples (i.e. blood and cerebrospinal fluid) are obtained. This may lead to a significant underestimation of the true disease burden and is likely to be a particular issue in many LMIC, where births do not occur in hospital facilities or where appropriate diagnostics are rarely utilized or available 16.

A recent meta-analysis reported an overall estimate of GBS incidence in infants 0-89 days of age of 0·53 per 1000 live births, with considerable regional variation. The incidence in those countries reporting IAP use was significantly lower than in those in which IAP was not in use. The incidence in African infants was highest at 1.21 per 1000 live births and the incidence was lowest in Asian infants 17 (Table 1).

The mortality from invasive GBS disease in young infants ranges from 3-20%. It is generally higher in EOD than in LOD and in premature and low birth weight infants as compared with term infants 8. The meta-analysis calculated a mean case fatality ratio of 9·6% (95% CI 7·5-11·8) although this was significantly higher in African infants (22%) 17.

Long-term neurological sequelae occur in approximately 50% of cases of GBS meningitis. These include global developmental delay, hearing loss, cortical blindness, cerebral palsy and language/learning disabilities 18,19. There is a paucity of data on long-term disabilities in meningitis cases in LMIC settings but it is likely that the burden is even higher. In all settings data are lacking on impairment after neonatal sepsis and pneumonia because of poor follow-up of survivors 20.

GBS also contributes to the burden of disease in pregnant and postpartum women (intraamniotic infection, bacteremia, early postpartum endometritis) 4. GBS also may contribute to birth asphyxia, prematurity and stillbirths; a recent systematic review estimated that GBS might account for up to 12% of stillbirths 21. *In vitro* and animal data demonstrate that components of GBS are capable of disrupting critical maternal-fetal barriers during pregnancy resulting in tissue damage and inflammatory changes and thereby the potential to precipitate preterm labour 22-25. However, it is more difficult to clearly establish this relationship in humans and the evidence currently is mixed 26.

*Intrapartum antibiotic prophylaxis:* IAP strategies have reduced the incidence of EOD, but have had no impact on LOD and only a limited impact on disease in pregnant women 11. Two major strategies for targeting women to receive IAP are used: risk factor based (RFB) or vaginal/rectal culture-based (V/RCB). The former is based on the presence of intrapartum risk factors while the latter requires swab of the lower vagina and rectal sites to identify women who are candidates for IAP, typically obtained at 35-37 weeks’ gestation and cultured for GBS using selective broth media 27. A potential alternative strategy is based on detection of GBS using real time PCR methodology from a vaginal swab obtained in labor 6. RFB strategies however, miss the significant proportion of cases that do not have risk factors 28,29 while V/RCB strategies will not prevent cases which are false-negative at screening 30. There are additional issues with compliance, cost and feasibility and more theoretical concerns about the excessive use of antibiotics.

There are 10 capsular polysaccharide (sero) types (ST) of GBS (Ia, Ib, II, III, IV, V, VI, VII, VIII, IX). Data from both the US and Europe indicate that the distribution of serotypes causing young infant disease has been relatively stable over time, with over 90% of cases attributable to serotypes Ia, Ib, II, III, and V 4,31,32. The recent meta-analysis showed that these five serotypes accounted for 94% of invasive disease in young infants globally, however, there were no serotype data reported from Southeast Asia and only two studies from the African region 17. Recently, however, serotype IV appears to be emerging as a cause of infant disease in the USA and Canada 33.

A number of proteins such as alpha-C-protein (*bca*), C alpha-like proteins 2 and 3 (alp2 and alp3), epsilon/Alp1, Rib (*rib*), and beta-C-protein (*bac*) are found in the surface of GBS. These proteins have a role in bacterial adherence and strain classification and some have been identified for inclusion in candidate vaccines 34,35. Other methods for classification of GBS are increasingly used, for example Multi-Locus Sequence Typing (MLST) and Whole Genome Sequencing (WGS). Epidemiological studies have identified certain sequence types to dominate in neonatal and young infant disease 36.

**RSV**

Respiratory Syncytial Virus (RSV) typically causes transient mild to moderate coryza that may be mildly symptomatic or result in difficulty in feeding. However, some infants develop viral bronchiolitis (inflammation of the lower airways) resulting in cough, noisy breathing, tachypnea and sometimes respiratory failure 37. Bronchiolitis appears to represent an excessive inflammatory response to infection, a concept supported by animal models in which the peak of disease coincides with the peak of inflammation 38. Infants that recover from severe RSV bronchiolitis are more likely to suffer from recurrent respiratory symptoms in later life and to be diagnosed with asthma 39,40.

Globally, it is estimated that 99% of RSV associated deaths occur in LMIC 41, with an estimated annual toll of 34 million cases of acute lower respiratory tract infection (LRTI) in infants under 5 years of age. RSV is estimated to account for 3-9% of all fatal LRTI in infants (5). However, as with GBS, it is difficult to accurately determine the incidence in areas with limited access to healthcare 42. In the USA and Europe, annual winter epidemics contribute around 20% of infant hospitalisations 41,43 and in the UK RSV is the most common cause for hospitalisation in the first year of life. The risk of bronchiolitis rises with age in young infants, peaking at about 10-12 weeks of age and declining thereafter, becoming lower after 6 months of age 43-46, but the risk of acute LRTI continues up to 5 years of age 43,47-49.

The RSV genome encodes 11 proteins, including three envelope proteins found on the surface of virions and infected cells, designated F (fusion) protein, G (attachment) protein and SH (small hydrophobic) integral membrane protein. The F protein plays a role in cell penetration by the virus and promotes spread of the virus from cell to cell through the formation of syncytia. The F-protein is relatively conserved between strains and is therefore an attractive antigenic target for use in vaccines. The F-protein contains four major neutralising antigenic sites I, II (the target of palivizumab), IV and Ø 50. The site Ø exists only in the pre-fusion conformation of F and is the major epitope recognised by the most potent neutralising antibodies 51. Monoclonal antibody studies also made it possible to detect strain differences and allows RSV isolates to be divided into two major groups, A and B.

**b. Immunity and correlates of protection**

**GBS**

The association between type-specific anti-capsular polysaccharide (CPS) antibody levels and invasive GBS disease in newborns was initially characterized in 1976 52. In the majority of subsequent studies, low levels of CPS-specific antibodies were found in maternal delivery sera of women who had neonates with EOD and LOD caused by that CPS type, compared with sera from women delivering infants who remained healthy. Different “protective” levels have been defined in case control studies using differing antibody assays as well as for the different CPS types.

In a recent meta-analysis the odds of having an antibody level <2 ug/ml was 6.56 (95% CI: 2.10–20.55) and 2.38 (95% CI: 1.20–4.70) times greater among those with types III and Ia GBS disease respectively, compared to those without GBS disease 53. A threshold of 1 μg/ml has also been proposed as a correlate for protection for CPSs Ia and III 54. Thresholds are much higher in other studies using different case-control designs 55,56 and different ELISA methods, making direct comparisons difficult 57.

An association between type-specific CPS antibody levels and maternal GBS colonisation has also been described. Cross-sectional studies generally report higher CPS-specific antibody concentrations in sera from colonised compared with non-colonised women 58, but a longitudinal study showed that lower antibody concentration was associated with subsequent colonisation and that new colonisation in turn resulted in higher antibody concentrations 59. Serum CPS-specific IgG concentrations of ≥3 μg/ml for types 1a and III and ≥1 μg/ml for type V were significantly associated with protection against acquisition of colonisation.

In general, CPS-specific antibodies, as measured by ELISAs, also correlate with *in vitro* killing activity and *in vivo* protection 54, although several studies have suggested that some ELISA methods may underestimate protection 59,60 61. There is now an urgent need for standardized assays, to allow comparisons and bridging between studies, both for serologic ELISAs and opsonophagocytic killing assays.

**RSV**

All adults have antibodies to RSV because of previous repeated infections (Fig 2a). These levels wane rapidly after infection and do not prevent re-infection, but they may provide partial protection against infection and symptomatic lower respiratory tract disease. Serum antibody is predictive of resistance to pulmonary infection, but mucosal RSV-specific IgA may be more important in resistance to nasal infection 62.

Maternally-derived high affinity RSV-specific serum IgG antibody is the best known correlate of protection against infection in infants (Fig 2d) and it is assumed that the relative rarity of severe RSV disease in the first weeks of life is due to virus-specific maternally derived antibody 44,45,63-67. However, some of this protection may be indirect, due to reduced rates of maternal infection in those with high levels of antibody. Mothers with the highest levels of antibody may have undergone recent infection with RSV (i.e. infection before or during pregnancy; Fig 2a) 68,69, so may be less likely to become re-infected and thus to expose their newborn infants. Nevertheless, severe RSV infection is consistently associated with low levels of pre-existing serum or cord blood RSV antibody 44,45,63-67. Infants in the top 50th percentile of cord blood antibody titres are at decreased risk of infection over the first 72 weeks of life, with a hazard ratio of 0.6 (CI 0.4-0.9)70. The risk of hospitalisation in the first 6 months is also inversely related to cord blood neutralising antibody levels with a 26% decrease in the incidence for every log2 increase in titre 71.

Animal models also support a direct protective role for maternal antibodies against RSV infection 72-77 and passive prophylactic monoclonal RSV antibody (palivizumab) in infants reduces the incidence of severe lower respiratory disease (Fig 2d), demonstrating that sufficiently high titre antibodies can afford some protection against RSV disease. Follow-up studies of infants who received palivizumab suggest that antibody mediated protection against infantile RSV disease may additionally affect the development of subsequent wheeze in high-risk children 39,78,79. However, motavizumab (a higher affinity derivative of palivizumab with enhanced neutralisation properties) does not reduce subsequent wheeze, despite being highly effective in preventing RSV infection 80. It seems evident that passively acquired RSV-specific antibody is beneficial in preventing lower respiratory disease due to RSV infection, thus vaccination in pregnancy would provide additional benefit to infants by increasing maternal antibody levels.

An increased initial titre of antibody can be assumed to extend the duration of infant protection. Palivizumab serum levels fall to about 30 to 80 μg/ml 30 days after first administration, which translates to around a 5 to 7 log2 titre of neutralizing antibody that results in an approximate 50-70% reduction in RSV hospitalisation (Pedro A., personal communication of unpublished results and 81). Naturally occurring maternal antibody undergoes a log-linear decay over the first 6 months of life, at an estimated rate of −0.58 (SD: 0.20) log2 neutralisation titre per month and a half-life of around 38 days (95% CI, 36–42 days) with antibody falling below a protective titre and reaching a low point at 3-5 months of age 70,82-84. Some variation in antibody half-life has been reported, with a half-life estimate of 79 (76-81) days reported in a study in Kenya 66. This compares to only 26 days in a study in a Dutch cohort 85. Based on a half-life of 38 days, the duration of protection afforded by maternal vaccination would be predicted to increase by 19 days for each 0.5 log2 increase in cord blood antibody titre 70.

Antibody avidity may also contribute to protection against severe RSV infection 67. The virus subtype specificity of antibody does not seem to influence the presence of infection or the viral type causing RSV LRTI 63,86,87, and antibodies to the viral F-protein correlate better with protection in infants than anti-G antibodies 88.

For clinical trials of vaccine efficacy there is currently little evidence that more complex assays are of additional use as correlates of protection than simple measurements of serum antibody titre 63, however measurement of local immunity in the airways should be considered. A study in infants hospitalised with RSV found that there was an inverse correlation between infant nasal IgG and viral load, but found no correlation with serum IgG 89. Future studies will be needed to determine whether nasal antibodies provide a better correlate of protection against severe disease in infants than serum. Well standardised and minimally invasive methods of sampling nasal fluids in infants may prove practical and informative 62,90.

It should be noted that maternal IgG antibody must work in conjunction with the immune system of the infant. Passive high affinity IgG may fail to confer complete protection against infection if immaturity of both innate and adaptive immunity in the infant limits antibody effector function. Antibody will interact with the infant innate immune system for example, via complement activation or binding to Fc receptors 91. T cell responses will be generated by the infant itself and are relatively weak and polarised in the very young 38, and are of particular relevance to protection against viral infections. Cellular immunity includes local CD8+ T-cells which are likely to be important in mediating viral clearance, and CD4+ T cells which determine the polarisation of the immune response and can profoundly influence the outcome of RSV infection 92,93. Besides immunological maturity, anatomical differences in the geometry of the early postnatal infant airways and chest wall may contribute to respiratory failure in RSV infection 94.

Basic studies to elucidate mechanisms of respiratory immunity in infants are needed in order to establish better correlates and to lead to a greater understanding of why some infants are susceptible to severe disease, despite the presence of maternal antibody, and it is clear that immunity to RSV needs to be studied in appropriate age-groups 95. Genetic and environmental factors will combine with the age of the infant to shape the developing immune response and determine the risk of severe RSV infection 38. Early innate immune events, which may ordinarily limit or prevent bronchiolitis in the infant airway (Fig 2f), are not yet fully defined. Understanding mechanisms of protection against severe disease in infants and how maternal antibodies interact with the immature infant immune system must be major research priorities.

**c. Transplacental transfer of immunity**

Transplacental transfer of immunoglobulin accelerates after 32 weeks gestation (Fig 2c). Prematurity is therefore associated with reduced transfer of antibodies 96 97 particularly in infants born before 28 weeks 98. This is particularly relevant as premature infants have a disproportionate burden of RSV and GBS infections. The properties of the IgG subclasses most efficiently transferred across the placenta also differ and this may ultimately influence the efficacy of maternal vaccination 99-102.

Maternal infections, such as HIV, helminth infections and malaria, may result in hyper­gamma­globulin­aemia and reduced RSV and GBS – specific transplacental antibody transfer 96,103,104. In one study, cord-maternal anti- GBS CPS antibody ratios for types Ia and III were 37.4% (P < .001) and 32.5% (P = .027) lower in HIV-infected compared to HIV-uninfected dyads, respectively 105. The adjusted odds of having CPS-specific IgG concentration ≥2 μg/mL when comparing HIV-infected to HIV-uninfected women were 0.33 (95% CI, 0.15-0.75) and 0.34 (95% CI, 0.12-1.00) for types Ia and III, respectively 105.

**d. Impact/role of breast milk on immunity**

For both pathogens, other factors present in breast milk may contribute to non-specific protection against infection in addition to antibodies, and the relative contribution of milk-derived (as opposed to placental) antibodies needs to be assessed.

The extent to which GBS CPS-specific antibodies contained in breast milk might prevent or ameliorate disease is not known. In an animal maternal immunization study, increased survival was shown in rodent pups exposed postnatally to breast milk with high titers of anti-GBS antibody compared to those exposed to breast milk with low titers 106. In a human study, type III CPS-specific IgG antibodies were not consistently detectable in breast milk, although samples with detectable IgG correlated with the highest serum values 107.

Breast-feeding is associated with reduction in RSV disease rates (Fig 2b), and may be particularly important in infants in which placental transfer of antibody has been reduced 108-111. Breast milk neutralising RSV antibody levels are highest in the first week of lactation and could potentially be boosted by vaccination during or after pregnancy 112-117. Foster feeding experiments in cotton rats support the concept that antibody in milk can be protective 76.

One limitation of maternal RSV vaccination is that passively transferred antibody against RSV may not protect as well as antibody actively, locally produced at the site of infection in the lung. Studies in adults suggest that locally produced antibody is qualitatively and quantitatively different from that in the serum, and airway IgA is likely to be important for excluding the virus from the mucosal surface of the lung 62. Colostrally derived maternal secretory IgA does not enter the circulation and reach the airways, limiting maternal antibody at the site of infection to the IgG isotype.

**II. VACCINES**

**a. Vaccines and studies in pregnant women**

**GBS**

In the 1930s, Rebecca Lancefield demonstrated that protection against GBS infection in mice could be achieved using CPS-specific rabbit sera 118 and CPS remains the best-studied virulence factor of GBS, and indeed until very recently, was the only target for which human vaccine trials have been undertaken. The first human trials in the 1980s tested plain CPS-based vaccines that had variable immunogenicity in healthy adults. Subsequently GBS polysaccharide-protein conjugate vaccines were developed and tested in several hundred healthy adults and pregnant women. Phase 1 clinical trials with a protein vaccine, made from the N-terminal domains of the Rib and AlphaC surface proteins of GBS have recently commenced (NCT02459262).

Monovalent (tetanus-toxoid, TT) conjugate vaccines incorporating each of the five major CPSs of GBS have been evaluated in phase 1 and 2 trials (Ia 119, Ib 120, II 121, III 122, V 123, and in one study, a bivalent TT-conjugate vaccine was assessed 124. More recent trivalent conjugate (Ia, Ib, III) vaccine trials are based on the carrier protein CRM197 125-127.

*Influence of adjuvants*: Adsorption of GBS type III CPS-tetanus toxoid (III-TT) conjugate vaccine to alum did not improve the immune response to a 12.5-ug dose in healthy adult recipients 128.

*Influence of the carrier protein:* One study has directly compared conjugate vaccines with different carrier proteins: recipients of a CPS V–TT conjugate vaccine had somewhat higher IgG concentrations than recipients of the CRM197 vaccine (week 4 geometric mean concentrations (GMC): 8.9 vs 6.5 μg/ml), but these differences were not statistically significant 123.

*Multiple doses*: In one study, adults previously vaccinated with a GBS III-TT conjugate were given a second 12.5 μg dose 21 months later. Four weeks after the second dose, the GMC of type III CPS-specific IgG was similar to those measured 4 weeks after the primary immunization, suggesting lack of booster response. However, 8 (22%) of the 36 participants who had undetectable III CPS-specific IgG (<0.05 μg/ml) before the first dose of III-TT conjugate exhibited a booster response to the second dose 128. In a dose-ranging trial with a trivalent Ia, Ib, III -CRM197-conjugate vaccine, a higher response against type Ia was seen with the (highest) 5 μg CPS dose for pregnant women who had undetectable antibody concentrations at baseline. No detectable effect on GMC was seen after receipt of a second dose of vaccine, 1 month later, in non-pregnant women 125.

*Duration of vaccine-induced immunity*: The duration of follow-up following immunization has been limited to approximately 2 years. With CPS TT- conjugate vaccines, a decline was described over time (using ELISA) but concentrations at 2 years nevertheless remained above baseline 129. In one study 61, substantial functional activity, exceeding 1 log (10) reduction in GBS cfu/mL, was retained at 18 months to 2 years post-immunization.

*Impact of immunization on colonisation*: In an unpublished trial, non-pregnant women receiving a III-TT conjugate vaccine were shown to have a significantly longer time to first vaginal acquisition than women in the control group (vaccine efficacy 36% [P=0.044]) 129. No clear effect of vaccination on colonisation was observed in a pregnancy trial with the Ia, Ib, III-CRM197 conjugate vaccine 125.

*Immunization in pregnancy & placental transfer*: In the only pregnancy trial with a III-TT conjugate vaccine (30 women) it was well tolerated, transplacental transfer ratio was 0.8, and elevated concentrations of antibody persisted in infants up to 2 months of age. Infant sera containing endogenous complement promoted significant opsonophagocytic killing of ST III GBS *in vitro* 130.

Around 560 women have received a trivalent CRM197-conjugated GBS vaccine (ST Ia, Ib and III) in pregnancy 125-127. The vaccine appeared to be well-tolerated and resulted in significantly higher serum anti-CPS IgG concentrations than measured in sera from the placebo group at delivery 125,127 . Of the three dosages tested in pregnant women, the 5 μg dosage was deemed the most suitable for continuation into future trials 125. In the South African trial the geometric mean transfer ratios varied slightly according to the dose used: type Ia 0.55-0.58, Ib 0.49-0.65 and III 0.61-0.72, although none of these differences were of statistical significance 125.

*Impact of maternal factors on immunogenicity*: All pregnancy vaccine studies have had strict inclusion criteria and have only included women “at low risk for obstetric complications”. However, a trial in HIV-infected pregnant women showed lower maternal antibody concentrations in delivery sera and lower infant cord antibody concentrations as compared with sera from HIV-uninfected mothers and their neonates. This trial excluded women who were severely compromised (CD4+ count ≤ 50 cells/µL, WHO stage III or IV disease) 127.

*Relevance of microbial characteristics:* A potential limitation of GBS CPS conjugate vaccines is the number of CPSs that can be incorporated into a vaccine although 5 CPSs (Ia, Ib, II, III, V) currently account for approximately 95% of all neonatal cases globally 17. There is also concern that selective pressure exerted by CPS-specific conjugate vaccines may lead to virulent genotypes switching capsules in order to escape vaccine coverage. The GBS CC17 hypervirulent lineage has spread globally and is almost exclusively composed of isolates belonging to type III strains. Several recent studies have shown CC17 isolates that are genetically related but belong to CPS IV 131-133. Type IV is recognized as an emerging cause of neonatal disease 33.

**RSV**

Vaccine development for RSV was impeded following fatal cases of vaccine enhanced disease in formalin-inactivated RSV (FI-RSV) vaccine recipients and there are no currently licenced vaccines for RSV. Animal models can aid vaccine development and have been used to test novel adjuvant and vaccine formulations. Such models may highlight potential safety issues, have the advantage of removing confounding factors (maternal exposure history, maternal health, level of exposure to RSV, host and viral genetic variability etc.) and allow carefully controlled exposure to infection, and timing and routes of vaccination etc. Complex investigation of the immune response at the site of infection, which is difficult in infected human infants, will aid a full and mechanistic understanding of protective immunity in this age group. Disadvantages of animal models are that mechanisms of transfer of antibody to offspring may differ to that in women. Furthermore, any vaccine for use in mothers will need to be efficacious in anamnestic adults, and the memory response in animals may differ from that seen in humans. Animal models have been used to demonstrate the feasibility of inducing protection against infection by maternal vaccination via placental and milk antibodies 72-77. Importantly, there is no evidence for enhanced disease in animal models of maternal immunisation, nevertheless it will be important to carefully monitor infants of immunised mothers.

A number of RSV vaccine candidates are under development and several have reached phase III trials 134. Candidates include gene based vector vaccines (adenovirus), particle based and live-attenuated vaccines (27). An RSV subunit vaccine containing purified RSV fusion protein has been tested in pregnant women in the third trimester, in a randomized, double-blind, placebo controlled study and demonstrated good safety and immunogenicity 135. Vaccine recipients and their infants had a 4-fold rise in serum RSV IgG concentration. Breast milk RSV IgA and IgG concentrations were also boosted. This study demonstrates the feasibility of boosting infant immunity to RSV by vaccination and a large, international, phase III efficacy trial in pregnant women is currently in progress (NCT02624947).

1. **Timing and Clinical Endpoints of Successful Vaccination**

The timing of maternal immunisation will need to be optimised to elicit appropriate protective immune responses and ensure maternal serum antibody concentrations are maintained throughout the third trimester and post-partum. A recent study of maternal tetanus-diphtheria-acellular pertussis immunisation found that cord blood antibody titres were higher if mothers were immunised in the second, rather than the third trimester 136, so the immunogenicity and placental transport of antibodies induced by RSV and GBS vaccines in different stages of pregnancy will need to be specifically tested.

In addition to measuring the induction of antibody, the clinical endpoints to be assessed in vaccine trials need to be carefully chosen. In the case of a RSV vaccine is the aim of maternal vaccination to prevent infection, lower airway disease or hospitalisation? How is severe disease to be defined and easily and consistently measured, particularly in resource poor settings: hospitalisation, capillary desaturation or failure to feed/thrive? Timing of trials with respect to seasonal RSV circulation and exposure needs to be carefully considered. In addition, risk factors for severe disease including prematurity, gender, genetic predisposition, exposure to older children and other household contacts of infants will need to be accounted for in any measures of success of a vaccine. Finally, the degree of protection and the health economic benefits afforded by candidate vaccines need to be established in relevant target populations.

In the case of a GBS vaccine further prospective studies in diverse settings, using standardised methods, of measuring antibody concentrations and function, are needed to establish protective thresholds for the most common GBS capsular types. Robust data could then potentially be used to facilitate the licensure of a GBS vaccine without the need for large-scale pre-licensure efficacy trials in pregnant women 137; the approach taken for licensure of meningococcal C [23] and meningococcal B vaccines. Recent guidance lays the groundwork for using this approach for vaccines developed for pregnancy [24]. This would then be coupled with enhanced post implementation surveillance to address effectiveness and additional safety.

*Alternative vaccination approaches:*For RSV, maternal vaccination is unlikely to offer antibody-mediated protection to infants over 6 months, at which age some infants still remain vulnerable to severe RSV infection. This limits the potential impact of maternal vaccination as a stand-alone strategy to completely mitigate RSV disease. ‘Cocooning’ by vaccination of infant contacts, including the mother, school age children, parents and health care workers may reduce community transmission and be more effective at protecting infants than a strategy focussed solely on maternal immunisation (Fig 2a) and the development of an effective paediatric vaccine should still be actively pursued 138.

**c. Interference with vaccine responses in infants**

There is evidence from measles and pertussis vaccination that high levels of maternally-derived antibody may limit infant antibody responses to subsequent infection or immunisation 139,140. Such a phenomenon could potentially occur following maternal vaccination against RSV (Fig 2e) 141,142. A significant reverse correlation has been observed between pre-existing (presumably maternal) RSV specific serum IgG and production of nasal sIgA in the neonate following primary infection 143,144. In children hospitalised with RSV, a negative association was found between pre-existing levels of maternal antibody and the generation of neutralising antibody by the infants 145. An alternative explanation of this correlation is that infants with higher levels of maternal antibody will experience less severe natural infection, which generates lower antibody responses in the infant.

Animal models allow vaccines to be tested in the presence or absence of maternal antibody. Cattle are natural hosts for RSV, pathology caused by bovine RSV infection is similar to that seen in human infants and maternal antibodies provide partial protection against the incidence and severity of disease in calves 146,147. There is no placental transfer of antibody in ruminants, which makes it possible to prevent transfer by deprivation of colostrum. Here there is evidence that maternal antibody can interfere with development of immunity to RSV, following vaccination or natural infection in the calves, although this is not consistently observed 148-152. In cotton rats, there is also evidence that high titres of antibody can interfere with vaccination against RSV in pups and adults 153,154. In contrast, in murine studies, no detrimental effect of maternal antibodies was observed following RSV vaccination 155-157 and maternal antibodies may enhance the response in pups 158.

Regardless of interference by maternal antibody, priming of a cellular memory response may occur following infant infection or vaccination, and this may provide immunological memory for protection in the long term 159,160 although high titres of serum antibodies, which result in more rapid clearance of virus, could potentially also reduce the cellular response 161. The quality of immune memory developed to RSV in neonates could also potentially be influenced by the presence of maternal antibody. Maternal vaccination with a pneumococcal 9-valent vaccine found a higher risk over the first 6 months of otitis media in infants of mothers who received the vaccine, potentially because the quality as well as the extent of the infant immune response may have been altered by maternal antibodies 162. There is the potential that maternal immunisation for RSV could influence the nature of the infant immune response and because inappropriate immune responses can drive pathology to RSV 95, could be detrimental. However, initial clinical trials demonstrated no adverse effects on infant health of RSV maternal vaccination 135.

In considering GBS capsular polysaccharide-protein conjugate vaccines there is also the potential for immune interference via immune responses to the chosen carrier protein. For example, CRM197-specific antibody at 2 months of age was shown to reduce later responses to infant immunization with a CRM197 conjugate meningococcal vaccine 163. In a recent UK study, not only were the concentration of specific antibodies to diphtheria toxoid lower in infants after the primary immunization series if their mothers had been vaccinated with a diphtheria containing vaccine in pregnancy, but the responses to the MenC and pneumococcal conjugate vaccines (in which CRM197 was the carrier protein) were also affected 139. If this is ultimately shown to be true for GBS CPS-CRM197 conjugates then other protein carriers could be considered as alternatives.

d. **Safety of vaccination in pregnancy**

No safety issues have been identified among recipients of any GBS candidate vaccines thus far. In the South African maternal immunization trial rates of stillbirth were concordant with those currently described for South Africa and indeed rates of preterm labour were lower than those reported for sub-Saharan and South Africa (6–9% compared with 8–12%) 125. In Malawi 7-23% of women reported adverse events that could be attributed to the vaccine but none of the events was considered serious and there were no associated stillbirths 127. Similarly, no safety issues have been identified in recent RSV vaccine phase I trials.

**e. Programmatic issues & social influences on vaccine acceptance**

The majority (79%) of respondents to a US survey indicated that they would be likely to accept a GBS vaccine during pregnancy, however potential safety was a key concern 164. An online survey in the UK showed that awareness of GBS was low (37%) but following provision of information about GBS, the vast majority (82%) of women then indicated they would be likely to accept a GBS vaccine 165.

**f. Cost-effectiveness of immunization**

Two recent cost-effectiveness studies of maternal GBS immunization have been published. In a USA-based study, the cost/QALY ($91,321) for a trivalent (Ia, Ib, III) GBS conjugate vaccine was found to be comparable to other recommended vaccines 166. A decision-analytic model based on South African data concluded that immunization alone would substantially reduce the burden of infant GBS disease in South Africa and would be very cost-effective by WHO guidelines 167.

The health economic benefits of maternal RSV vaccination are difficult to estimate in the absence of knowledge of any future vaccine regimen, efficacy, duration of protection against disease and impact on transmission. The possibility that prevention of severe RSV disease in infants could reduce the incidence of asthma will greatly influence any cost-benefit analysis. Predictive models of infant RSV vaccination do suggest that vaccination to prevent early life disease is likely to be cost effective 168-170. At a population level, it is possible that the introduction of an RSV vaccine will cause changes in the circulation of RSV and other respiratory infections in communities. If childhood vaccination displaces first infection to adolescence or adulthood, the severity of resulting RSV disease is currently unpredictable.

**Key messages:**

For both of these infectious diseases there is an association between maternal antibody and infant protection, but the correlation is inexact and variations in antibody alone do not fully explain variations in susceptibility to disease in infants. Vaccination in pregnancy has the potential to protect young infants during the period of greatest vulnerability to severe disease and, in the case of RSV, perhaps to prevent longer-term sequelae of infection (including recurrent childhood wheeze and asthma diagnosis).

Awareness of the gaps in our understanding of the immunobiology of GBS and RSV disease is expected to inform future research (see Boxes 1 and 2).

**Key gaps in the GBS field**

Epidemiology & surveillance:

• epidemiological data from South America, African and Asian countries where the burden, strain and serotype distribution is not currently known or not adequately assessed.

• the contribution of GBS to prematurity, birth asphyxia and stillbirths.

Laboratory assays:

• standardisation of assay methods (quantitative ELISA and functional) and standardized reference ranges for CPS-specific IgG antibody concentrations.

Immunology & vaccination:

• correlates of protection against maternal and infant colonization, early and late onset infections and other perinatal outcomes (e.g. prematurity, stillbirths).

• CPS type-specific immunogenicity of conjugate vaccines, and of protein-based vaccines, in pregnant women, duration of protective antibody concentrations, need for further doses in subsequent pregnancies, placental transfer and duration of antibody protection in infants.

• potential for interference of maternal vaccine induced antibodies with active immune response in infants.

• impact of immunization in pregnancy on GBS colonization (density / non-CPS vaccine types) at delivery, on vertical transmission, on infant colonization

• immunogenicity of immunization in HIV-infected women who are severely immunocompromised; role of different doses or schedules in HIV-infected women in order to maximise protection.

• influence of breast feeding on vaccine-induced protection from neonatal GBS disease.

• immune responses of pregnant women of different ethnicities and different health backgrounds (including impact of malaria and nutritional status) to candidate GBS vaccines.

• overall public health benefit (including cost effectiveness) of a GBS vaccine in pregnancy, including direct and indirect protection and against etiologically confirmed and unconfirmed disease.

**Box 1. Identified gaps in current understanding of the immunobiology of GBS disease**

**Box 2. Identified gaps in current understanding of the immunobiology of RSV disease**

**Key gaps in the RSV field**

A better understanding of the mechanisms of protection against RSV infection and severe disease in infants

An understanding of the mechanisms of protection against lower respiratory tract infection and severe disease in infants and intrinsic and environmental influences on infant respiratory immunity

Identification of key, measurable correlates of protection against infection and severe disease in infants and of key endpoints and outcomes for studies of vaccine efficacy

Development of an effective, safe RSV vaccine to induce high affinity neutralising antibody in pregnant women

Identification of the properties of a protective maternal immune response and the factors influencing the transfer and decay of maternal antibodies in infants

Assessment of the potential impact of widespread maternal immunisation on infant immunity to RSV and RSV epidemiology

An understanding of the impact of RSV vaccination and prevention of longer term outcomes such as asthma and wheeze

**Contributors:** PTH, ZC, CEJ and FJC searched the scientific literature and wrote the first draft; all authors reviewed and edited the manuscript and approved the final version.

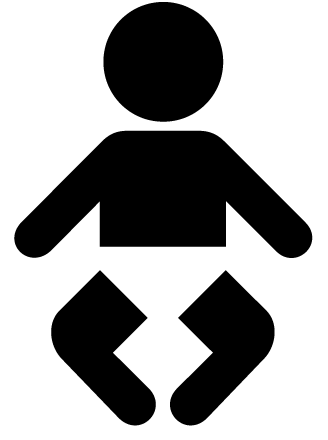
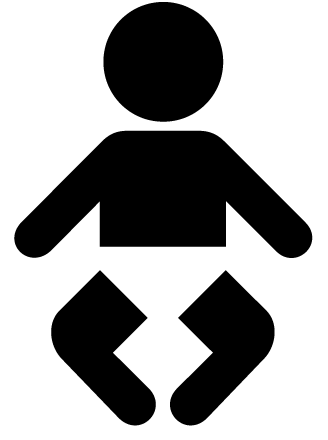
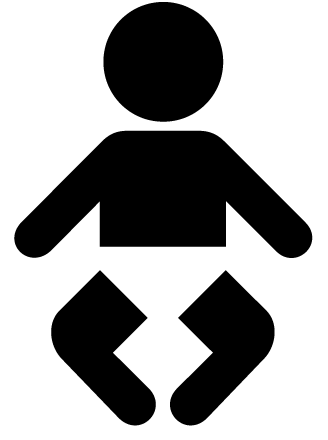
**Declaration of interests:** PTH is an investigator for clinical trials done on behalf of St George’s, University of London, UK, sponsored by various vaccine manufacturers including Novartis, Novavax, Pfizer and GSK. He has been a consultant to Novartis and Pfizer on group B streptococcus vaccines and to Novavax on RSV vaccine but received no funding for these activities. BK is a consultant to Pfizer regarding GBS vaccines. CJB is a consultant to Pfizer for development of a GBS vaccine. PO is in receipt of a Wellcome Trust Translational Award to test a MUCOSIS vaccine against RSV infection and has served on Advisory Boards for Janssen, Johnston and Johnston and Medimmune. He is Imperial Lead Investigator for EMINENT (an MRC/GSK collaborative award). MS has been an investigator on investigator-initiated research grants from Pfizer, but received no personal payments. KLD has received funding for travel to meetings from Pfizer and GSK but received no personal payments. FJC, CJ and MCN report no potential conflicts.

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**Figure 1. Relationship between maternal colonization, infant colonization and infant disease with GBS.**

♀♀♀♀♀



**1000**

**100/1000**

**2/1000**

**20-35% women are colonised**

**50% of babies born to these mothers are colonised**

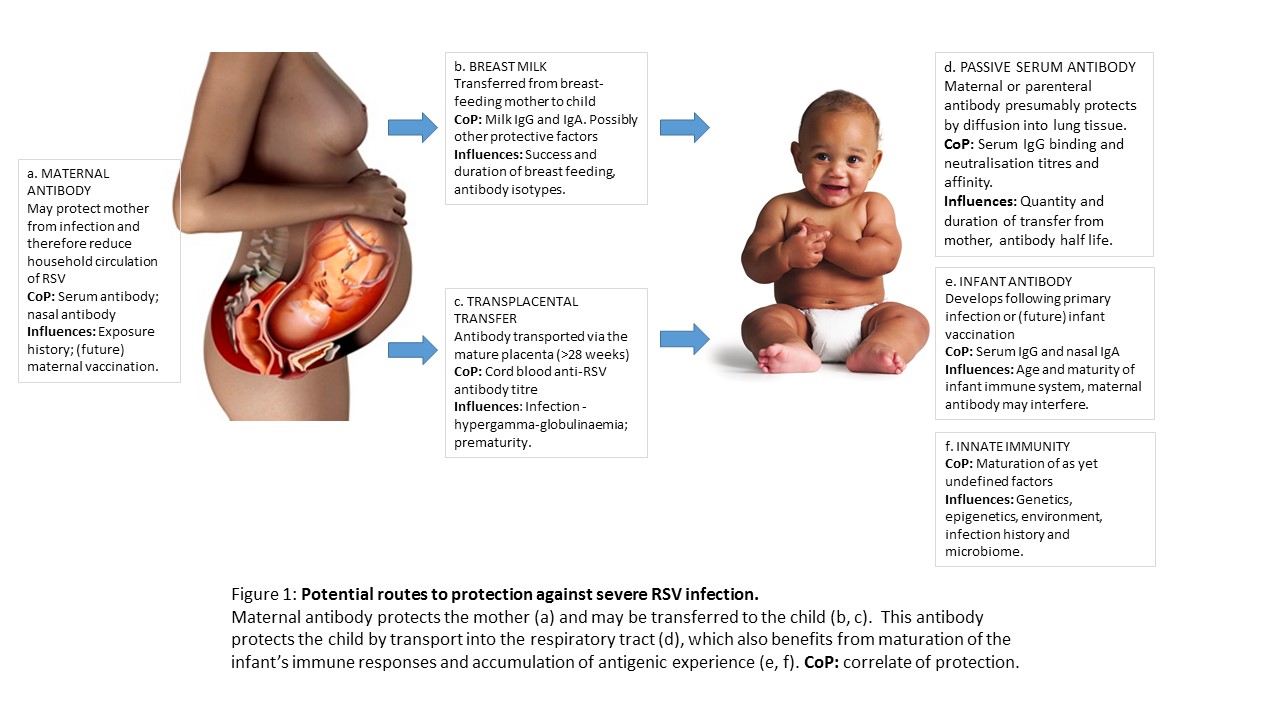
**1-2% of babies develop sepsis/meningitis**

**Table 1.**

**Meta-analysis of studies that reported incidence of GBS in infants with disease onset 0–89 days, 2000–11, by region (adapted from 17).**

|  |  |
| --- | --- |
| **WHO Region** | **Incidence (95% CI)**  **Per 1000 live births** |
| **Europe** | **0.57 (0.44-0.71)** |
| **The Americas** | **0.67 (0.54-0.80)** |
| **Africa** | **1.21 (0.50-1.91)** |
| **Eastern Mediterranean** | **0.35 (0.07-0.62)** |
| **Western Pacific** | **0.15 (0.04-0.27)** |
| **Southeast Asia** | **0.02 (-0.03-0.07)** |

**Figure 2. Potential routes to protection against severe RSV infection.**

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