Maternal Immunisation 3

Group B streptococcus and respiratory syncytial virus immunisation during pregnancy: a landscape analysis

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Group B streptococcus and respiratory syncytial virus are leading causes of infant morbidity and mortality worldwide. No licensed vaccines are available for either disease, but vaccines for both are under development. Severe respiratory syncytial virus disease can be prevented by passively administered antibody. The presence of maternal IgG antibody specific to respiratory syncytial virus is associated with reduced prevalence and severity of respiratory syncytial virus disease in the first few weeks of life, whereas maternal serotype-specific anticapsular antibody is associated with protection against both early-onset and late-onset group B streptococcus disease. Therefore, vaccination in pregnancy might protect infants against both diseases. This report describes what is known about immune protection against group B streptococcus and respiratory syncytial virus, identifies knowledge gaps regarding the immunobiology of both diseases, and aims to prioritise research directions in maternal immunisation.

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This is the third in a Series of three papers about maternal immunisation

Introduction

The transfer of antibodies from pregnant women to their infants is profoundly important for the health and survival of neonates and young infants. Active immunisation of women before or during pregnancy can enhance infant protection against specific infections[1]—the near-elimination of neonatal tetanus is an important example of successful application of such a strategy.[2] Vaccination in pregnancy has been shown to be effective for the prevention of influenza[3] and pertussis[4] in infants, providing support for similar strategies to prevent group B streptococcus and respiratory syncytial virus infections.[5]

The specific aim of this report is to describe the knowledge gaps that exist about the immunobiology of maternal immunisation against group B streptococcus and respiratory syncytial virus through a comprehensive review of the published literature and global consultation with leaders in the field. Awareness of these important knowledge gaps is expected to inform future research in this area (panels 1, 2). For the search strategy, see the appendix of the first report in this Series.

Disease burden

Group B streptococcus is the leading cause of neonatal sepsis and meningitis in most countries. The bacteria is also an important cause of disease in pregnant women, immunocompromised adults, and elderly people.[6] The highest incidence of group B streptococcus disease is in the first 3 months of life, and the condition is traditionally divided into early-onset disease (occurring in individuals aged <7 days) or late-onset disease (occurring in individuals aged between 7 and 89 days).

Overall, early-onset disease accounts for 70–80% of group B streptococcus disease in the first 3 months of life. However, the relative proportions of early-onset disease and late-onset disease vary depending on whether and to what extent intrapartum antibiotic prophylaxis is used. Maternal carriage of group B streptococcus in the gastrointestinal tract or genital tract is a prerequisite for early-onset disease with vertical transmission occurring

Panel 1: Identified knowledge gaps for group B streptococcus disease

Epidemiology and surveillance

- Epidemiological data from South American, African, and Asian countries where the burden, strain, and serotype distribution is not adequately assessed
- Contribution to prematurity, birth asphyxia, and stillbirths

Laboratory assays

- Standardisation of assay methods (quantitative ELISA and functional assays) and standardised reference ranges for capsular polysaccharide-specific IgG antibody concentrations

Immunology and vaccination

- Correlates of protection against maternal and infant colonisation, early-onset and late-onset infections, and other perinatal outcomes (eg, prematurity and stillbirths)
- Immunogenicity of conjugate vaccines and 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 responses in infants
- Effect of immunisation in pregnancy on group B streptococcus colonisation at delivery, on vertical transmission, and infant colonisation
- Immunogenicity of immunisation in pregnant women with HIV who are severely immunocompromised, the role of different doses or schedules in women with HIV to maximise protection
- Influence of breastfeeding on vaccine-induced protection
- Immune responses of pregnant women of different ethnicities and different health backgrounds (including effect of malaria and nutritional status) to candidate group B streptococcus vaccines
- Overall public health benefit (including cost-effectiveness) of a group B streptococcus vaccine in pregnancy, including direct and indirect protection against both confirmed (culture proven) and unconfirmed (probable) group B streptococcus disease

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Panel 2: Identified knowledge gaps for respiratory syncytial virus disease

- 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 respiratory syncytial virus 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 effect of widespread maternal immunisation on infant immunity to respiratory syncytial virus and on respiratory syncytial virus epidemiology
- The effect of respiratory syncytial virus vaccination and prevention of longer-term outcomes such as asthma and wheeze

	Mean incidence per 1000 livebirths (95% CI)
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)

***Table*: Incidence of group B streptococcus disease in infants with disease onset 0–89 days between 2000 and 2011 by WHO region[19]**

during or just before birth. An estimated 20–35% of pregnant women are colonised with group B streptococcus,[7,8] with vertical transmission occurring in approximately 50% of cases, and 1% of neonates born to women colonised by the bacteria develop invasive disease. Early-onset disease can occur rapidly, with signs evident at birth or within 12 h in most cases, and individuals typically present with sepsis, pneumonia, or meningitis.[9]

Prematurity and low birthweight are major risk factors for the disease, especially late-onset disease,[10] although most babies with invasive group B streptococcus disease are born at full term. Maternal HIV infection is another well described risk factor,[11] particularly evident for late-onset disease,[11] but maternal HIV is not associated with a higher prevalence of maternal group B streptococcus colonisation.[11,12]

In high-income countries the burden of group B streptococcus disease is generally well defined and intrapartum antibiotic prophylaxis policies have been established in many countries. The incidence of early-onset group B streptococcus disease in the USA in the 1990s, before the introduction of intrapartum antibiotic prophylaxis, was around 1·7 cases per 1000 livebirths.[13] Other countries had lower baseline figures (around 0·5 cases per 1000 livebirths) but some, including the Netherlands[14] and the UK,[15] have reported increases in both early-onset disease and late-onset disease.

In low-income and middle-income countries (LMICs), the disease burden is less clear, although in several countries in southern Africa the burden is similar to or higher than that of high-income countries.[16,17] Early-onset disease can be rapid in onset and cases can be missed before appropriate diagnostic samples (ie, blood and cerebrospinal fluid) are obtained. These missed cases might lead to a substantial underestimation of the true disease burden, which is likely to be an issue in many LMICs, where births do not occur in hospital facilities or where appropriate diagnostics are rarely used or available.[18]

A 2012 meta-analysis[19] estimated that the overall incidence of group B streptococcus is 0·53 cases per 1000 livebirths in infants aged 0–89 days, with substantial regional variation. The incidence in countries that reported intrapartum antibiotic prophylaxis use was significantly lower than in those where intrapartum antibiotic prophylaxis was not in use. The incidence of group B streptococcus disease was highest in African infants (1·21 cases per 1000 livebirths) and lowest in southeast Asian infants (0·02 cases per 1000 livebirths)[19] (table).

Mortality due to invasive group B streptococcus disease in young infants ranges from 3–20% and is generally higher in early-onset disease than in late-onset disease and in premature and low birthweight infants compared with full-term infants.[10] The 2012 meta-analysis[19] found a mean case fatality ratio of 9·6% (95% CI 7·5–11·8), although this was significantly higher in African infants at 22% (12–32).

Long-term neurological sequelae occur in roughly 50% of cases of group B streptococcus meningitis. Sequalae include global developmental delay, hearing loss, cortical blindness, cerebral palsy, and language and learning disabilities.[20,21] Little data about long-term disabilities in meningitis cases in LMICs are available, and in all settings data about long-term outcomes of neonatal sepsis and pneumonia are scarce because of poor follow-up of survivors.[22]

Group B streptococcus also contributes to the burden of disease in pregnant and post-partum women (intra-amniotic infection, bacteraemia, early post-partum endometritis)[6] and possibly plays a part in birth asphyxia, prematurity, and stillbirths. A 2015 systematic review[23] estimated that the disease could account for up to 12% of stillbirths. In-vitro and animal data show that components of group B streptococcus are capable of disrupting crucial maternal–fetal barriers during

pregnancy, resulting in tissue damage and inflammatory changes that can potentially precipitate preterm labour.[24–27] However, it is more difficult to establish this association in human beings and clinical evidence is mixed.[28]

Intrapartum antibiotic prophylaxis strategies have reduced the incidence of early-onset disease, but have had no effect on late-onset disease and only a small effect on disease in pregnant women.[13] Two major strategies have been established that target women to receive intrapartum antibiotic prophylaxis: risk factor-based or vaginal or rectal culture-based screening. The risk factor-based strategy is based on the presence of intrapartum risk factors, whereas the vaginal or rectal culture-based strategy requires a swab of the lower vagina and rectal sites to identify women who are candidates for intrapartum antibiotic prophylaxis, typically obtained at 35–37 weeks' gestation and cultured for group B streptococcus by the use of selective broth media.[29] However, risk factor-based strategies miss the substantial proportion of women who do not have risk factors[30,31] and vaginal or rectal culture-based strategies will not prevent infection in women who are false-negative at screening.[32] Additional issues exist with compliance, cost, and feasibility, and more theoretical concerns about the excessive use of antibiotics.

Ten capsular polysaccharide serotypes of group B streptococcus (Ia, Ib, II, III, IV, V, VI, VII, VIII, IX) have been identified. Data from both the USA and Europe indicate that the distribution of serotypes that cause young infant disease has been relatively stable over time, with over 90% of cases attributable to serotypes Ia, Ib, II, III, and V.[6,33,34] A 2012 meta-analysis[19] showed that these five serotypes accounted for 94% of invasive disease in young infants globally; however, no serotype data were reported for southeast Asia and only two studies were from Africa. Serotype IV has also been shown to cause infant disease in the USA and Canada.[35]

Various proteins, such as α-C-protein, C α-like proteins 2 and 3, α-like protein 1, Rib, surface-immunogenic protein, pilus islands (PIs) that contain backbone and ancillary proteins (PI-1, PI-2a, and PI-2b), and C5a peptidase are found on the surface of group B streptococcus bacteria. These proteins have a role in bacterial adherence and strain classification, and PI-1, PI-2b, α-C-protein, and Rib have been selected for inclusion in candidate vaccines.[36,37] The use of other methods for classification of group B streptococcus is increasing (eg, multilocus sequence typing and whole genome sequencing). Epidemiological studies have identified specific sequence types that dominate in neonatal and young infant disease.[38]

Respiratory syncytial virus typically causes transient mild to moderate coryza that can 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, tachypnoea, and sometimes respiratory failure.[39] Bronchiolitis seems to represent an excessive inflammatory response to infection, a hypothesis supported by animal models in which the peak of disease coincides with the peak of inflammation.[40] Infants who recover from severe respiratory syncytial virus bronchiolitis are more likely to have recurrent respiratory symptoms in later life and to be diagnosed with asthma.[41,42]

Globally, 99% of respiratory syncytial virus-associated deaths are estimated to occur in LMICs,[43] with approximately 34 million cases of acute lower respiratory tract infection in infants younger than 5 years occurring annually. Respiratory syncytial virus is estimated to account for 3–9% of all fatal lower respiratory tract infections in infants. However, as with group B streptococcus, accurate measurement of disease incidence is difficult in areas with poor access to health care and diagnostic facilities.[44] In the USA and Europe, annual winter epidemics contribute to around 20% of infant hospitalisations.[43,45] The risk of bronchiolitis rises with age in young infants, peaking around age 10–12 weeks and declining thereafter (decreasing after age 6 months[45–48]), but the risk of acute lower respiratory tract infection remains up to age 5 years.[45,49–51]

The respiratory syncytial virus genome encodes 11 proteins, including three envelope proteins found on the surface of virions and infected cells: designated fusion protein, attachment protein, and small hydrophobic integral membrane protein. The fusion protein plays a part in cell penetration by the virus and promotes spread of the virus from cell to cell through the formation of syncytia. The fusion protein is relatively well conserved between strains and is therefore an attractive antigenic target for use in vaccines. The fusion protein contains four major neutralising antigenic sites: I, II (target of palivizumab), IV, and Ø.[52] The Ø site exists only in the pre-fusion conformation of the fusion protein and is the major epitope recognised by the most potent neutralising antibodies.[53] Monoclonal antibody studies enable the detection of strain differences and allow respiratory syncytial virus isolates to be divided into two major groups, A and B.

Immunity and correlates of protection

The association between type-specific anti-capsular polysaccharide antibody concentrations and invasive group B streptococcus disease in newborn babies was initially characterised in 1976.[54] In most subsequent studies, low concentrations of capsular polysaccharide-specific antibodies were found in maternal delivery serum samples of women who had neonates with early-onset disease and late-onset disease caused by that capsular polysaccharide type, compared with serum samples from women delivering infants who remained healthy (figure).

In a 2015 meta-analysis[55] the probability of having an antibody concentration less than 2 μg/mL was 6·56 (95% CI 2·10–20·55) and 2·38 (1·20–4·70) times greater

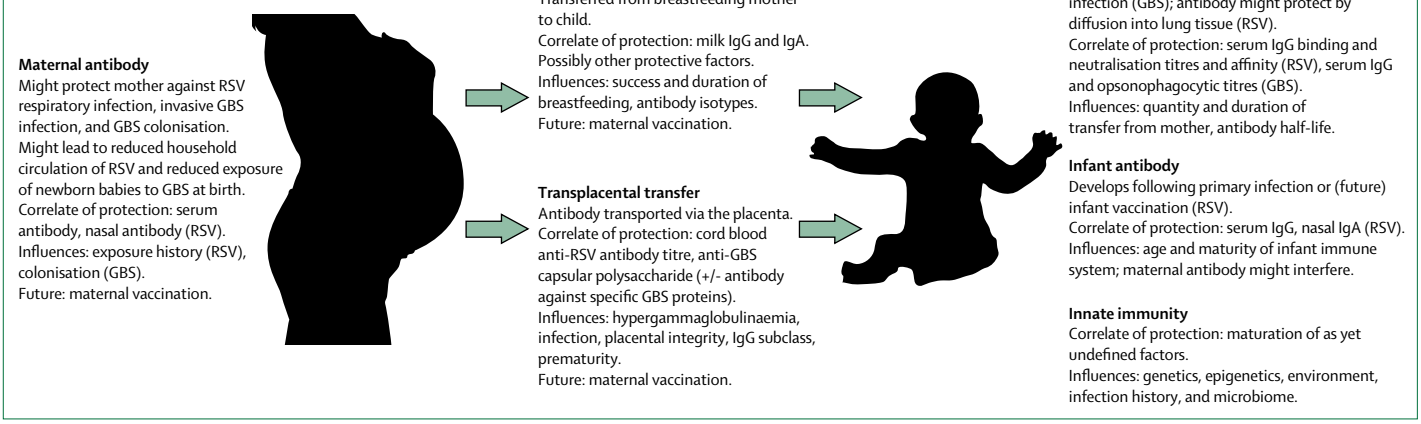

***Figure*: Potential sources of protection against severe respiratory syncytial virus and invasive group B streptococcus infections**
GBS=group B streptococcus. RSV=respiratory syncytial virus.

among individuals with types III and Ia group B streptococcus disease respectively, compared with those without group B streptococcus disease. A threshold of 1 µg/mL has been proposed as a correlate for protection for capsular polysaccharides Ia and III.[56] Thresholds are much higher in other studies that use different case-control designs[57,58] and different ELISA methods, making direct comparisons difficult.[59]

An association between type-specific capsular polysaccharide antibody concentrations and maternal group B streptococcus colonisation has also been found (figure). Cross-sectional studies generally show higher capsular polysaccharide-specific antibody concentrations in serum samples from colonised women compared with non-colonised women,[60] but a longitudinal study[61] showed that lower antibody concentration was associated with subsequent colonisation and that new colonisation resulted in higher antibody concentrations. Serum capsular polysaccharide-specific IgG concentrations of 3 µg/mL or more for types Ia and III and 1 µg/mL or more for type V were significantly associated with protection against acquisition of colonisation.

In general, capsular polysaccharide-specific antibodies measured by ELISAs also correlate with in-vitro killing activity and in-vivo protection,[56] although several studies have suggested that some ELISA methods might underestimate protection.[61–63]

All adults have antibodies against respiratory syncytial virus because of previous repeated infections (figure). These antibody concentrations decline rapidly after infection and do not prevent re-infection, but can provide partial protection against infection and symptomatic lower respiratory tract disease. Serum antibody is predictive of resistance to pulmonary infection, but mucosal respiratory syncytial virus-specific IgA might be more important in resistance to nasal infection and in the exclusion of the virus from the mucosal surface of the lung.[64]

High-affinity respiratory syncytial virus-specific serum IgG antibody derived from the mother is the best known correlate of protection against infection in infants (figure). Thus, the relative rarity of severe respiratory syncytial virus disease in the first weeks of life is postulated to be because of virus-specific maternally derived antibody.[46,47,65–69] However, some of this protection might be indirect as a result of reduced rates of maternal infection in women with high concentrations of antibody. Mothers with the highest concentrations of antibody might have had recent exposure to the respiratory syncytial virus (ie, infection before or during pregnancy; figure),[70,71] and therefore might be less likely to become re-infected and less likely to expose their newborn infants. Severe respiratory syncytial virus infection is consistently associated with low concentrations of pre-existing serum or cord-blood respiratory syncytial virus antibody.[46,47,65–69] Infants in the top 50th percentile of cord-blood antibody titres are at decreased risk of infection during the first 72 weeks of life, with a hazard ratio of 0·6 (95% CI 0·4–0·9).[72] The risk of hospital admission in the first 6 months is also inversely correlated with concentrations of cord-blood neutralising antibody with a 26% decrease in the incidence for every $\log_2$ increase in titre.[73]

Animal models also support a direct protective role for maternal antibodies against respiratory syncytial virus infection[74–79] and passive prophylactic monoclonal respiratory syncytial virus antibody (palivizumab) in infants reduces the incidence of severe lower respiratory disease (figure), indicating that sufficiently high titre antibodies can afford some protection against respiratory syncytial virus disease. Follow-up studies of infants who received palivizumab suggest that antibody-mediated protection against infantile respiratory syncytial virus disease might additionally affect the development of subsequent wheeze in high-risk children.[41,80–82]

An increased initial titre of antibody can be assumed to extend the duration of infant protection. Palivizumab serum concentrations of about 30–80 µg/mL measured 30 days after first administration, translate to around a 5–7 $\log_2$ titre of neutralising antibody and result in an estimated 50–70% reduction in hospital admissions due to respiratory syncytial virus (A Piedra, Baylor College of Medicine, Houston, TX, USA, personal communication).[80] Naturally occurring maternal antibody undergoes a log-linear decay during the first 6 months of life, at an estimated rate of –0·58 (SD 0·20) $\log_2$ neutralisation titre per month with a half-life of around 38 days (95% CI 36–42), whereby antibody concentrations fall below a protective titre and reach a low point between age 3–5 months.[72,83–85] Some variation in antibody half-life has been observed, with an estimated half-life of 79 days (95% CI 76–81) reported in a Kenyan study[68] and 26 days in a Dutch cohort.[86] On the basis of a half-life of 38 days, the duration of protection afforded by maternal vaccination is predicted to increase by 19 days for each 0·5 $\log_2$ increase in cord-blood antibody titre.[72]

Antibody avidity might also contribute to protection against severe respiratory syncytial virus infection.[69] The virus subtype specificity of antibody does not seem to influence the development of infection or the viral type that causes respiratory syncytial virus lower respiratory tract infection,[65,87,88] and antibodies against the viral fusion protein correlate better with protection in infants than anti-attachment protein antibodies.[89]

Clinical trials[65] have provided little evidence that more complex assays are of additional use as correlates of protection compared with simple measurements of serum antibody titre; however, measurement of local immunity in the airways should be considered. A study[90] in infants hospitalised with respiratory syncytial virus found an inverse correlation between infant nasal IgG and viral load, but found no correlation with serum IgG. Future studies will be needed to establish whether nasal antibodies provide a better correlate of protection against severe disease in infants than serum.[64,91]

Maternal IgG antibody is postulated to work in conjunction with the immune system of the infant (figure). Passive high-affinity IgG might fail to confer complete protection against infection if immaturity of both innate and adaptive immunity in the infant restricts antibody effector function. Antibody will interact with the infant innate immune system—eg, via complement activation or binding to Fc receptors.[92] T-cell responses, generated by the infant itself, are relatively weak and polarised in very young infants[40] and are of particular importance for 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 respiratory syncytial virus infection.[93,94] In addition to immunological maturity, anatomical differences in the geometry of the early postnatal infant airways and chest wall might contribute to respiratory failure in respiratory syncytial virus infection.[95]

Basic studies to elucidate mechanisms of respiratory immunity in infants are needed to establish better correlates and to improve understanding of why some infants are susceptible to severe disease, despite the presence of maternal antibody, and it is clear that immunity to respiratory syncytial virus needs to be studied in appropriate age groups.[96] Genetic and environmental factors and the age of the infant shape the developing immune response and determine the risk of severe respiratory syncytial virus infection.[40] Early innate immune events, which might ordinarily prevent bronchiolitis or reduce the risk of infection in the infant airway (figure), are not yet fully defined. Understanding the mechanisms of protection against severe disease in infants and how maternal antibodies interact with the immature infant immune system must be major research priorities (panels 1, 2).

Transplacental transfer of immunity

Transplacental transfer of immunoglobulin accelerates after 32 weeks' gestation. Prematurity is therefore associated with reduced transfer of antibodies,[97,98] particularly in infants born before 28 weeks' gestation.[99] Reduced transfer of maternal antibodies is important because premature infants have a disproportionate burden of respiratory syncytial virus and group B streptococcus infections.[100–103]

Maternal infections, such as HIV, helminth infections, and malaria, might result in hypergammaglobulinaemia and reduced transplacental transfer of respiratory syncytial virus and group B streptococcus-specific antibodies.[97,104,105] In one study,[106] cord–maternal anti-group B streptococcus capsular polysaccharide antibody ratios for type Ia and III were 37·4% ($p<0·001$) and 32·5% ($p=0·027$) lower in mother and infant pairs with HIV compared with those without HIV, respectively.

Effect of breastmilk on immunity

The extent to which group B streptococcus capsular polysaccharide-specific antibodies contained in breastmilk might prevent or ameliorate disease is not known. In a maternal immunisation study in rats,[107] increased survival was shown in rodent pups exposed postnatally to breastmilk with high titres of anti-group B streptococcus antibody compared with those exposed to breastmilk with low titres. In a human study,[108] type III capsular polysaccharide-specific IgG antibodies were not consistently detected in breastmilk, although samples with detectable IgG correlated with the highest serum concentrations.

Breastfeeding is associated with a reduction in respiratory syncytial virus disease prevalence, and might be particularly important in infants in whom placental transfer of antibody has been reduced.[109–112] Breastmilk concentrations of neutralising respiratory syncytial virus antibody are highest in the first week of lactation and

could potentially be boosted by vaccination during or after pregnancy.[113–118] Foster feeding experiments in cotton rats support the hypothesis that antibody in milk can be protective.[78]

Vaccines and studies in pregnant women

In the 1930s, Rebecca Lancefield[119] reported that protection against group B streptococcus infection in mice could be achieved by the use of capsular polysaccharide-specific rabbit serum. Capsular polysaccharide remains the best studied virulence factor of group B streptococcus, and until 2015, was the only target for which human vaccine trials have been done. Phase 1 clinical trials with a protein vaccine made from the N-terminal domains of the Rib and α-C surface proteins of group B streptococcus are ongoing (NCT02459262).

Monovalent tetanus toxoid-conjugate vaccines that incorporate each of the five major capsular polysaccharides of group B streptococcus have been evaluated in phase 1 and 2 trials (Ia,[120] Ib,[121] II,[122] III,[123] V,[124]) and in one study, a bivalent tetanus toxoid-conjugate vaccine was assessed.[125] Trivalent conjugate (Ia, Ib, III) vaccine trials are based on the carrier protein CRM197 (non-toxic mutant of diphtheria toxin).[126–128] The influence of adjuvants has also been investigated. Adsorption of group B streptococcus type III capsular polysaccharide-tetanus toxoid-conjugate vaccine to alum did not improve the immune response to a 12·5 µg dose in healthy adult recipients.[129] The carrier protein might also influence vaccine efficacy. One study[124] directly compared conjugate vaccines with different carrier proteins and found that recipients of a capsular polysaccharide V–tetanus toxoid-conjugate vaccine had slightly higher geometric mean IgG concentrations 4 weeks after immunisation than recipients of the CRM197 vaccine (8·9 µg/mL *vs* 6·5 µg/mL), but these differences were not statistically significant.

Multiple vaccine doses might affect immune responses against group B streptococcus. In one study,[129] adults previously vaccinated with a group B streptococcus III-tetanus toxoid conjugate received a second dose 21 months later and in a subgroup, who had undetectable III capsular polysaccharide-specific IgG before the first dose of III-tetanus toxoid conjugate, a booster response was evident. In a dose-ranging trial[126] with a trivalent Ia, Ib, III-CRM197-conjugate vaccine, a higher response against type Ia was seen compared with the other doses of type Ia, with the highest capsular polysaccharide dose (5 µg) for pregnant women who had undetectable antibody concentrations at baseline. No effect on geometric mean concentration was observed after receipt of a second dose of vaccine 1 month later in non-pregnant women.[126]

The duration of vaccine-induced immunity is an important consideration for maternal immunisation. With capsular polysaccharide tetanus toxoid-conjugate vaccines, a decline in antibodies against group B streptococcus was observed over time using ELISA, but concentrations 2 years after vaccination remained above baseline.[130] In one study,[63] substantial functional activity, exceeding 1 log reduction in group B streptococcus cfu/mL, was retained between 18 months and 2 years postimmunisation.

Immunisation might also affect colonisation. Non-pregnant women who received a III-tetanus toxoid-conjugate vaccine were found to have a significantly longer time to first vaginal acquisition than women in the tetanus toxoid control group (vaccine efficacy 36%, p=0·044).[130] No clear effect of vaccination on colonisation was observed in a pregnancy trial with the Ia, Ib, III-CRM197 conjugate vaccine.[126]

In the only pregnancy trial[131] with a monovalent III-tetanus toxoid conjugate vaccine (n=30), the vaccine was well tolerated with a mean transplacental transfer ratio of 0·8, and elevated concentrations of antibody persisted in infants up to age 2 months. Infant serum samples that contained endogenous complement promoted extensive opsonophagocytic killing of serotype III group B streptococcus in vitro.[131]

Around 560 women have received a trivalent CRM197-conjugated group B streptococcus vaccine (serotype Ia, Ib, and III) during pregnancy.[126–128] The vaccine was well tolerated and resulted in significantly higher serum anti-capsular polysaccharide IgG concentrations than that measured in serum samples from the placebo group at delivery.[126,128] In a South African trial,[126] 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.

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 serum samples and lower infant cord antibody concentrations when compared with serum samples from HIV-uninfected mothers and their neonates. This trial excluded women who were severely immunocompromised (CD4+ count ≤50 cells per µL, WHO stage III or IV disease).[128]

A potential limitation of group B streptococcus capsular polysaccharide conjugate vaccines is the number of capsular polysaccharides that can be incorporated into a vaccine, although five capsular polysaccharides (Ia, Ib, II, III, V) account for about 95% of all neonatal cases globally.[19] Additionally, selective pressure exerted by capsular polysaccharide-specific conjugate vaccines might lead to virulent genotypes switching capsules to escape vaccine coverage. The group B streptococcus CC17 hypervirulent lineage has spread globally and is almost exclusively composed of isolates that belong to type III strains. Several studies[35,132–134] have found CC17 isolates that are genetically related but belong to capsular polysaccharide IV, an emerging cause of neonatal disease.

Vaccine development for respiratory syncytial virus was impeded following fatalities due to vaccine-enhanced disease in individuals who received formalin-inactivated respiratory syncytial virus vaccine.[135] Thus, no licenced vaccines for respiratory syncytial virus are available. Animals have been used to test novel adjuvant and vaccine formulations and to investigate the feasibility of inducing protection against infection by maternal vaccination via placental and milk antibodies.[74–79] No evidence for enhanced disease has been found in animal models of maternal immunisation.

Numerous respiratory syncytial virus vaccine candidates are under development and several have reached phase 3 trials.[136] Candidates include gene-based vector vaccines (adenovirus), particle-based vaccines, and live-attenuated vaccines. A respiratory syncytial virus subunit vaccine containing purified respiratory syncytial virus fusion protein has been tested in pregnant women in the third trimester, in a randomised, double-blind, placebo-controlled study,[137] and showed good safety and immunogenicity. Vaccine recipients and their infants had a four-fold increase in serum respiratory syncytial virus IgG concentration. Breastmilk respiratory syncytial virus IgA and IgG concentrations were also boosted. This study shows the feasibility of boosting infant immunity to respiratory syncytial virus by vaccination and a large, international, phase 3 efficacy trial in pregnant women is in progress (NCT02624947).

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 2006 study[138] 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, so the immunogenicity and placental transport of antibodies induced by respiratory syncytial virus and group B streptococcus 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. The aim of maternal vaccination with respiratory syncytial virus vaccine needs to be established (eg, to prevent infection, lower airway disease, and decrease hospital admissions). The method by which severe disease is defined and easily and consistently measured (eg, hospital admission, capillary desaturation, or failure to feed), particularly in resource poor settings, also needs to be established. The timing of trials with respect to seasonal respiratory syncytial virus circulation and exposure also needs to be carefully considered. Additionally, risk factors for severe disease, including prematurity, sex, genetic predisposition, exposure to older children, and household members of of infants will need to be accounted for when measuring the success of a vaccine. Furthermore, the degree of protection and the health economic benefits afforded by candidate vaccines need to be established in target populations.

In the case of a group B streptococcus vaccine, further prospective studies in diverse settings by the use of standardised methods that measure antibody concentrations and function, are needed to establish protective thresholds for the most common group B streptococcus capsular types. Robust data could potentially be used to facilitate the licensure of a group B streptococcus vaccine without the need for large-scale pre-licensure efficacy trials in pregnant women[139]—the approach used for licensure of meningococcal C[140] and meningococcal B vaccines. Guidance[141] published in 2015 described the basic concepts of this approach for vaccines developed for pregnancy. This approach would be coupled with enhanced post-implementation surveillance to address effectiveness and additional safety.

For respiratory syncytial virus, maternal vaccination is unlikely to offer antibody-mediated protection to infants older than 6 months, at which age some infants remain susceptible to severe respiratory syncytial virus infection. This susceptibility restricts the potential effect of maternal vaccination as a standalone strategy to completely mitigate respiratory syncytial virus disease. Therefore, alternative vaccination approaches might be needed. So-called cocooning, by vaccination of infant contacts, might be more effective at protecting infants than a strategy focused solely on maternal immunisation and the development of an effective paediatric vaccine should still be actively pursued.[142]

Interference with vaccine responses in infants

Evidence from studies of measles and pertussis vaccination indicates that high levels of maternally derived antibody might restrict infant antibody responses to subsequent infection or immunisation.[143,144] Such an event could potentially occur after maternal vaccination against respiratory syncytial virus.[145,146] A significant reverse correlation has been observed between pre-existing respiratory syncytial virus specific serum IgG and production of nasal IgA in the neonate following primary infection.[147,148] In children hospitalised with respiratory syncytial virus, a negative association was found between pre-existing levels of maternal antibody and the generation of neutralising antibody by the infants.[149]

Animal models allow vaccines to be tested in the presence or absence of maternal antibody. Cattle are natural hosts for respiratory syncytial virus and pathology caused by infection with the bovine virus is similar to that seen in human infants. Furthermore, maternal antibodies provide partial protection against the incidence and severity of disease in calves.[150,151] Evidence suggests that following vaccination or natural infection in calves,

maternal antibody can interfere with development of immunity to respiratory syncytial virus,[152–154] although some vaccine formulations might overcome this suppressive effect.[155,156] In cotton rats, evidence indicates that high titres of antibody can interfere with vaccination against respiratory syncytial virus in pups and adults.[157,158] By contrast, in murine studies, no detrimental effect of maternal antibodies was observed after respiratory syncytial virus vaccination[159–161] and maternal antibodies might enhance the response in pups.[162]

Regardless of interference by maternal antibody, priming of a cellular memory response might occur after infant infection or vaccination, and this might provide immunological memory for protection in the long term,[163,164] although high titres of serum antibodies, which result in more rapid clearance of virus, could potentially also reduce the cellular response.[165] The quality of immune memory developed against respiratory syncytial virus in neonates could also potentially be influenced by the presence of maternal antibody,[166] and because inappropriate immune responses can drive pathology to respiratory syncytial virus,[96] this could be detrimental.

Capsular polysaccharide-protein conjugate vaccines for group B streptococcus disease have the potential to interfere with the immune system via immune responses to the specific carrier protein; CRM197-specific antibody at age 2 months was shown to reduce later responses to infant immunisation with a CRM197 conjugate meningococcal vaccine.[167] In a 2015 study,[143] the concentration of specific antibodies to diphtheria toxoid were lower in infants after the primary immunisation series if their mothers had been vaccinated with a diphtheria-containing vaccine in pregnancy as were the responses to the menC-conjugate and pneumococcal-conjugate vaccines (in which CRM197 was the carrier protein).

Safety of vaccination in pregnancy

No safety issues have been identified among recipients of any group B streptococcus candidate vaccines. In the South African maternal immunisation trial[126] rates of stillbirth were concordant with those currently described for South Africa and rates of preterm labour were lower (6–9% *vs* 8–12%). In Malawi, 7–23% of women reported adverse events that could be attributed to the vaccine but none of the events was considered serious or associated with stillbirths.[128] Similarly, initial clinical trials have demonstrated no adverse effects on infant health of respiratory syncytial virus maternal vaccination.[137]

Cost-effectiveness of immunisation

Two cost-effectiveness studies of maternal group B streptococcus immunisation have been published. In a USA-based study,[168] the cost per quality-adjusted life year gained (US$91 321) for a trivalent (Ia, Ib, III) group B streptococcus conjugate vaccine was found to be similar to other recommended vaccines. A decision-analytic model based on South African data found that immunisation alone would substantially reduce the burden of infant group B streptococcus disease in South Africa and would be very cost-effective by WHO guidelines.[169]

The possibility that prevention of severe respiratory syncytial virus disease in infants could reduce the incidence of asthma will greatly influence any cost-benefit analysis of respiratory syncytial virus vaccines. Predictive models of infant respiratory syncytial virus vaccination suggest that vaccination to prevent disease in early life is likely to be cost-effective.[170–172]

Future directions

For both group B streptococcus disease and respiratory syncytial virus, an association has been found between maternal antibody and infant protection, but the correlation is unclear 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 susceptibility to severe disease and, in the case of respiratory syncytial virus, to prevent longer-term sequelae of infection (eg, recurrent childhood wheeze and asthma).

Awareness of the gaps in understanding of group B streptococcus and respiratory syncytial virus disease is expected to inform future research (panels 1, 2).

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 GlaxoSmithKline, and has been a consultant to Novartis and Pfizer on group B streptococcus vaccines and to Novavax on respiratory syncytial virus vaccine, but received no personal funding for these activities. BK is a consultant to Pfizer and GSK on group B streptococcus vaccines. CJB is a consultant to Pfizer for development of a group B streptococcus vaccine. PJMO received a Wellcome Trust Translational Award to test a MUCOSIS vaccine against respiratory syncytial virus infection; served on advisory boards for Janssen, Johnson and Johnson, and Medimmune; and is principal lead investigator for EMINENT (Medical Research Council and GlaxoSmithKline collaborative award). MS has been an investigator on investigator-initiated research grants from Pfizer, but received no personal fees. KLD has received funding for travel to meetings from Pfizer and GlaxoSmithKline. FJC, CEJ, ZC, and MCN declare no competing interests.

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