Group B Streptococcus and Respiratory Syncytial Virus immunization during pregnancy: a landscape analysis

Paul T Heath* FRCPCH, Professor 1; Fiona J Culley* PhD 2; Christine E. Jones PhD 1, 3; Beate Kampmann PhD, Professor 4; Kirsty Le Doare PhD 4; Marta C. Nunes PhD 5; Manish Sadarangani DPhil 6; Zain Chaudhry MB BS BSc 2; Carol J. Baker MD, Professor 7; and Peter JM Openshaw FMedSci, Professor 2.

Affiliations

1 Vaccine Institute, Institute of Infection & Immunity, St. Georges, University of London and St George's University Hospitals NHS Foundation Trust, London, UK.

2 Respiratory Medicine, National Heart and Lung Institute, Imperial College London, St Mary's Campus, Norfolk Place, London, W2 1PG, UK.

3 Faculty of Medicine and Institute for Life Sciences, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.

4 Centre for international Child Health, Department of Paediatrics, Imperial College London, UK and Medical Research Council Unit, Fajara, The Gambia.

5 Department of Science and Technology /National Research Foundation: Vaccine Preventable Diseases & Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Faculty of Health Science, Johannesburg, South Africa.

6 Department of Paediatrics, University of Oxford, Oxford, UK and Vaccine Evaluation Center, BC Children's Hospital Research Institute, University of British Columbia, Vancouver BC, Canada

7 Department of Pediatrics, Molecular Virology and Microbiology, Baylor College of Medicine, Houston, USA.

***signifies equal contribution**

Correspondence:

Professor Paul T. Heath, St. Georges Vaccine Institute, Institute of Infection & Immunity, St. Georges, University of London, London, SW170RE, UK (pheath@sgul.ac.uk) and Professor Peter JM Openshaw, Respiratory Medicine, National Heart and Lung Institute, Imperial College London, St Mary's Campus, Norfolk Place, London, W2 1PG, UK (p.openshaw@imperial.ac.uk).

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 of about 30 to 80 µg/ml achieved 30 days after first administration, translate to around a 5 to 7 log2 titre of neutralizing antibody and result 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).

b. 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.

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.

Acknowledgements

We thank Denise Gardner for assistance in compiling our literature survey; The Wellcome Trust, The Rosetrees Trust, The Stoneygate Trust, The Medical Research Council, the Comprehensive Local Research Network (CLRN), the National Institute for Health Research (NIHR) and Biomedical Research Centre (BRC) at Imperial College London for financial support and Charles Sande, Janet Englund, Max Habibi, Chris Chiu, Trevor Hansel, Laura Lambert and Tony Piedra for discussions and helpful suggestions.

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

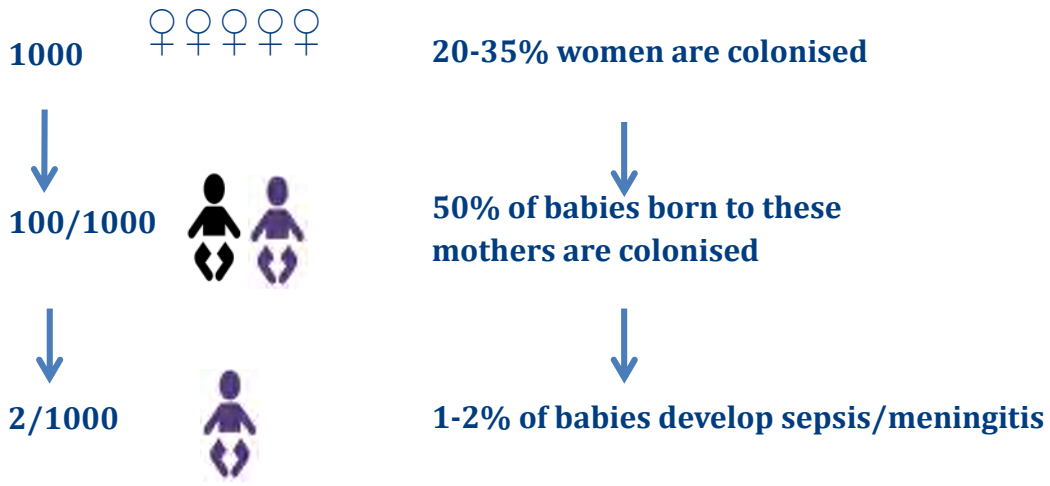

Table 1.

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.

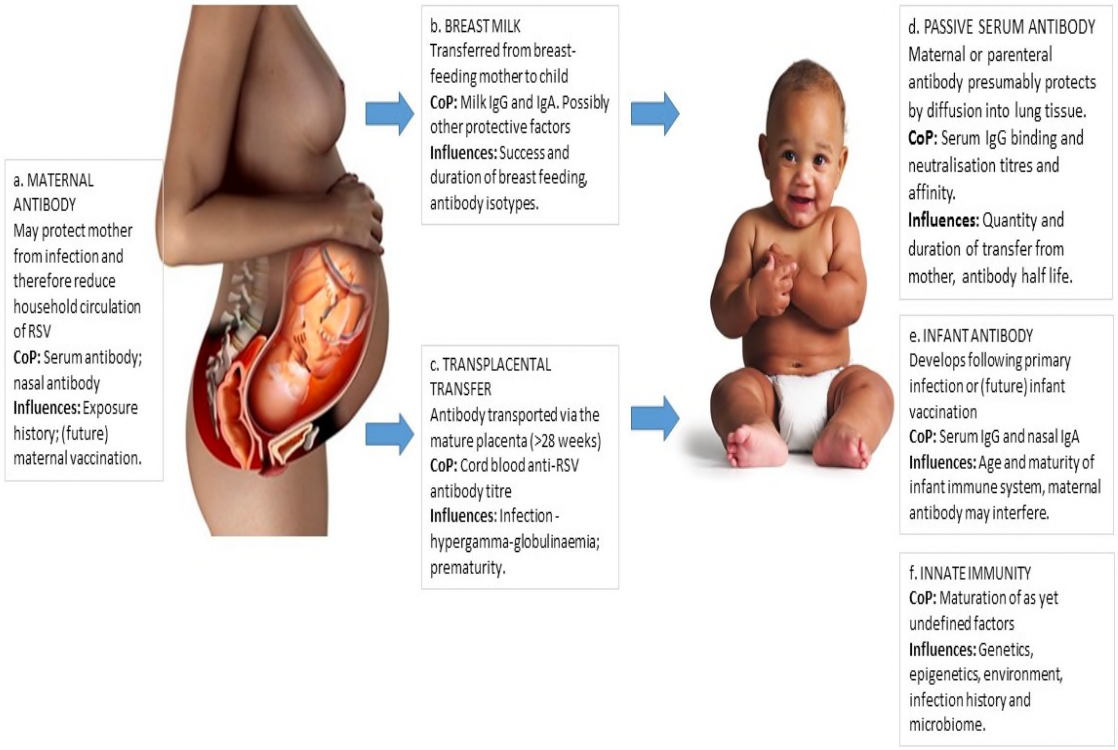

Figure 1: **Potential routes to protection against severe RSV infection.**
Maternal antibody protects the mother (a) and may be transferred to the child (b, c). This antibody protects the child by transport into the respiratory tract (d), which also benefits from maturation of the infant's immune responses and accumulation of antigenic experience (e, f). **CoP:** correlate of protection.

References.

1. Thwaites CL, Beeching NJ, Newton CR. Maternal and neonatal tetanus. *Lancet* 2015; **385**(9965): 362-70.
2. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med* 2014; **371**(10): 918-31.
3. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; **384**(9953): 1521-8.
4. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA* 2008; **299**(17): 2056-65.
5. Jones N, Oliver K, Jones Y, Haines A, Crook D. Carriage of group B streptococcus in pregnant women from Oxford, UK. *J Clin Pathol* 2006; **59**(4): 363-6.
6. Bergeron MG, Ke D, Menard C, et al. Rapid detection of group B streptococci in pregnant women at delivery. *N Engl J Med* 2000; **343**(3): 175-9.
7. Heath PT, Balfour GF, Tighe H, et al. Group B streptococcal disease in infants: a case control study. *Archives of disease in childhood* 2009; **94**(9): 674-80.
8. Heath PT, Balfour G, Weisner AM, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. *Lancet* 2004; **363**(9405): 292-4.
9. Cutland CL, Schrag SJ, Thigpen MC, et al. Increased Risk for Group B Streptococcus Sepsis in Young Infants Exposed to HIV, Soweto, South Africa, 2004-2008(1). *Emerging Infectious Diseases 21(4):638-45, 2015 Apr*.
10. Gray KJ, Kafulafula G, Matemba M, Kamdolozi M, Membe G, French N. Group B Streptococcus and HIV infection in pregnant women, Malawi, 2008-2010. *Emerg Infect Dis*; **17**(10): 1932-5.
11. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 2000; **342**(1): 15-20.
12. Bekker V, Bijlsma MW, van de Beek D, Kuijpers TW, van der Ende A. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. *The Lancet Infectious diseases* 2014; **14**(11): 1083-9.
13. C O'Sullivan, T Lamagni, A Efstratiou, et al. Group B Streptococcal (GBS) disease in UK and Irish infants younger than 90 days, 2014–2015. . *Archives of disease in childhood* 2016; **101**(Suppl 1): A2.
14. Gray KJ, Bennett SL, French N, Phiri AJ, Graham SM. Invasive group B streptococcal infection in infants, Malawi. *Emerg Infect Dis* 2007; **13**(2): 223-9.
15. Madhi SA, Radebe K, Crewe-Brown H, et al. High burden of invasive Streptococcus agalactiae disease in South African infants. *Ann Trop Paediatr* 2003; **23**(1): 15-23.
16. Dagnew AF, Cunnington MC, Dube Q, et al. Variation in reported neonatal group B streptococcal disease incidence in developing countries. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **55**(1): 91-102.
17. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet* 2012; **379**(9815): 547-56.
18. Libster R, Edwards KM, Levent F, et al. Long-term outcomes of group B streptococcal meningitis. *Pediatrics* 2012; **130**(1): e8-15.
19. Bedford H, de Louvois J, Halket S, Peckham C, Hurley R, Harvey D. Meningitis in infancy in England and Wales: follow up at age 5 years. *BMJ* 2001; **323**(7312): 533-6.
20. Seale AC, Blencowe H, Zaidi A, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. *Pediatr Res* 2013; **74 Suppl 1**: 73-85.
21. Nan C, Dangor Z, Cutland CL, Edwards MS, Madhi SA, Cunnington MC. Maternal group B Streptococcus-related stillbirth: a systematic review. *BJOG* 2015; **122**(11): 1437-45.

22. Randis TM, Gelber SE, Hooven TA, et al. Group B Streptococcus beta-hemolysin/cytolysin breaches maternal-fetal barriers to cause preterm birth and intrauterine fetal demise in vivo. *The Journal of infectious diseases* 2014; **210**(2): 265-73.
23. Surve MV, Anil A, Kamath KG, et al. Membrane Vesicles of Group B Streptococcus Disrupt Feto-Maternal Barrier Leading to Preterm Birth. *PLoS pathogens* 2016; **12**(9): e1005816.
24. Vornhagen J, Quach P, Boldenow E, et al. Bacterial Hyaluronidase Promotes Ascending GBS Infection and Preterm Birth. *mBio* 2016; **7**(3).
25. Whidbey C, Harrell MI, Burnside K, et al. A hemolytic pigment of Group B Streptococcus allows bacterial penetration of human placenta. *J Exp Med* 2013; **210**(6): 1265-81.
26. Valkenburg-van den Berg AW, Sprij AJ, Dekker FW, Dorr PJ, Kanhai HH. Association between colonization with Group B Streptococcus and preterm delivery: a systematic review. *Acta Obstet Gynecol Scand* 2009; **88**(9): 958-67.
27. Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1996; **45**(RR-7): 1-24.
28. Vergnano S, Embleton N, Collinson A, Menson E, Russell AB, Heath P. Missed opportunities for preventing group B streptococcus infection. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**(1): F72-3.
29. Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med* 2002; **347**(4): 233-9.
30. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics* 2011; **127**(5): 817-26.
31. Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. *The Pediatric infectious disease journal* 2008; **27**(12): 1057-64.
32. Weisner AM, Johnson AP, Lamagni TL, et al. Characterization of group B streptococci recovered from infants with invasive disease in England and Wales. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2004; **38**(9): 1203-8.
33. Ferrieri P, Lynfield R, Creti R, Flores AE. Serotype IV and invasive group B Streptococcus disease in neonates, Minnesota, USA, 2000-2010. *Emerg Infect Dis* 2013; **19**(4): 551-8.
34. Larsson C, Stalhammar-Carlemalm M, Lindahl G. Protection against experimental infection with group B streptococcus by immunization with a bivalent protein vaccine. *Vaccine* 1999; **17**(5): 454-8.
35. Margarit I, Rinaudo CD, Galeotti CL, et al. Preventing bacterial infections with pilus-based vaccines: the group B streptococcus paradigm. *The Journal of infectious diseases* 2009; **199**(1): 108-15.
36. Jones N, Bohnsack JF, Takahashi S, et al. Multilocus sequence typing system for group B streptococcus. *J Clin Microbiol* 2003; **41**(6): 2530-6.
37. Meissner HC. Viral Bronchiolitis in Children. *N Engl J Med* 2016; **374**(1): 62-72.
38. Lambert L, Sagfors AM, Openshaw PJ, Culley FJ. Immunity to RSV in Early-Life. *Front Immunol* 2014; **5**: 466.
39. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013; **368**(19): 1791-9.
40. Feldman AS, He Y, Moore ML, Hershenson MB, Hartert TV. Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. *Am J Respir Crit Care Med* 2015; **191**(1): 34-44.
41. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010; **375**(9725): 1545-55.
42. Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Trop Med Int Health* 1998; **3**(4): 268-80.

43. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009; **360**(6): 588-98.
44. Piedra PA, Jewell AM, Cron SG, Atmar RL, Glezen WP. Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: establishment of minimum protective threshold levels of serum neutralizing antibodies. *Vaccine* 2003; **21**(24): 3479-82.
45. Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. *J Pediatr* 1981; **98**(5): 708-15.
46. Parrott RH, Kim HW, Arrobio JO, et al. Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race and sex. *Am J Epidemiol* 1973; **98**(4): 289-300.
47. Nolan T, Borja-Tabora C, Lopez P, et al. Prevalence and Incidence of Respiratory Syncytial Virus and Other Respiratory Viral Infections in Children Aged 6 Months to 10 Years With Influenza-like Illness Enrolled in a Randomized Trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; **60**(11): e80-9.
48. Houben ML, Bont L, Wilbrink B, et al. Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. *Pediatrics* 2011; **127**(1): 35-41.
49. Simoes EA, Mutyara K, Soh S, Agustian D, Hibberd ML, Kartasasmita CB. The epidemiology of respiratory syncytial virus lower respiratory tract infections in children less than 5 years of age in Indonesia. *The Pediatric infectious disease journal* 2011; **30**(9): 778-84.
50. McLellan JS, Ray WC, Peeples ME. Structure and Function of RSV Surface Glycoproteins. *Current topics in microbiology and immunology* 2013; **372**: 83-104.
51. McLellan JS, Chen M, Leung S, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. *Science* 2013; **340**(6136): 1113-7.
52. Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. *N Engl J Med* 1976; **294**(14): 753-6.
53. Dangor Z, Kwatra G, Izu A, Lala SG, Madhi SA. Review on the association of Group B Streptococcus capsular antibody and protection against invasive disease in infants. *Expert Review of Vaccines 14(1):135-49, 2015 Jan*.
54. Baker CJ, Carey VJ, Rench MA, et al. Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. *Journal of Infectious Diseases 209(5):781-8, 2014 Mar 1*.
55. Lin FY, Philips JB, 3rd, Azimi PH, et al. Level of maternal antibody required to protect neonates against early-onset disease caused by group B Streptococcus type Ia: a multicenter, seroepidemiology study. *The Journal of infectious diseases* 2001; **184**(8): 1022-8.
56. Lin FYC, Weisman LE, Azimi PH, et al. Level of maternal IgG anti-group B streptococcus type III antibody correlated with protection of neonates against early-onset disease caused by this pathogen. *Journal of Infectious Diseases*; (of Publication: 01 Sep 2004): 190 (5) (pp 928-34), 2004.
57. Kasper DL, Wessels MR, Guttormsen HK, Paoletti LC, Edwards MS, Baker CJ. Measurement of human antibodies to type III group B Streptococcus. *Infection and immunity* 1999; **67**(8): 4303-5.
58. Beachler CW, Baker CJ, Kasper DL, Fleming DK, Webb BJ, Yow MD. Group B streptococcal colonization and antibody status in lower socioeconomic parturient women. *Am J Obstet Gynecol* 1979; **133**(2): 171-3.
59. Kwatra G, Adrian PV, Shiri T, Buchmann EJ, Cutland CL, Madhi SA. Natural acquired humoral immunity against serotype-specific group B Streptococcus rectovaginal colonization acquisition in pregnant women. *Clin Microbiol Infect*.
60. Brigtsen AK, Kasper DL, Baker CJ, Jennings HJ, Guttormsen HK. Induction of cross-reactive antibodies by immunization of healthy adults with types Ia and Ib group B streptococcal polysaccharide-tetanus toxoid conjugate vaccines. *The Journal of infectious diseases* 2002; **185**(9): 1277-84.

61. Edwards MS, Lane HJ, Hillier SL, Rench MA, Baker CJ. Persistence of functional antibodies to group B streptococcal capsular polysaccharides following immunization with glycoconjugate vaccines. *Vaccine*; **30**(28): 4123-6.
62. Habibi MS, Jozwik A, Makris S, et al. Impaired Antibody-mediated Protection and Defective IgA B-Cell Memory in Experimental Infection of Adults with Respiratory Syncytial Virus. *Am J Respir Crit Care Med* 2015; **191**(9): 1040-9.
63. Roca A, Abacassamo F, Loscertales MP, et al. Prevalence of respiratory syncytial virus IgG antibodies in infants living in a rural area of Mozambique. *J Med Virol* 2002; **67**(4): 616-23.
64. Ogilvie MM, Vathenen AS, Radford M, Codd J, Key S. Maternal antibody and respiratory syncytial virus infection in infancy. *J Med Virol* 1981; **7**(4): 263-71.
65. Eick A, Karron R, Shaw J, et al. The role of neutralizing antibodies in protection of American Indian infants against respiratory syncytial virus disease. *The Pediatric infectious disease journal* 2008; **27**(3): 207-12.
66. Ochola R, Sande C, Fegan G, et al. The level and duration of RSV-specific maternal IgG in infants in Kilifi Kenya. *PloS one* 2009; **4**(12): e8088.
67. Freitas GR, Silva DA, Yokosawa J, et al. Antibody response and avidity of respiratory syncytial virus-specific total IgG, IgG1, and IgG3 in young children. *J Med Virol* 2011; **83**(10): 1826-33.
68. Stensballe LG, Ravn H, Kristensen K, Meakins T, Aaby P, Simoes EA. Seasonal variation of maternally derived respiratory syncytial virus antibodies and association with infant hospitalizations for respiratory syncytial virus. *J Pediatr* 2009; **154**(2): 296-8.
69. Le Saux N, Gaboury I, MacDonald N. Maternal respiratory syncytial virus antibody titers: season and children matter. *The Pediatric infectious disease journal* 2003; **22**(6): 563-4.
70. Chu HY, Steinhoff MC, Magaret A, et al. Respiratory syncytial virus transplacental antibody transfer and kinetics in mother-infant pairs in Bangladesh. *The Journal of infectious diseases* 2014; **210**(10): 1582-9.
71. Stensballe LG, Ravn H, Kristensen K, et al. Respiratory syncytial virus neutralizing antibodies in cord blood, respiratory syncytial virus hospitalization, and recurrent wheeze. *J Allergy Clin Immunol* 2009; **123**(2): 398-403.
72. Kwon YM, Hwang HS, Lee JS, et al. Maternal antibodies by passive immunization with formalin inactivated respiratory syncytial virus confer protection without vaccine-enhanced disease. *Antiviral Res* 2014; **104**: 1-6.
73. Buraphacheep W, Sullender WM. The guinea pig as a model for the study of maternal immunization against respiratory syncytial virus infections in infancy. *The Journal of infectious diseases* 1997; **175**(4): 935-8.
74. Peri BA, Theodore CM, Losonsky GA, Fishaut JM, Rothberg RM, Ogra PL. Antibody content of rabbit milk and serum following inhalation or ingestion of respiratory syncytial virus and bovine serum albumin. *Clin Exp Immunol* 1982; **48**(1): 91-101.
75. Suffin SC, Prince GA, Muck KB, Porter DD. Immunoprophylaxis of respiratory syncytial virus infection in the infant ferret. *J Immunol* 1979; **123**(1): 10-4.
76. Wong DT, Ogra PL. Neonatal respiratory syncytial virus infection: role of transplacentally and breast milk-acquired antibodies. *J Virol* 1986; **57**(3): 1203-6.
77. Prince GA, Horswood RL, Camargo E, Koenig D, Chanock RM. Mechanisms of immunity to respiratory syncytial virus in cotton rats. *Infection and immunity* 1983; **42**(1): 81-7.
78. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics* 1998; **102**(3 Pt 1): 531-7.
79. Blanken MO, Rovers MM, Bont L, Dutch RSVNN. Respiratory syncytial virus and recurrent wheeze. *N Engl J Med* 2013; **369**(8): 782-3.

80. O'Brien KL, Chandran A, Weatherholtz R, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *The Lancet Infectious diseases* 2015; **15**(12): 1398-408.
81. Group TI-RS. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998; **102**(3 Pt 1): 531-7.
82. Nyiro JU, Sande C, Mutunga M, et al. Quantifying maternally derived respiratory syncytial virus specific neutralising antibodies in a birth cohort from coastal Kenya. *Vaccine* 2015; **33**(15): 1797-801.
83. Dunn SR, Ryder AB, Tollefson SJ, Xu M, Saville BR, Williams JV. Seroepidemiologies of human metapneumovirus and respiratory syncytial virus in young children, determined with a new recombinant fusion protein enzyme-linked immunosorbent assay. *Clinical and vaccine immunology : CVI* 2013; **20**(10): 1654-6.
84. Cox MJ, Azevedo RS, Cane PA, Massad E, Medley GF. Seroepidemiological study of respiratory syncytial virus in Sao Paulo state, Brazil. *J Med Virol* 1998; **55**(3): 234-9.
85. Brandenburg AH, Groen J, Steensel-Moll HAv, et al. Respiratory syncytial virus specific serum antibodies in infants under six months of age: Limited serological response upon infection. *Journal of Medical Virology* 1997; **52**(1): 97-104.
86. Vieira SE, Gilio AE, Durigon EL, Ejzenberg B. Lower respiratory tract infection caused by respiratory syncytial virus in infants: the role played by specific antibodies. *Clinics (Sao Paulo)* 2007; **62**(6): 709-16.
87. McGill A, Greensill J, Craft AW, Fenwick F, Toms GL. Measurement of antibody against contemporary virus lineages of human respiratory syncytial virus sub-group A in infants and their mothers. *J Clin Virol* 2004; **30**(1): 73-80.
88. Kasel JA, Walsh EE, Frank AL, Baxter BD, Taber LH, Glezen WP. Relation of serum antibody to glycoproteins of respiratory syncytial virus with immunity to infection in children. *Viral Immunol* 1987; **1**(3): 199-205.
89. Vissers M, Ahout IM, de Jonge MI, Ferwerda G. Mucosal IgG Levels Correlate Better with Respiratory Syncytial Virus Load and Inflammation than Plasma IgG Levels. *Clinical and vaccine immunology : CVI* 2016; **23**(3): 243-5.
90. Dhariwal J, Kitson J, Jones RE, et al. Nasal Lipopolysaccharide Challenge and Cytokine Measurement Reflects Innate Mucosal Immune Responsiveness. *PloS one* 2015; **10**(9): e0135363.
91. Jans J, Vissers M, Heldens JG, de Jonge MI, Levy O, Ferwerda G. Fc gamma receptors in respiratory syncytial virus infections: implications for innate immunity. *Rev Med Virol* 2014; **24**(1): 55-70.
92. Jozwik A, Habibi MS, Paras A, et al. RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection. *Nat Commun* 2015; **6**: 10224.
93. Openshaw PJ, Chiu C. Protective and dysregulated T cell immunity in RSV infection. *Curr Opin Virol* 2013; **3**(4): 468-74.
94. Openshaw P, Edwards S, Helms P. Changes in rib cage geometry during childhood. *Thorax* 1984; **39**(8): 624-7.
95. Culley FJ, Pollott J, Openshaw PJ. Age at first viral infection determines the pattern of T cell-mediated disease during reinfection in adulthood. *J Exp Med* 2002; **196**(10): 1381-6.
96. Okoko JB, Wesumperuma HL, Hart CA. The influence of prematurity and low birthweight on transplacental antibody transfer in a rural West African population. *Trop Med Int Health* 2001; **6**(7): 529-34.
97. van den Berg JP, Westerbeek EA, Berbers GA, van Gageldonk PG, van der Klis FR, van Elburg RM. Transplacental transport of IgG antibodies specific for pertussis, diphtheria, tetanus, haemophilus influenzae type b, and Neisseria meningitidis serogroup C is lower in preterm compared with term infants. *The Pediatric infectious disease journal*; **29**(9): 801-5.

98. de Sierra TM, Kumar ML, Wasser TE, Murphy BR, Subbarao EK. Respiratory syncytial virus-specific immunoglobulins in preterm infants. *J Pediatr* 1993; **122**(5 Pt 1): 787-91.
99. Wilczynski J, Lukasik B. Transplacental transfer of antibodies to some respiratory viruses. *Acta Microbiol Pol* 1994; **43**(3-4): 347-58.
100. Griffiths PD, Berney SI, Argent S, Heath RB. Antibody against viruses in maternal and cord sera: specific antibody is concentrated on the fetal side of the circulation. *J Hyg (Lond)* 1982; **89**(2): 303-10.
101. Heijtink RA, Backx G, Van Der Horst JM, Masurel N. Complement fixation and neutralization RS antibodies in maternal and neonatal sera. *J Hyg (Lond)* 1977; **78**(3): 411-7.
102. Crowe JE, Jr. Influence of maternal antibodies on neonatal immunization against respiratory viruses. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2001; **33**(10): 1720-7.
103. Okoko BJ, Wesumperuma LH, Ota MO, et al. The influence of placental malaria infection and maternal hypergammaglobulinemia on transplacental transfer of antibodies and IgG subclasses in a rural West African population. *The Journal of infectious diseases* 2001; **184**(5): 627-32.
104. Le Doare K, Allen L, Kampmann B, et al. Anti-group B Streptococcus antibody in infants born to mothers with human immunodeficiency virus (HIV) infection. *Vaccine* 2015; **33**(5): 621-7.
105. Dangor Z, Kwatra G, Izu A, et al. HIV-1 Is Associated With Lower Group B Streptococcus Capsular and Surface-Protein IgG Antibody Levels and Reduced Transplacental Antibody Transfer in Pregnant Women. *The Journal of infectious diseases*.
106. Heiman HS, Weisman LE. Transplacental or enteral transfer of maternal immunization-induced antibody protects suckling rats from type III group B streptococcal infection. *Pediatr Res* 1989; **26**(6): 629-32.
107. Edwards MS, Munoz FM, Baker CJ. Antibodies to type III group B streptococcal polysaccharide in breast milk. *The Pediatric infectious disease journal* 2004; **23**(10): 961-3.
108. Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM, Lebowitz MD. Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. *Am J Epidemiol* 1991; **133**(11): 1135-51.
109. Sommer C, Resch B, Simoes EA. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. *Open Microbiol J* 2011; **5**: 144-54.
110. Bulkow LR, Singleton RJ, Karron RA, Harrison LH, Alaska RSVSG. Risk factors for severe respiratory syncytial virus infection among Alaska native children. *Pediatrics* 2002; **109**(2): 210-6.
111. Dixon DL, Griggs KM, Forsyth KD, Bersten AD. Lower interleukin-8 levels in airway aspirates from breastfed infants with acute bronchiolitis. *Pediatr Allergy Immunol* 2010; **21**(4 Pt 2): e691-6.
112. Tsutsumi H, Honjo T, Nagai K, Chiba Y, Chiba S, Tsugawa S. Immunoglobulin A antibody response to respiratory syncytial virus structural proteins in colostrum and milk. *J Clin Microbiol* 1989; **27**(9): 1949-51.
113. Nandapalan N, Taylor C, Scott R, Toms GL. Mammary immunity in mothers of infants with respiratory syncytial virus infection. *J Med Virol* 1987; **22**(3): 277-87.
114. Toms GL, Gardner PS, Pullan CR, Scott M, Taylor C. Secretion of respiratory syncytial virus inhibitors and antibody in human milk throughout lactation. *J Med Virol* 1980; **5**(4): 351-60.
115. Fishaut M, Murphy D, Neifert M, McIntosh K, Ogra PL. Bronchomammary axis in the immune response to respiratory syncytial virus. *J Pediatr* 1981; **99**(2): 186-91.
116. Ogra PL, Losonsky GA, Fishaut M. Colostrum-derived immunity and maternal-neonatal interaction. *Ann N Y Acad Sci* 1983; **409**: 82-95.
117. Nandapalan N, Taylor CE, Greenwell J, et al. Seasonal variations in maternal serum and mammary immunity to RS virus. *J Med Virol* 1986; **20**(1): 79-87.
118. Lancefield RC. A Serological Differentiation of Specific Types of Bovine Hemolytic Streptococci (Group B). *J Exp Med* 1934; **59**(4): 441-58.

119. Baker CJ, Paoletti LC, Wessels MR, et al. Safety and immunogenicity of capsular polysaccharide-tetanus toxoid conjugate vaccines for group B streptococcal types Ia and Ib. *Journal of Infectious Diseases 179(1):142-50, 1999 Jan*.
120. Anderson DC, Hughes BJ, Edwards MS, Buffone GJ, Baker CJ. Impaired chemotaxigenesis by type III group B streptococci in neonatal sera: relationship to diminished concentration of specific anticapsular antibody and abnormalities of serum complement. *Pediatr Res* 1983; **17**(6): 496-502.
121. Baker CJ, Paoletti LC, Rench MA, et al. Use of capsular polysaccharide-tetanus toxoid conjugate vaccine for type II group B Streptococcus in healthy women. *The Journal of infectious diseases* 2000; **182**(4): 1129-38.
122. Kasper DL, Paoletti LC, Wessels MR, et al. Immune response to type III group B streptococcal polysaccharide-tetanus toxoid conjugate vaccine. *J Clin Invest* 1996; **98**(10): 2308-14.
123. Baker CJ, Paoletti LC, Rench MA, Guttormsen HK, Edwards MS, Kasper DL. Immune response of healthy women to 2 different group B streptococcal type V capsular polysaccharide-protein conjugate vaccines. *The Journal of infectious diseases* 2004; **189**(6): 1103-12.
124. Baker CJ, Rench MA, Fernandez M, Paoletti LC, Kasper DL, Edwards MS. Safety and immunogenicity of a bivalent group B streptococcal conjugate vaccine for serotypes II and III. *The Journal of infectious diseases* 2003; **188**(1): 66-73.
125. Madhi SA, Cutland CL, Jose L, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. *The Lancet Infectious diseases* 2016; **16**(8): 923-34.
126. Donders GG, Halperin SA, Devlieger R, et al. Maternal Immunization With an Investigational Trivalent Group B Streptococcal Vaccine: A Randomized Controlled Trial. *Obstet Gynecol* 2016; **127**(2): 213-21.
127. Heyderman RS, Madhi SA, French N, et al. Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a non-randomised phase 2, open-label, multicentre trial. *The Lancet Infectious diseases* 2016; **16**(5): 546-55.
128. Paoletti LC, Rench MA, Kasper DL, Molrine D, Ambrosino D, Baker CJ. Effects of alum adjuvant or a booster dose on immunogenicity during clinical trials of group B streptococcal type III conjugate vaccines. *Infection and immunity* 2001; **69**(11): 6696-701.
129. Hillier S, Ferris D, Fine D, Ferrieri P, Edwards M, Carey V. Women receiving group B Streptococcus serotype III tetanus toxoid (GBS III–TT) vaccine have reduced vaginal and rectal acquisition of GBS type III. Annual meeting of the Infectious Diseases Society of America; 2009; Philadelphia, PA; 2009.
130. Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. *Vaccine 21(24):3468-72, 2003 Jul 28*.
131. Bellais S, Six A, Fouet A, et al. Capsular switching in group B Streptococcus CC17 hypervirulent clone: a future challenge for polysaccharide vaccine development. *The Journal of infectious diseases* 2012; **206**(11): 1745-52.
132. Tien N, Ho CM, Lin HJ, et al. Multilocus sequence typing of invasive group B Streptococcus in central area of Taiwan. *J Microbiol Immunol Infect* 2011; **44**(6): 430-4.
133. Meehan M, Cunney R, Cafferkey M. Molecular epidemiology of group B streptococci in Ireland reveals a diverse population with evidence of capsular switching. *Eur J Clin Microbiol Infect Dis* 2014; **33**(7): 1155-62.
134. Guvenel AK, Chiu C, Openshaw PJ. Current concepts and progress in RSV vaccine development. *Expert Rev Vaccines* 2014; **13**(3): 333-44.
135. Munoz FM, Piedra PA, Glezen WP. Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women. *Vaccine* 2003; **21**(24): 3465-7.

136. Eberhardt CS, Blanchard-Rohner G, Lemaître B, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clinical Infectious Diseases* 2016; **62**(7): 829-36.
137. Madhi SA, Dangor Z, Heath PT, et al. Considerations for a phase-III trial to evaluate a group B Streptococcus polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young-infants. *Vaccine* 2013; **31 Suppl 4**: D52-7.
138. Kinyanjui TM, House TA, Kiti MC, Cane PA, Nokes DJ, Medley GF. Vaccine Induced Herd Immunity for Control of Respiratory Syncytial Virus Disease in a Low-Income Country Setting. *PloS one* 2015; **10**(9): e0138018.
139. Ladhani SN, Andrews NJ, Southern J, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015; **61**(11): 1637-44.
140. Gans H, Yasukawa L, Rinki M, et al. Immune Responses to Measles and Mumps Vaccination of Infants at 6, 9, and 12 Months. *Journal of Infectious Diseases* 2001; **184**(7): 817-26.
141. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants. *Vaccine* 2003; **21**(24): 3406-12.
142. Edwards KM. Maternal antibodies and infant immune responses to vaccines. *Vaccine* 2015; **33**(47): 6469-72.
143. Murphy BR, Alling DW, Snyder MH, et al. Effect of age and preexisting antibody on serum antibody response of infants and children to the F and G glycoproteins during respiratory syncytial virus infection. *J Clin Microbiol* 1986; **24**(5): 894-8.
144. Yamazaki H, Tsutsumi H, Matsuda K, Nagai K, Ogra PL, Chiba S. Effect of maternal antibody on IgA antibody response in nasopharyngeal secretion in infants and children during primary respiratory syncytial virus infection. *J Gen Virol* 1994; **75 (Pt 8)**: 2115-9.
145. Shinoff JJ, O'Brien KL, Thumar B, et al. Young infants can develop protective levels of neutralizing antibody after infection with respiratory syncytial virus. *The Journal of infectious diseases* 2008; **198**(7): 1007-15.
146. Taylor G. Bovine model of respiratory syncytial virus infection. *Curr Top Microbiol Immunol* 2013; **372**: 327-45.
147. Taylor G, Thom M, Capone S, et al. Efficacy of a virus-vectored vaccine against human and bovine respiratory syncytial virus infections. *Sci Transl Med* 2015; **7**(300): 300ra127.
148. van der Sluijs MT, Kuhn EM, Makoschey B. A single vaccination with an inactivated bovine respiratory syncytial virus vaccine primes the cellular immune response in calves with maternal antibody. *BMC Vet Res* 2010; **6**: 2.
149. Vangeel I, Antonis AF, Fluess M, Riegler L, Peters AR, Harmeyer SS. Efficacy of a modified live intranasal bovine respiratory syncytial virus vaccine in 3-week-old calves experimentally challenged with BRSV. *Vet J* 2007; **174**(3): 627-35.
150. Hagglund S, Hu KF, Larsen LE, et al. Bovine respiratory syncytial virus ISCOMs--protection in the presence of maternal antibodies. *Vaccine* 2004; **23**(5): 646-55.
151. Kimman TG, Westenbrink F, Schreuder BE, Straver PJ. Local and systemic antibody response to bovine respiratory syncytial virus infection and reinfection in calves with and without maternal antibodies. *J Clin Microbiol* 1987; **25**(6): 1097-106.
152. Uttenthal A, Larsen LE, Philipsen JS, et al. Antibody dynamics in BRSV-infected Danish dairy herds as determined by isotype-specific immunoglobulins. *Vet Microbiol* 2000; **76**(4): 329-41.
153. Jones BG, Sealy RE, Surman SL, et al. Sendai virus-based RSV vaccine protects against RSV challenge in an in vivo maternal antibody model. *Vaccine* 2014; **32**(26): 3264-73.

154. Prince GA, Potash L, Horswood RL, et al. Intramuscular inoculation of live respiratory syncytial virus induces immunity in cotton rats. *Infection and immunity* 1979; **23**(3): 723-8.
155. Noh Y, Shim BS, Cheon IS, et al. Neonatal immunization with respiratory syncytial virus glycoprotein fragment induces protective immunity in the presence of maternal antibodies in mice. *Viral Immunol* 2013; **26**(4): 268-76.
156. Siegrist CA, Plotnicky-Gilquin H, Cordova M, et al. Protective efficacy against respiratory syncytial virus following murine neonatal immunization with BBG2Na vaccine: influence of adjuvants and maternal antibodies. *The Journal of infectious diseases* 1999; **179**(6): 1326-33.
157. Brandt C, Power UF, Plotnicky-Gilquin H, et al. Protective immunity against respiratory syncytial virus in early life after murine maternal or neonatal vaccination with the recombinant G fusion protein BBG2Na. *The Journal of infectious diseases* 1997; **176**(4): 884-91.
158. Okamoto Y, Tsutsumi H, Kumar NS, Ogra PL. Effect of breast feeding on the development of anti-idiotype antibody response to F glycoprotein of respiratory syncytial virus in infant mice after post-partum maternal immunization. *J Immunol* 1989; **142**(7): 2507-12.
159. Kimman TG, Westenbrink F, Straver PJ. Priming for local and systemic antibody memory responses to bovine respiratory syncytial virus: effect of amount of virus, virus replication, route of administration and maternal antibodies. *Vet Immunol Immunopathol* 1989; **22**(2): 145-60.
160. Sandbulte MR, Roth JA. T-cell populations responsive to bovine respiratory syncytial virus in seronegative calves. *Vet Immunol Immunopathol* 2002; **84**(1-2): 111-23.
161. Bangham CR. Passively acquired antibodies to respiratory syncytial virus impair the secondary cytotoxic T-cell response in the neonatal mouse. *Immunology* 1986; **59**(1): 37-41.
162. Daly KA, Scott Giebink G, Lindgren BR, et al. Maternal immunization with pneumococcal 9-valent conjugate vaccine and early infant otitis media. *Vaccine* 2014; **32**(51): 6948-55.
163. Blanchard-Rohner G, Snape MD, Kelly DF, et al. Seroprevalence and placental transmission of maternal antibodies specific for Neisseria meningitidis Serogroups A, C, Y and W135 and influence of maternal antibodies on the immune response to a primary course of MenACWY-CRM vaccine in the United Kingdom. *The Pediatric infectious disease journal*; **32**(7): 768-76.
164. Dempsey AF, Pyrzanowski J, Donnelly M, et al. Acceptability of a hypothetical group B strep vaccine among pregnant and recently delivered women. *Vaccine* 2014; **32**(21): 2463-8.
165. McQuaid F, Jones C, Stevens Z, et al. Attitudes towards vaccination against group B streptococcus in pregnancy. *Archives of disease in childhood* 2014; **99**(7): 700-1.
166. Oster G, Edelsberg J, Hennegan K, et al. Prevention of group B streptococcal disease in the first 3 months of life: would routine maternal immunization during pregnancy be cost-effective? *Vaccine* 2014; **32**(37): 4778-85.
167. Kim SY, Russell LB, Park J, et al. Cost-effectiveness of a potential group B streptococcal vaccine program for pregnant women in South Africa. *Vaccine* 2014; **32**(17): 1954-63.
168. Régnier SA. Respiratory syncytial virus immunization program for the United States: Impact of performance determinants of a theoretical vaccine. *Vaccine* 2013; **31**(40): 4347-54.
169. Meijboom MJ, Rozenbaum MH, Benedictus A, et al. Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands. *Vaccine* 2012; **30**(31): 4691-700.

170. Pouwels KB, Bozdemir SE, Yegenoglu S, et al. Potential Cost-Effectiveness of RSV Vaccination of Infants and Pregnant Women in Turkey: An Illustration Based on Bursa Data. *PloS one* 2016; **11**(9): e0163567.