Abstract

Group B streptococcus (GBS) is estimated to have caused 319,000 cases of neonatal disease resulting in 90,000 infant deaths globally in 2015. It is also associated with maternal sepsis, preterm births, stillbirths and neonatal encephalopathy. There is a significant burden of neurological impairment amongst survivors of infant GBS disease. Intrapartum antibiotic prophylaxis strategies have reduced the incidence of newborn early-onset GBS (occurring days 0-6) in some settings, but they are not feasible in many low and middle income countries. A maternal vaccine given to pregnant women to stimulate passive transplacental transfer of protective antibodies has the potential to reduce maternal disease, adverse pregnancy outcomes and newborn disease. Phase I and II vaccine studies are occurring, but conducting phase III efficacy studies of a GBS vaccine candidate would require very large numbers due to the relatively low incidence of invasive GBS disease. It has therefore been proposed that alternative pathways to vaccine licensure should be explored, for example, through use of a regulatory approved correlate of protection and safety evaluation in mothers, foetuses and infants. These studies would then be followed-up with post-licensure phase IV studies in which vaccine effectiveness is evaluated.

Title - Group B Streptococcus: Trials and Tribulations

Running Title - GBS: Trials and Tribulations

Authors - Dr Hannah G Davies[a], Dr Clara Carreras-Abad[a], Dr Kirsty Le Doare[a], Professor Paul Heath[a]

[a] Paediatric Infectious Diseases Research Group, Department of Infection & Immunity, St George's, University of London

Corresponding Author -
Dr Hannah G Davies,
Paediatric Infectious Diseases Research Group,
Department of Infection & Immunity,
St George's University of London,
Jenner Wing,
Level 2,
Mailpoint J2C,
Cranmer Terrace
London
SW17 0RE
hdavies@sgul.ac.uk
020 8725 5382

Joint first author -
Dr Clara Carreras-Abad
ccarrera@sgul.ac.uk

Dr Kirsty Le Doare
kiledoar@sgul.ac.uk

Professor Paul Heath
pheath@sgul.ac.uk

Conflict of interest

KLD has received funds from Pfizer to attend a meeting regarding GBS vaccination.

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, but received no personal funding for these activities.

HGD and CCA declare no conflicts of interest.

Group B Streptococcus: Trials and Tribulations

Dr Hannah G Davies, Dr Clara Carreras-Abad, Dr Kirsty Le Doare, Professor Paul Heath

KEYWORDS - *Streptococcus agalactiae*, Immunisation, Newborn, Infection

Introduction

Group B streptococcus (GBS; *Streptococcus agalactiae*) colonises the female gastrointestinal and rectovaginal tracts of an estimated 18% (95% confidence interval 17-19%) of women globally (1). It causes a spectrum of disease that includes puerperal sepsis, neonatal sepsis and stillbirth. It may also contribute to premature birth and neonatal encephalopathy (2). A comprehensive, 2017 systematic review and meta-analysis estimated a global pooled incidence of invasive infant GBS disease of 0.49 (95%CI 0.43-0.56) per 1000 live births (3). Worldwide in 2015, GBS was estimated to have caused 319,000 (119,000-417,000) cases of invasive neonatal GBS disease, resulting in 90,000 deaths (4). It is the most important cause of neonatal early-onset sepsis in high-income countries such as the United Kingdom (5). In many high-income countries it is also the most common cause of bacterial meningitis in young children (6) (7).

The incidence of early onset GBS infections (0-6 days) has declined significantly in many settings that have adopted intrapartum antibiotic prophylaxis (IAP), however, different strategies have been implemented globally (8, 9). In settings such as Africa, IAP implementation is challenging due to overstretched health systems and the burden of invasive GBS disease is high, with an estimated incidence of 1.12/1000 live births (3).

A recent Cochrane review demonstrated that IAP strategies have no impact on reducing mortality from early onset disease (EOGBS) (10) and case-fatality rates from both EOGBS and late onset disease (LOGBS) remain high (4). Moreover, the incidence of LOGBS has been unaffected by the introduction of IAP strategies. Other prevention strategies are urgently required to decrease morbidity and mortality from invasive neonatal GBS disease.

Multivalent vaccines are in development which could be delivered to pregnant women to protect their infants against GBS disease. Trivalent polysaccharide-protein conjugate formulations were found to be safe and effective in a small number of non-pregnant adults and pregnant women (11). Phase I and II clinical trials are underway with hexavalent conjugate vaccines as well as protein-based vaccines (12). Phase III efficacy trials however, will require very large numbers of pregnant women due to the relatively low baseline incidence of invasive GBS disease (13). An alternative pathway to licensure for such vaccines could be based on serocorrelates of protection – in which the antibody levels that confer protection against invasive GBS disease in the infant are quantified - and suitable vaccines are those capable of achieving such levels. (14). A similar method has been utilised for licensing *Neisseria meningitidis* group C and *Haemophilus influenzae* type b vaccines (15). Several retrospective case control studies provide data that indicate that serocorrelates of protection against GBS disease might be determined (16) (17) (18). These studies have

compared anti-GBS antibody in maternal serum, infant serum and cord blood of infants that develop GBS disease compared to healthy controls.

This review paper aims to outline global prevention strategies for neonatal GBS disease with a focus on GBS vaccine development and assay methods for evaluation of the clinical efficacy of GBS vaccines.

Neonatal GBS disease

Early Onset GBS Disease

Early-onset invasive GBS disease (EOGBS) in infants (occurring day 0-6) is caused by vertical transmission from a colonised mother (19). Maternal colonisation is the greatest risk factor for early onset (0-6 days) invasive GBS disease. The prevalence of global maternal colonisation is estimated to be 18%. However, there appears to be regional variations in colonisation rates (11-35%), with highest rates reported in the Caribbean and Southern Africa (1). Other risk factors include prolonged rupture of membranes, preterm delivery, GBS bacteriuria during pregnancy, birth of a previous infant with invasive GBS disease, maternal chorioamnionitis, intrapartum fever, young maternal age and low levels of antibody to type-specific capsular polysaccharide (20, 21). In the absence of intrapartum antibiotic policies around 50% of babies born to colonised mothers become colonised and 1-2% of them progress to develop invasive disease (22). Most cases of EOGBS occur within 24-48 hours of birth (23). The most common manifestation of EOGBS is sepsis, but infants with EOGBS may also present with pneumonia and meningitis and the condition may progress rapidly (24). Overall the estimated case fatality rate from EOGBS disease is 10% (7-12%) with case fatality rates fourfold higher in Africa (18.9%, 95% CI 13.7%-24%) than in developed countries (4.7%, 3.3-6.1%) (3). Serotypes Ia, Ib, II, III and V are responsible for more than 90% of EOGBS, however, overall there is a paucity of data from low and middle income countries (LMICs) (4).

Late Onset GBS Disease

Late-onset disease (LOGBS) (occurring days 7-90) can be caused by either vertical transmission or horizontal transmission from environmental exposures (19). Risk factors for late onset (7-90 days) invasive GBS disease are less well understood and prevention strategies have not yet been developed. Prematurity may be a major risk factor for LOGBS with studies demonstrating that the risk increases with each week of reducing gestation (25, 26). HIV exposed infants are also at higher risk of developing LOGBS compared to HIV unexposed infants. A South African study reported that the risk ratio for LOGBS was 3.2 (95% CI 2.3-4.4) for HIV-exposed infants compared to HIV-unexposed infants (27). Meningitis is one of the leading presentations of LOGBS with up to 50% cases presenting in this way (24). Serotype III is the predominant cause of LOGBS (4). Case fatality rates from LOGBS are estimated to be 7% (4-9%).

Disease Outcomes

Survivors of infant GBS disease are at risk of neurodevelopmental impairment. A 2017 systematic review and meta-analysis of 18 studies showed that 32% (95% CI 25-38%) of infants with GBS meningitis from middle and high-income countries had

neurodevelopmental impairment at 18 months follow-up, 18% (95% CI 12-24%) of these had moderate to severe impairment (28). There are no studies in low and middle income countries, where the burden may be higher.

Intrapartum Antibiotic Prophylaxis

Intrapartum antibiotic prophylaxis screening strategies

There are currently two different approaches used to identify pregnant women that require IAP: the culture-based strategy used in countries such as the US, Canada and parts of Australia and the risk factor-based strategy used in the UK, the Netherlands and South Africa, among others (9). The former identifies GBS colonisation at 35-37 weeks' gestation (using a rectovaginal swab); intravenous benzylpenicillin or ampicillin is then offered to colonised women during labour. The second strategy is based on the presence of clinical risk factors including preterm labour (<37 weeks), prolonged rupture of membranes, maternal pyrexia (temperature >38ºC), previous infant with GBS disease and GBS bacteriuria (29).

Culture based versus risk-factor based screening strategies

The decision to implement a risk factor-based strategy rather than a culture-based one is often based on the perception that a culture-based strategy would be more expensive than a risk-based strategy. There are also no randomised trials which compare the efficacy of the 2 strategies. However a large US cohort study suggested that a culture-based strategy was around twice as effective as a risk-based strategy (30).

Risk-based strategies might be less effective as not all women whose babies develop EOGBS will have risk factors evident during labour. For example, in the recent UK national surveillance study, only 35% of EOGBS cases had one or more of the conventional risk factors (31). Furthermore, those identified with risk factors during labour may not receive IAP in a timely fashion (30).

There are data that demonstrate that rectovaginal colonisation during pregnancy is not constant; there is both a high rate of new acquisition and a loss of colonisation over the course of the pregnancy. Culture-based strategies may therefore be less effective as they may fail to detect all women colonised at delivery due to the time delay between screening and labour. Conversely, women who lose colonisation between screening and delivery may be given unnecessary antibiotics (32).

An intrapartum screening strategy using rapid tests has been proposed as a means to avoid this issue (33) as there have been significant advances in PCR technologies and new detection platforms for bacterial identification. However, it has technical and logistic challenges such as test availability, its use in busy maternity settings and the fact that women need to arrive at an earlier stage of labour. The sensitivity and specificity of the PCR from a meta-analysis was 90% (95%CI 88%–93%) and 92% (95%CI 91–94%) respectively compared with culture (34, 35). Additionally, PCR will not currently define antimicrobial resistance, an important deficiency when considering the optimal antibiotic to offer a women who is allergic to penicillin.

"Costs" of IAP

The number of deliveries exposed to IAP in the US has increased from 12% in the pre-prevention era to 32% in the prevention era (36). This is an important issue considering the international efforts to control antimicrobial resistance and conserve antibiotics. Resistance to penicillin is very rare but resistance to clindamycin, commonly used as a second line treatment in women allergic to β-lactam antibiotics, is becoming more common. Rates of clindamycin resistance in the UK are now up to 17%(37). In addition to the concern regarding antimicrobial resistance, the use of IAP might produce long-term effects on infant gut flora, cause an increase in culture negative GBS sepsis and non-GBS sepsis and result in maternal anaphylaxis (38).

In addition to the large proportion of deliveries exposed to intrapartum antibiotics, a significant number of infants are exposed to antibiotics due to suspected early onset neonatal sepsis (EOS), of which GBS is one of the most important aetiological agents. In the European Union an estimated 395,000 infants (7.9% of live births at term) are given antibiotics for suspected EOS, whilst only 0.1% of liveborn infants have culture proven sepsis (39).

Maternal vaccination for GBS

Vaccine Development

In 2014 the World Health Organisation (WHO) convened the first meeting of the Product Development for Vaccines Advisory Committee (PDVAC). The committee reviewed the status of vaccine development against 18 pathogens that contribute significantly to disease burden in LMICs. GBS was identified as one of the pathogens with a high burden amongst neonates and infants that may be amenable to prevention by immunisation. In April 2016, a WHO consultation on GBS vaccines was convened with representatives from industry, academia, public health agencies and funding bodies. The discussion in this meeting concentrated on the development of vaccines for maternal immunisation with a focus on the needs of LMICs (40).

Maternal Vaccination: Closing the window of vulnerability

In 1976, it was reported for the first time that transplacental transfer of native maternal antibodies to type III capsular polysaccharide was associated with protection against infant invasive disease with this serotype (16). Results from subsequent studies supported this initial finding and showed that it was also true of other GBS serotypes. This provided a rationale for maternal vaccination. Vaccinating women during pregnancy in order to increase transplacental transfer of protective antibodies may prevent disease in their young infants. This concept has been demonstrated successfully for neonatal tetanus (41), pertussis (42) and influenza (43) infections.

Potential vaccine targets

GBS expresses a number of virulence factors that are involved in colonisation, adherence, mucosal invasion and immune evasion (44). These are potential vaccine candidates. The capsular polysaccharide is the most well-studied virulence factor. Other potential candidates include proteins such as surface anchoring adhesins(45, 46). To initiate infection and invasion of a specific organ, bacterial pathogens must first be able to attach to an

appropriate target tissue by specific multiple tropisms between bacterial surface ligands and host receptors. Surface-anchoring adhesion molecules of GBS may therefore represent good candidates for vaccine development.

CPS Conjugate Vaccines

Favourable safety of CPS vaccines has been shown in small studies of non-pregnant and pregnant women (47). Glycoconjugate vaccines have the potential to produce a stronger and more functional IgG response than plain polysaccharide vaccines as the immunogenicity of polysaccharides is enhanced by covalent conjugation with a carrier protein. Initially, GBS vaccine studies used tetanus toxoid (TT) as the carrier protein but there have been concerns about possible adverse events (48, 49). Another carrier protein used is CRM_{197}, a nontoxic mutant of diphtheria toxin. However, TT-conjugated GBS vaccines might still be considered where maternal and neonatal tetanus remain a concern, replacing one of the current tetanus boosters(15).

Currently, there are four large companies undertaking efforts to develop a GBS conjugate vaccine. The most advanced candidates are hexavalent vaccines (serotypes Ia, Ib, II, III, IV, V), which are now in phase I/II trials.

Protein Vaccines

CPS conjugate vaccines only provide protection against serotypes included in the vaccine, or closely related ones. Therefore, efforts to identify common proteins to all GBS strains have been made in order to find a vaccine that confers broad protection against GBS. The most well-known and abundant surface protein is the Alp protein family. MinervaX Inc. recently announced that their protein vaccine based on the fusion of highly immunogenic N-terminal domains of Alpha C and Rib proteins (Alp family proteins) showed positive results from a phase I trial in 240 healthy non-pregnant women (50). Other surface proteins included in experimental vaccine studies are serine-rich repeat (SRR) glycoproteins, C5a peptidase and Pilus proteins (51).

Cost-effectiveness evaluations

Several studies in high and middle-income countries have evaluated the cost-effectiveness of a GBS vaccine compared to 'doing nothing', screening or risk-based IAP strategies. These analyses concluded that maternal immunisation would lead to important reductions in the burden of infant GBS disease and be considered very cost-effective (52) (53, 54)

There is a modelling study of different sub-Saharan African country scenarios which concluded that maternal GBS immunisation could be a cost-effective intervention, with cost-effectiveness ratios similar to other recently introduced vaccines. However, the vaccination cost at which introduction is cost-effective depends on disease incidence and vaccine efficacy. Mathematical modelling studies might be helpful in predicting effectiveness and cost-effectiveness in different LMICs but more data on disease burden are required (55).

Antibody and protection

Seroepidemiological studies have shown some evidence in favour of an association between low maternal CPS specific antibody and the risk of invasive GBS disease in their infants (56).

Associations between maternal GBS surface-protein concentrations and infant invasive disease have been less clearly established (57) (15).

There are two potential assays for measuring immune responses to GBS, an enzyme-linked immunosorbent assay (ELISA) and an opsonophagocytic killing assay (OPKA) which is a measure of functional antibody rather than total concentration or titre (58). Several issues have been highlighted in historical studies: the lack of standard reference sera for standardisation of GBS ELISA, immobilisation of GBS-CPS on ELISA plates need to be optimised and the low affinity of natural and non-specific binding antibodies needs to be resolved. Furthermore assays need to be optimised and validated in multiple laboratories (51) (59). Such standardization efforts are underway

Conclusions

Despite the availability in many countries of IAP, GBS persists as an infection of significant public health importance and is responsible for around 90,000 deaths in infants in the first 90 days of life (4). Up to 50% of infants that survive neonatal meningitis are left with long-term neurological sequelae (60). A maternal GBS vaccine has the potential to decrease the burden of neonatal early and late onset invasive disease, maternal puerperal sepsis and adverse birth outcomes such as stillbirth, prematurity and disability following neonatal disease. GBS vaccine development is underway and a panel of experts convened by the World Health Organisation have developed two key documents in order to provide guidance on research and development pathways (40) (61). Among the research priorities identified to accelerate vaccine development efforts, the development of a quality-assured, regulatory-acceptable immune correlate of protection has been highlighted.

Acknowledgements

The authors would like to thank the organisers of the infection and immunity in children course for arranging the event.

Funding

KLD is funded by the Bill and Melinda Gates Foundation (OPP1153630, 1195841, 1189053)

Conflict of interest

KLD has received funds from Pfizer to attend a meeting regarding GBS vaccination.

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.

HGD and CCA declare no conflicts of interest.

Bibliography

1. Russell NJ, Seale AC, O'Driscoll M, O'Sullivan C, Bianchi-Jassir F, Gonzalez-Guarin J, et al. Maternal Colonization With Group B Streptococcus and Serotype Distribution Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S100-S11.
2. Lawn JE, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J, et al. Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children: Why, What, and How to Undertake Estimates? Clin Infect Dis. 2017;65(suppl_2):S89-S99.
3. Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, et al. Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S160-S72.
4. Seale AC, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J, et al. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children. Clin Infect Dis. 2017;65(suppl_2):S200-S19.
5. Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland M, et al. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed. 2011;96(1):F4-8.
6. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998-2007. The New England journal of medicine. 2011;364(21):2016-25.
7. Okike IO, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, Ladhani SN, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(10):e150-7.
8. Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases NCfI, Respiratory Diseases CfDC, Prevention. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(RR-10):1-36.
9. Le Doare K, O'Driscoll M, Turner K, Seedat F, Russell NJ, Seale AC, et al. Intrapartum Antibiotic Chemoprophylaxis Policies for the Prevention of Group B Streptococcal Disease Worldwide: Systematic Review. Clin Infect Dis. 2017;65(suppl_2):S143-S51.
10. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev. 2014(6):CD007467.
11. Heyderman RS, Madhi SA, French N, Cutland C, Ngwira B, Kayambo D, et al. Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a non-randomised phase 2, open-label, multicentre trial. Lancet Infect Dis. 2016;16(5):546-55.
12. World Health Organisation. Group B Streptococcus Vaccine Development Technology Roadmap. Geneva; 2017.
13. Madhi SA, Dangor Z, Heath PT, Schrag S, Izu A, Sobanjo-Ter Meulen A, 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.
14. Heath PT, Culley FJ, Jones CE, Kampmann B, Le Doare K, Nunes MC, et al. Group B streptococcus and respiratory syncytial virus immunisation during pregnancy: a landscape analysis. Lancet Infect Dis. 2017;17(7):e223-e34.
15. Kobayashi M, Vekemans J, Baker CJ, Ratner AJ, Le Doare K, Schrag SJ. Group B Streptococcus vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries. F1000Res. 2016;5:2355.

16. 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.
17. Lin FY, Weisman LE, Azimi PH, Philips JB, 3rd, Clark P, Regan J, et al. Level of maternal IgG anti-group B streptococcus type III antibody correlated with protection of neonates against early-onset disease caused by this pathogen. J Infect Dis. 2004;190(5):928-34.
18. Dangor Z, Kwatra G, Izu A, Adrian P, Cutland CL, Velaphi S, et al. Correlates of protection of serotype-specific capsular antibody and invasive Group B Streptococcus disease in South African infants. Vaccine. 2015;33(48):6793-9.
19. Anthony BF, Okada DM, Hobel CJ. Epidemiology of the group B streptococcus: maternal and nosocomial sources for infant acquisitions. J Pediatr. 1979;95(3):431-6.
20. Baker CJ, Edwards MS, Kasper DL. Role of antibody to native type III polysaccharide of group B Streptococcus in infant infection. Pediatrics. 1981;68(4):544-9.
21. Adair CE, Kowalsky L, Quon H, Ma D, Stoffman J, McGeer A, et al. Risk factors for early-onset group B streptococcal disease in neonates: a population-based case-control study. CMAJ. 2003;169(3):198-203.
22. Yow MD, Leeds LJ, Thompson PK, Mason EO, Jr., Clark DJ, Beachler CW. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. I. Colonization studies. Am J Obstet Gynecol. 1980;137(1):34-8.
23. Baker CJ. Early onset group B streptococcal disease. J Pediatr. 1978;93(1):124-5.
24. O'Sullivan C LT, Efstratiou A, Patel D, Cunney R, Meehan M, Reynolds A, Campbell R, Doherty L, Boyle M, Davies E, Heath PT. Group B Streptococcal (GBS) disease in UK and Irish infants younger than 90 days, 2014–2015. Arch Dis Child. 2016;101(Suppl 1):A2.
25. Lin FY, Weisman LE, Troendle J, Adams K. Prematurity is the major risk factor for late-onset group B streptococcus disease. J Infect Dis. 2003;188(2):267-71.
26. Pintye J, Saltzman B, Wolf E, Crowell CS. Risk Factors for Late-Onset Group B Streptococcal Disease Before and After Implementation of Universal Screening and Intrapartum Antibiotic Prophylaxis. J Pediatric Infect Dis Soc. 2016;5(4):431-8.
27. Cutland CL, Schrag SJ, Thigpen MC, Velaphi SC, Wadula J, Adrian PV, et al. Increased risk for group B Streptococcus sepsis in young infants exposed to HIV, Soweto, South Africa, 2004-2008(1). Emerg Infect Dis. 2015;21(4):638-45.
28. Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, et al. Neurodevelopmental Impairment in Children After Group B Streptococcal Disease Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S190-S9.
29. Almeida A, Rosinski-Chupin I, Plainvert C, Douarre PE, Borrego MJ, Poyart C, et al. Parallel Evolution of Group B Streptococcus Hypervirulent Clonal Complex 17 Unveils New Pathoadaptive Mutations. mSystems. 2017;2(5).
30. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, 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.
31. O'Sullivan CP LT, Patel D, Efstratiou A, Cunney R, Meehan M, Ladhani S, Reynolds AJ, Campbell R, Doherty L, Boyle M, Kapatai G, Chalker, Lindsay D, Smith A, Davies E, Jones CE, Heath PT. Group B streptococcal (GBS) disease in UK and Irish infants younger than 90 days, 2014-2015: results from prospective surveillance. Lancet Infectious Disease 2018;In press.
32. Kwatra G, Adrian PV, Shiri T, Buchmann EJ, Cutland CL, Madhi SA. Serotype-specific acquisition and loss of group B streptococcus recto-vaginal colonization in late pregnancy. PLoS One. 2014;9(6):e98778.

33. Akker-van Marle ME, Rijnders ME, Dommelen P, Fekkes M, Wouwe JP, Amelink-Verburg MP, et al. Cost-effectiveness of different treatment strategies with intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease. BJOG. 2005;112(6):820-6.
34. Hakansson S, Kallen K, Bullarbo M, Holmgren PA, Bremme K, Larsson A, et al. Real-time PCR-assay in the delivery suite for determination of group B streptococcal colonization in a setting with risk-based antibiotic prophylaxis. J Matern Fetal Neonatal Med. 2014;27(4):328-32.
35. Daniels JP, Gray J, Pattison HM, Gray R, Hills RK, Khan KS, et al. Intrapartum tests for group B streptococcus: accuracy and acceptability of screening. BJOG. 2011;118(2):257-65.
36. Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B streptococcus. The New England journal of medicine. 2009;360(25):2626-36.
37. Kimura K, Suzuki S, Wachino J, Kurokawa H, Yamane K, Shibata N, et al. First molecular characterization of group B streptococci with reduced penicillin susceptibility. Antimicrobial agents and chemotherapy. 2008;52(8):2890-7.
38. Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2010;104(1):55-9.
39. van Herk W, Stocker M, van Rossum AM. Recognising early onset neonatal sepsis: an essential step in appropriate antimicrobial use. J Infect. 2016;72 Suppl:S77-82.
40. Kobayashi M, Schrag SJ, Alderson MR, Madhi SA, Baker CJ, Sobanjo-Ter Meulen A, et al. WHO consultation on group B Streptococcus vaccine development: Report from a meeting held on 27-28 April 2016. Vaccine. 2016.
41. Thwaites CL, Beeching NJ, Newton CR. Maternal and neonatal tetanus. Lancet. 2015;385(9965):362-70.
42. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014;384(9953):1521-8.
43. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med. 2014;371(10):918-31.
44. Rajagopal L. Understanding the regulation of Group B Streptococcal virulence factors. Future Microbiol. 2009;4(2):201-21.
45. Grandi G. Bacterial surface proteins and vaccines. F1000 biology reports. 2010;2.
46. Raynes JM, Young PG, Proft T, Williamson DA, Baker EN, Moreland NJ. Protein adhesins as vaccine antigens for Group A Streptococcus. Pathogens and disease. 2018;76(2).
47. Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. Vaccine. 2003;21(24):3468-72.
48. Paoletti LC, Madoff LC. Vaccines to prevent neonatal GBS infection. Seminars in neonatology : SN. 2002;7(4):315-23.
49. Nuccitelli A, Rinaudo CD, Maione D. Group B Streptococcus vaccine: state of the art. Therapeutic advances in vaccines. 2015;3(3):76-90.
50. Lin SM, Zhi Y, Ahn KB, Lim S, Seo HS. Status of group B streptococcal vaccine development. Clinical and experimental vaccine research. 2018;7(1):76-81.
51. Song JY, Lim JH, Lim S, Yong Z, Seo HS. Progress toward a group B streptococcal vaccine. Human vaccines & immunotherapeutics. 2018:1-13.

52. Giorgakoudi K, O'Sullivan C, Heath PT, Ladhani S, Lamagni T, Ramsay M, et al. Cost-effectiveness analysis of maternal immunisation against group B Streptococcus (GBS) disease: A modelling study. Vaccine. 2018.
53. Oster G, Edelsberg J, Hennegan K, Lewin C, Narasimhan V, Slobod 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.
54. Kim SY, Russell LB, Park J, Verani JR, Madhi SA, Cutland CL, et al. Cost-effectiveness of a potential group B streptococcal vaccine program for pregnant women in South Africa. Vaccine. 2014;32(17):1954-63.
55. Russell LB, Kim SY, Cosgriff B, Pentakota SR, Schrag SJ, Sobanjo-Ter Meulen A, et al. Cost-effectiveness of maternal GBS immunization in low-income sub-Saharan Africa. Vaccine. 2017;35(49 Pt B):6905-14.
56. 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 Rev Vaccines. 2015;14(1):135-49.
57. Dangor Z, Kwatra G, Izu A, Adrian P, Cutland CL, Velaphi S, et al. Association between maternal Group B Streptococcus surface-protein antibody concentrations and invasive disease in their infants. Expert Rev Vaccines. 2015;14(12):1651-60.
58. Choi MJ, Noh JY, Cheong HJ, Kim WJ, Lin SM, Zhi Y, et al. Development of a multiplexed opsonophagocytic killing assay (MOPA) for group B Streptococcus. Hum Vaccin Immunother. 2018;14(1):67-73.
59. Vekemans J, Moorthy V, Friede M, Alderson MR, Sobanjo-Ter Meulen A, Baker CJ, et al. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. Vaccine. 2018.
60. Libster R, Edwards KM, Levent F, Edwards MS, Rench MA, Castagnini LA, et al. Long-term outcomes of group B streptococcal meningitis. Pediatrics. 2012;130(1):e8-15.
61. World Health Organization. WHO Preferred Product Characteristics for Group B Streptococcus Vaccines. Geneva; 2017.