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Group B streptococcal disease in the mother and newborn—A review

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ABSTRACT

Group B Streptococcus, a common commensal in the gut of humans and in the lower genital tract in women, remains an important cause of neonatal mortality and morbidity. The incidence of early onset disease has fallen markedly in countries that test women for carriage at 35–37 weeks of pregnancy and then offer intrapartum prophylaxis with penicillin during labour. Countries that do not test, but instead employ a risk factor approach, have not seen a similar fall. There are concerns about the effect on the neonatal microbiome of widespread use of antibiotic prophylaxis during labour, but so far the effects seem minor and temporary. Vaccination against GBS would be acceptable to most women and GBS vaccines are in the early stages of development.

Tweetable abstract: Group B Strep is a key cause of infection, death and disability in young babies. Antibiotics given in labour remain the mainstay of prevention, until a vaccine is available.

What is group B Streptococcus (GBS)?

Antony Van Leeuwenhoek (1632–1723) was the first to identify microscopic one-celled organisms, which he called 'animalcules'. He described bacteria of the genus Selenomonas (crescent shaped bacteria from the human mouth) in 1676. The understanding of bacteria was greatly increased by the work of Louis Pasteur (1822–1895), but it was Robert Koch (1843–1910) who first linked specific microorganisms to particular diseases, such as tuberculosis, cholera and anthrax. A Viennese surgeon, Theodor Billroth (1829–1894) coined the term Streptococcus to describe a group of bacteria within the order Lactobacillales and phylum Firmicutes. Beta-haemolytic Streptococci are so-called because when they are cultured on blood agar (a growth medium made from algae and enriched with mammalian blood, usually from sheep or horses), the red blood cells are lysed and the haemoglobin the cells contained is denatured so that its red colour disappears. Group A beta-haemolytic Streptococci (characterised by possessing the Lancefield group A antigen, a carbohydrate structure found in the cell wall) tend to cause severe infections. An example is S.pyogenes, part of the skin microbiome in 2–17 % of individuals, which causes diseases such as rheumatic and scarlet fevers.

Group B beta-haemolytic Streptococci (GBS) are called S.agalactiae (Latin for "without milk") because they cause mastitis in cows [1]. It is a common bowel commensal in many animals including fish, cattle - and humans, in which it is present in 20–40 % of adults [2]. It can be divided into ten serotypes based on a serological reaction directed against the polysaccharide capsule [3] and which are thought to influence virulence and antibiotic resistance. The most frequently identified serotypes that cause invasive disease in neonates are III (60.6 %) and Ia (17.3 %), whereas type VI (32.7 %), Ib (19.4 %), and V (19.4 %) are the most common cause of invasive disease in adults. Serotype VI is the leading type that colonizes pregnant women (35.0 %) [4]. However, the differences are not currently thought to be sufficient to make them useful in clinical practice.

Clinical importance of GBS

Maternal infection – incidence

The clinical importance of group B Streptococcus is that, although it is commonly a commensal in the gut and vagina, it can

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occasionally cause severe infections in humans, especially those with relatively low levels of immunity such as the elderly and the newborn. Maternal infection is uncommon; GBS is responsible for only about 1–2 % of urinary tract infections and about 3% of post-caesarean section infections [5]. Data are not available for developing countries, but significant maternal infections occur in about 1 in 2600 pregnancies in developed countries, with a mortality rate in those infected of 1 in 500 [6].

Neonatal infection – incidence

Hood et al. in 1961 were among the first to draw attention to the particular role of GBS in neonatal infection [7]. Muller-Pebody et al. [8] reported in 2011 on the UK Health Protection Agency's voluntary surveillance scheme in England and Wales from January 2006 until March 2008. There were 1516 reports of bacteraemia for neonates <48 h old and 3482 reports for neonates 2–28 days old. For infections at <48 h, GBS was the most frequent pathogen (31 %) followed by coagulase-negative staphylococci (22 %), non-pyogenic streptococci (9%) and *Escherichia coli* (9%). GBS was also responsible for 9% of late onset infections. The British Paediatric Surveillance Unit (BPSU) active national surveillance of invasive group B streptococcal disease in infants younger than 90 days from April 1, 2014, to April 30, 2015 reported that of 856 cases of GBS infection, 517 (60.4 %) were early onset for a rate of 0.57 per 1000 livebirths and 339 (39.6 %) were late onset for a rate of 0.37 per 1000 live births [9]. However, blood and cerebro-spinal fluid culture confirmed rates likely underestimate the true burden of disease caused by GBS, as cultures can often be falsely negative: data collected prospectively in the UK over 1 year from February 2000 to February 2001 for neonates who required a septic screen in the first 72 h of life indicated a combined rate of definite and probable early onset group B Streptococcus (EOGBS) infection of 3·6 per 1000 live-births [10].

It is not possible to quote a global rate and type of GBS neonatal infection because of the introduction over the years of various preventative measures, such as antenatal screening for maternal carriage and intrapartum antibiotic prophylaxis, which have altered the frequency and distribution of disease. However a paper by Schuchat in 1998 of the pattern of infection in the neonate before the universal adoption of screening in the USA [11] reported that 30 % occurred in preterm babies, and 70 % in otherwise healthy term babies. 75 % of infections occurred within 0–6 days (90 % within 12 h), which they termed 'early onset'. 90 % of these cases were septicaemia / pneumonia and 10 % meningitis, with a 10 % mortality and a 7% long term morbidity. A similar distribution of timing in relation to birth was seen in the UK in 2000, with 377 of 568 (66.4 %) occurring at 0–6 days and 191 of 568 (33.6 %) at 7–90 days [12] (cf 60.4 % and 39.6 % in 2014–15 [9]). The falling incidence of early vs late onset disease is usually attributed to the effect of prevention of early onset disease by intrapartum antibiotic prophylaxis and the absence of such an effect on late onset disease.

Although numerically fewer preterm babies are affected than term babies, those with low gestational age or birthweight have the highest incidence of GBS infection. In the BPSU study [9], the incidence in infants below 28 weeks gestation or 2500 g birthweight was approximately 14 times higher than in more mature and heavier infants. The most common clinical syndrome resulting from GBS disease in this study was septicaemia (62 %), followed by meningitis (22 %), bacteraemic pneumonia (5%), and focal infections (<1%). Presentation differed according to age at onset: Infants with late-onset disease were more likely to present with meningitis than those with early-onset disease (29 % *vs* 11 %). Tachypnoea is the most common presenting sign of EOGBS, with or without grunting, recession or nasal flaring, and may be very subtle. Hypothermia is a more common presentation than fever [13].

Stillbirth

Although antenatal infections are much less common, GBS is an important cause of stillbirth, especially in Africa. A 2017 meta-analysis estimated that 1% of all stillbirths in developed countries and 4% in Africa are associated with GBS (there are no data from Asia, and these incidences may be underestimated due to incomplete case ascertainment) [14]. Fetal demise due to GBS infection can occur antepartum and during labour.

Epidemiology and mechanisms of disease

Because of poor medical and reporting infrastructure, we do not have an accurate assessment of the incidence of GBS infections in developing countries. However, there is some evidence of a differential susceptibility to GBS disease in different racial groups. Nanduri et al. [15] reported that in the USA in 2015, the incidence of early-onset disease was 0.55 per thousand in black African Americans compared with 0.15 per thousand in white Europeans (the rate of late-onset disease was also higher with a rate ratio of 2.9). In a racially diverse area of London (UK), GBS colonisation rates of pregnant women in 2014–15 were 39.5 % in black Africans, 27.4 % in white British, and 23.3 % in South Asians [16]. Such differences may be related to variations in the vaginal microbiota [17], with black African women having lower prevalences of lactobacilli in their vaginal flora.

While the incidence of invasive GBS disease in neonates is significant in American, European and African countries, the incidence in several Asian countries has been shown to be low, and rates of gram-negative sepsis higher. These differences in incidence raise the questions of whether the prevalent local colonising bacteria may differ in their ability to induce invasive disease, whether genetic differences in host immune response are the major determinant of invasive disease and cytokine production, or whether the outcome may depend on both factors [18]. It has been suggested by Borghesi et al. [19] that monogenic immune mutation might lead to invasive GBS in some cases. While this is potentially possible, the high incidence of GBS disease and the rarity of monogenic immune deficiency suggests that the majority of cases will be determined by less profound immune variation, due to common genetic polymorphisms.

GBS strains differ in their ability to induce proinflammatory cytokine responses in human macrophage cell lines, with the hypervirulent strain ST-17, and isolates obtained from cases of invasive disease, driving a significantly higher response, in particular for the highly pro-inflammatory cytokine, TNF-α [20]. Thus carriage during pregnancy of an enhanced TNF-α inducing serotype may provide a higher risk for invasive disease.

Colonisation of the mother will depend upon factors that impact on her own gut microbiome, and her own immune responses. The protective immune response for the infant is mediated by the adaptive immune response of the mother, with transfer of protective antibody to the infant, (enhanced by breast milk which contains maternal-specific secretory IgG), and by his/her own innate immune responses to GBS. With respect to GBS, three key elements of the innate immune response have emerged.

Firstly, response to GBS components is largely via membrane-bound Toll-like receptors (TLR), which are pattern-recognition molecules. After recognition of specific molecular patterns on the surface of microbes such as the cell wall lipoprotein of GBS, TLRs induce activation of distinct signalling pathways, which in turn lead to innate and adaptive immune responses. Following

recognition of GBS by TLR2, signalling via the MyD88 pathway induces a pro-inflammatory response. The rare condition of MyD88 deficiency leads to a 1000-fold increase in early and late neonatal sepsis in affected infants [18]. TLR2 deficiency has been associated with predisposition to invasive bacterial infection in mice, although also protecting from lethality in invasive GBS infection, as a result of reduced cytokine responses [21]. In a study of women with pelvic inflammatory disease, the TLR2 polymorphism RS3804099 was significantly more frequent in African American women with pelvic inflammatory disease [22]. This same polymorphism has been shown separately to be significantly associated with gram-positive, but not gram-negative, neonatal sepsis [23].

Secondly, a distinct intracellular response to GBS is via the NLRP3 inflammosome. A critical element of host defence against GBS in mice is a response to GBS β-haemolysis via the inflammosome [24]. An important regulatory system for NLRP3, inflammosome responses are mediated via sialic acid-binding Ig-like lectin (SIGLEC) receptors. In response to GBS, SIGLEC-14 enhances and SIGLEC-5 reduces inflammasome activation and IL-1β production (Tsai et al). In view of the reported reduction of invasive disease in Asian countries, it is notable that absent SIGLEC-14 function due to a SIGLEC 5–14 fusion polymorphism occurs in 70 % of Chinese, 60 % of South-east Asians, 50 % of Middle_Eastern, 39 % of Indian subcontinent origin, 33 % of sub-Saharan Africans and 10 % of North Europeans [25].

Thirdly, an additional protective response is induced by intracellular GBS DNA, which triggers cyclic GMP-AMP synthase (cGAS) to bind to Stimulator of Interferon Genes (STING), leading to interferon-β production [18]. The recently recognised cGAS-STING pathway is a highly potent and tightly regulated pathway [26]. Its role in the pathogenesis of invasive GBS infection has yet to be fully characterised.

Overall, effective host defences against GBS need to lie in a "Goldilocks zone" which is sufficient to prevent invasion or eliminate GBS rapidly, but not so great that the immune response causes breakdown of epithelial and endothelial barriers and promotes organ failure and sepsis syndrome.

Prevention and screening

To date, no effective strategies have been devised for the prevention of antenatal GBS infection causing stillbirth, or the prevention of late onset GBS infection. However Yow et al. showed in 1979 that when 34 women known to be colonised with GBS were treated with intravenous ampicillin during labour (intrapartum antibiotic prophylaxis, IAP), none of their infants were colonised at birth or within 48 h, compared with 14 of 24 women who received no antibiotic therapy [27].

Easmon et al. in 1983 showed that penicillin was equally effective [28]. They commented that "we preferred to use antibiotics with a narrower spectrum of activity because of problems with the emergence of antibiotic resistant gram negative organisms which can arise with broad-spectrum agents such as ampicillin". To date GBS remains sensitive to penicillin, although some reduction in susceptibility both to penicillin and cephalosporins (which can be used if the woman gives a history of a previous non-anaphylactic reaction following administration of penicillin) has been reported from Japan [29]. Fortunately, these reductions have not diminished the clinical efficacy of the doses used in treatment and prophylaxis. In contrast, resistance to erythromycin and clindamycin (previously used if a woman had an anaphylactic reaction to penicillin, in which case use of a cephalosporin is contraindicated) has increased sufficiently [30] that vancomycin is now recommended for women with previous penicillin induced anaphylaxis [31].

In the USA, prior to 1993, the incidence of early onset GBS disease varied between 1.5 and 1.7 cases per thousand live births, and this prompted both the American College of Obstetricians and Gynaecologists (ACOG) and the American Academy of Pediatrics (AAP) to recommend antibiotic prophylaxis during labour, ACOG on the basis of risk factors [32] (such as known previous colonisation with GBS and fever in labour) and AAP on the basis of testing with vaginal swabs and culture at 26–28 weeks of gestation [33]. However, the acceptance of antenatal testing strategies for the prevention of early-onset neonatal group B streptococcal sepsis was limited because of concerns about the accuracy of cultures in predicting women who were colonised with GBS at the onset of labour. Serial cultures suggested that vaginal carriage was intermittent [34]. The recommended timing for antenatal testing was therefore moved to 35–37 weeks. Yancey et al. reported in 1996 [35] that in 219 women with cultures positive for GBS, culture six or more weeks before delivery resulted in a sensitivity of carriage at the onset of labour of only 43 %, with a negative predictive value of 81 %. However, when cultures were obtained at 35–36 weeks' gestation, the sensitivity rose to 87 % and the negative predictive value to 96 %.

As a result of such studies, by 1996 the Centre for Disease Control in the USA was recommending intravenous antibiotic prophylaxis against GBS, either on the basis of risk factors or by antenatal swab testing [36], and by 2002 the recommendation had changed to the universal use of antenatal swab testing [37]. By 2015, the rate of early onset GBS disease (EOGBSD) in the USA had fallen to 0.23 per 1000 live births, lower than the late onset rate of 0.31 per 1000 live births [15]. Similar falls were seen in the number of other countries, particularly in Europe [38].

In contrast, the rate of EOGBSD in the UK, where to date the National Screening Committee has continued to advocate the use of risk factors for prophylaxis, had risen from 0.48 per 1000 live births in 2000 to 0.57 per 1000 in 2015 [9]. In response to concern about the rise in GBS infection rates, guidelines for the prevention of early-onset neonatal group B streptococcal disease of the Royal College of Obstetricians and Gynaecologists were reviewed and published in 2017 [31]. In addition to the previously recognised indications for offering IAP (a baby affected by GBS disease in relation to a previous pregnancy, GBS detected through bacteriological investigation during pregnancy (for example, a urine infection or a swab taken to investigate a vaginal discharge), and pyrexia in labour), the updated guidelines additionally recommended intrapartum antibiotic prophylaxis in all cases of preterm labour. A particular concern was that the previous 2012 guidelines had not recommended any action (either testing or IAP) in labour where GBS had been found in a previous pregnancy. The 2017 guidelines recommended that women be offered either IAP, or testing at 35–37 weeks to establish carrier status.

Testing for GBS

Public Health England published in 2006 (updated 2014, 2015, 2018) a standard for the detection of GBS carriage [39]. This emphasised the importance of collecting not only a low (not high) vaginal swab but also a rectal swab, with insertion of the swab into the rectum. This can be done conveniently using a single swab, taking the lower vaginal sample first. The specimens can be transported in a non-nutritive transport medium such as Amies or Stuarts and then cultured in a selective enrichment broth that inhibits the growth of organisms other than the GBS (The most widely used selective enrichment broth is Todd-Hewitt broth with nalidixic acid and colistin (e.g. Lim broth) or nalidixic acid and gentamicin further sub-cultured on a blood agar plate). Several options are available for sub culture of a selective enrichment broth for isolation of GBS including selective and chromogenic agar.

The advantage of antenatal testing at 36–37 [6] weeks of gestation age (as recommended by the 2020 guidelines of the American College of Obstetricians and Gynaecologists [40]) is that it allows unhurried counselling of women found to be carriers, and establishment of antibiotic sensitivity for women who are intolerant of penicillin. Although at one time clindamycin was recommended if women were intolerant of penicillin, increasing rates of resistance mean it is often no longer effective [41]. First generation cephalosporins such as cefazolin can be used instead if there is a low risk of anaphylaxis. Women with a previous history suggestive of anaphylaxis who are carriers of a clindamycin resistant strain of GBS can be given vancomycin. The major disadvantage is that it takes up to 48 h before an antibiotic sensitivity result is available, which is a particular problem if women go into labour shortly after the swab is taken.

More recently, rapid polymerase chain reaction testing for the presence of GBS, with claimed 100 % sensitivity and 97.5 % specificity [42], has become feasible at the beginning of labour [43]. It is more accurate at defining the women whose babies are at risk, and can for example reduce the number of women receiving IAP for uncomplicated pyrexia (commonly secondary to epidural anaesthesia [44] rather than chorioamnionitis) when they are not GBS carriers. The disadvantage is that PCR testing is considerably more expensive than swab culture, and moreover getting a result can take up to 2 h. This is important because the maximum benefit from IAP is only achieved when it is given for at least two (and preferably four) hours before the birth. When low risk women are being encouraged to give birth at home, or to stay at home as long as possible before attending a maternity or midwifery unit to give birth, this can result in failure to start antibiotic infusion early enough to achieve adequate prophylaxis. An additional disadvantage of PCR based intrapartum testing is that it cannot provide information regarding the resistance of GBS to antibiotics used for IAP. This may lead to the choice of an antibiotic to which the GBS strains are resistant, especially in the context of increasing and emerging resistance to the second line antibiotics used in IAP.

Although testing for GBS, with intrapartum antibiotic prophylaxis for mothers found to be carriers is associated with impressive falls in early-onset GBS disease in epidemiological studies, there has never been a prospective randomised controlled trial of this approach. The GBS3 trial, a cluster randomised trial in 80 UK maternity units of risk-based prophylaxis versus antenatal culture based testing and PCR testing at the onset of labour is being coordinated by the Nottingham clinical trials unit (https://www.gbs3trial.ac.uk/home.aspx). It started officially on the 1st April 2019 but recruitment has been postponed due to the Covid-19 pandemic.

Intrapartum antibiotic prophylaxis and the microbiome

In recent years, there has been a growing appreciation of the importance of the five main microbiomes (nasal, oral, skin, urogenital (vagina) and gut) to human health. The gut microbiome has a major influence on metabolism through its role in nutrition [45]. By 2008 it had become clear that elective Caesarean section (before labour) is associated with increases in diabetes, asthma, allergy, and obesity in the offspring [46]. This mode of delivery was subsequently shown to be associated with a marked influence on the microbiome of the newborn [47], with a particular initial paucity of Bifidobacterium [48]. Bifidobacteria are suggested to play a crucial role in protecting against susceptibility to diverse diseases later in life [49].

Concern has been expressed about the possibility that intrapartum antibiotic prophylaxis adversely affects the establishment of the gut microbiome in the newborn. Jess et al. reported in 2014 that low-dose penicillin exposure altered the microbiota of mice, and when this altered microbiota was transferred to germfree mice, they gained total mass and fat mass at a significantly faster rate than mice receiving normal microbiota T [50]. However, although a small USA study of 436 mother-child dyads followed to the age of seven years reported an 84 % increase in obesity in children exposed to antibiotics during the second or third trimester [51], a subsequent study of 43,365 mother-child dyads from a nationwide cohort of pregnant women and their offspring in the Danish National Prescription Registry found only a small increase in overweight at the age of seven (odds ratio of 1.27 (95 % CI, 1.05–1.53) for ampicillin) and no significant increase by the age of 11 [52]. Moreover, they found that prenatal exposure to narrow spectrum antibiotics was not associated with overweight in the offspring.

Similarly, Metz et al. reported in 2019 that exposure to intrapartum antibiotic prophylaxis for GBS was not associated with higher early childhood BMI Z-scores compared to healthy controls [53]. Consistent with this, Corvaglia et al. reported that while the Bifidobacteria count was significantly lower in the newborns of mothers given IAP at 7 days of life, no differences in Bifidobacteria count at 30 days or in Lactobacilli and B fragilis counts at any time point were found [54].

Reassuringly, Stearns et al. reported in 2017 that while the faecal microbiota from infants exposed to IAP for GBS prior to vaginal birth differed from that of unexposed infants at 10 days and 6 weeks of age ($p < 0.05$), no differences were seen by 12 weeks [55]. It seems reasonable to conclude that any adverse effect of IAP with penicillin is heavily outweighed by the reduction in early-onset GBS disease.

The risk of developing necrotizing enterocolitis (NEC) is increased following antenatal exposure to ampicillin [56] or co-amoxiclav [57]. This association is biologically plausible in view of the evidence linking disordered immune development with antibiotic-induced changes in intestinal microflora and pathogenic intestinal bacteria with the development of NEC.

The use of broad spectrum antibiotics in the perinatal and early neonatal period reduces bacterial diversity within the gut, and allows increased expansion of bacteria such as GBS through reduced bacterial competition. An important consequence of broad spectrum antibiotic use, identified in a murine model, is the abolition of the constitutive anaerobic state within the colon, by depletion of butyrate producing anaerobes [58]. Butyrate activates an intracellular butyrate sensor called PPAR-γ (peroxisome proliferator–activated receptor), within gut epithelial cells. This signals to a homeostatic pathway which prevents dysbiotic expansion of potentially inflammatory pathogens such as *Escherichia* and *Salmonella*, and maintains growth of non-pathogenic anaerobic bacteria, in the lumen of the colon. Butyrate deficiency leads to defective butyrate-PPAR-γ signalling, and uninhibited growth of pathogenic bacteria [58]. In addition to uninhibited overgrowth of aerobes within the gut lumen, with decrease of protective anaerobes such as bifidobacterial, there is consequent depletion of the regulatory T cell pool within the gut mucosa. Thus any induced inflammatory response might proceed unchecked and has been associated with an increased tendency to gut inflammation such as that seen in NEC.

Breast feeding

Breastfeeding shapes the neonatal gut microbiota, both because of exposure to the milk microbiota and via factors such as milk oligosaccharides, secretory IgA and antimicrobial antibodies [59] which are thought to guide the infant's developing mucosal

immune system [60]. There has been a concern that some cases of late onset GBS disease are secondary to transmission via the mother's milk [61], but in other cases the immune factors in breast milk may be protective [60,62]. One small study has suggested that "our results demonstrate the benefit of continued breastfeeding after emergency CS in promoting a post-weaning gut microbiota profile comparable to vaginally born infants without IAP" [63] but no such ameliorating effect was seen with babies born vaginally. Any effect of breast feeding on the microbiota following IAP needs further study.

Neonatal management

Sound clinical acumen is critical in prompt recognition of neonatal illness. In recognition of the challenges of ensuring prompt diagnosis of early onset sepsis (EOS), the American Academy of Pediatrics committee on fetus and newborn and committee on infectious disease recommended that infants born at 35 + 0 weeks gestation or more should be stratified by level of risk for EOS using multivariate risk assessment, based on both intrapartum risk factors and infant examinations [64], for example using the Kaiser Permanente Neonatal Sepsis Early Onset sepsis calculator: (https://neonatalsepsiscalculator.kaiserpermanente.org). This tool has been helpful in reducing the numbers of babies unnecessarily screened for infection and treated with antibiotics. However, there are significant reservations regarding potentially missed cases, as the tool depends on clinical acumen to judge if a baby is well or not. The tool calculates a risk-score based on GBS sepsis rates and if the incidence used to calculate the score is lower than the actual rate, this can potentially result in a lower risk score in babies who are actually infected. In addition, it cannot be used in countries which rely on a risk factor approach because it includes the result of antenatal testing for GBS carriage.

Accurate diagnosis of neonatal sepsis has traditionally depended on positive blood culture alone, but is now increasingly dependent on the use of the real-time polymerase chain reaction (PCR) for the detection of invasive GBS infections. The advantage of PCR is that a result can be obtained rapidly, and may detect other pathogens, leading to improved targeting of antibiotic therapy. A 2017 Cochrane review [65] and a 2020 study [13] suggest that PCR has the potential to be a highly valuable additional tool for the diagnosis of infection, including in those babies where conventional cultures were negative.

Following recognition of illness and immediate supportive care, the cornerstone of neonatal GBS infection management is prompt antibiotic administration, initially within the age appropriate critical care setting. The gold standard from decision to treat to antibiotics being administered should be no longer than one hour [66]. In many settings this has appropriately become a key performance indicator and is often termed the "golden hour" for antibiotic administration. Ampicillin/amoxycillin, with a broader spectrum than penicillin, are often prescribed for early onset sepsis because of the perceived need to cover the possibility of infection with *Listeria monocytogenes*. This is usually unnecessary as listeria infection is rare in pregnancy (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/765214/listeriosis_in_england_and_wales_summary_for_2017.pdf), and in any case has partial sensitivity to penicillin. Additionally, use of broad spectrum antibiotic regimens have been associated with a significantly greater risk of colonisation with resistant gram negative bacteria, especially when the combination includes a cephalosporin [67]. The most appropriate antibiotic regimen initially is benzylpenicillin and gentamicin, pending culture results (https://www.nice.org.uk/guidance/cg149/chapter/1-Guidance#antibiotics-for-suspected-infection-2). In cases of meningitis, a cephalosporin such as cefotaxime is usually recommended as tissue penetration is believed to be more optimal.

Women's views about GBS

GBSS (Group B Strep Support, GBSS.org.uk)) is a UK charity that campaigns to reduce group B Streptococcus infection in babies through improved awareness, education and prevention strategies. In June 2019 Bounty (a UK promotions company, pregnancy and parenting club) on behalf of GBSS circulated their online prenatal and postnatal members with an unbranded survey (GBSS was not mentioned) to ascertain women's views on GBS and pregnancy. 5205 members responded, all of whom were pregnant and/or had a child under 2 years of age. 98 % agreed with the statement that "all pregnant women should be informed about group B Strep by their doctor or midwife during their pregnancy", preferring this information to come from midwives (87 %) or obstetricians (76 %). If offered a vaccine against GBS, 91 % said they were likely to accept it (70 % very likely).

Vaccines against GBS

In 1976, it was established that infants could be protected from invasive GBS infection through the transplacental transfer of antibodies from pregnant women and this led to the concept of GBS vaccine development for pregnant women [68]. There was initially little investment in GBS vaccine development because of limited data on the global burden of disease, the view that in high-income countries, IAP based strategies were sufficient to deal with the disease, and the concerns and challenges of developing vaccines for use in pregnant women [69]. Increasing appreciation of the high global disease burden, limitations of the IAP control strategies, and the development of regulatory and policy strategies to develop vaccines for pregnant women led to renewed interest in GBS vaccines [69,70].

The Advisory Committee on Immunization Practices of the Centre for Disease Control in the USA currently recommends vaccination in pregnancy for Influenza and Tetanus, diphtheria and pertussis (https://www.cdc.gov/vaccines/pregnancy/vacc-during-after.html) and these are now being widely administered in developed countries. This has made the concept of vaccination familiar and acceptable to the majority of pregnant women [71–73]. An effective vaccine against GBS would have a number of advantages over the testing and IAP paradigm. It could prevent maternal invasive disease and antenatal stillbirth due to GBS infection as well as intrapartum and early onset disease. As preterm labour is more common in carriers of GBS [74] it might prevent cases where GBS has a causal role. It might also reduce the incidence of late onset disease if the maternal antibodies transferred to the baby in utero remain effective. It would make policy decisions much easier, and licencing quicker, if antibody levels or an equivalent immune marker could be shown to correlate with clinical effectiveness in terms of prevention [75]. A licence could then be granted on the basis of the demonstration of appropriate antibody generation, with a requirement that clinical effectiveness be shown in follow-up studies [76], a process used for the accelerated licensure of meningococcal C and B vaccines [77].

The biggest challenge is that the vaccines will be strain specific, and vaccines are likely to need to be at least pentavalent to achieve 90 % protection. While it is relatively easy to assess whether a particular vaccine induces an antibody response, the level of response required to give protection against disease is currently unknown [78]. This means that any test of efficacy will have to have as its end point reduction in disease burden, and not the much more easily measured endpoint of antibody response.

The World Health Organisation (WHO) has identified the development of GBS vaccines for maternal immunization as a

priority, based on the high unmet medical need, assessment of technical feasibility of vaccine development and the potential value of WHO involvement. In order to accelerate GBS vaccine development, the WHO has developed a vaccine development technology roadmap, to highlight priority activities for vaccine developers, researchers and funders. It has identified 'preferred Product Characteristics' which describe the vaccine characteristics that need to be considered in relation to the public health need [79].

The goal is to develop a vaccine for global use that can protect against GBS related stillbirth and invasive disease in neonates and young infants by immunizing pregnant women in the second and third trimester. The target is to provide 80 percent protection in fetuses/neonates against the combined risk of laboratory-confirmed GBS invasive disease causing stillbirth and neonatal death. There are a number of challenges for GBS vaccine development. An effective vaccine needs to target over 90 percent of the current invasive disease isolates, either overcoming the diversity of GBS capsular types, or targeting protein expression polymorphism and prevalence. The potential exists for GBS invasive disease strain evolution and capsular switching, for which long-term strain composition is required[69;79]. Data are required on the potential public health impact of the vaccine, especially in low income countries. The immunogenicity determinants in pregnant women and the effectiveness of antibody transfer to the fetus needs to be determined. Keeping in mind the challenges of pregnant women accessing antenatal care in low and middle income countries, a one dose regimen is preferred. The role of past GBS exposure and vaccines received in previous pregnancies needs to be determined. The vaccine's immunogenicity on co-administration with other recommended vaccines in pregnancy and the impact on the immune responses to infant vaccines needs to be characterised, considering both the target antigen and similar carrier proteins. The impact of the vaccine in the presence of co-infections such as HIV and malaria in the pregnant women needs to be evaluated. An adjuvant, if used, should have a well-demonstrated safety profile in pregnant women [69,79].

An immune-correlate of protection (the level of antibody in the circulation that has been shown from adequate and well-controlled trials to be associated with protection from clinical disease), which is well accepted by regulatory authorizes and is quality assured, will speed up vaccine development considerably. It must be determined through clinical trials and immune-epidemiological studies if the size of phase 3 clinical trials required to determine the vaccine efficacy are to be kept to a feasible level, or if post phase 2b trials, licensure is to be feasible with pilot implementation projects and health impact evaluation being done post licensure [79,80]. For clinical trials, the case definitions of endpoints, including stillbirth, which have been developed, will need to be standardised [81].

There are currently no licensed vaccines that protect against GBS disease. An initial Glaxo Smith Kline trivalent vaccine that was in phase II trials has been put back into 'discovery' as the results were not 'convincing enough' (https://www.gsk.com/media/5714/transcript-gsk-vaccines-event-26sep19.pdf). In addition, 55%–85% current vaccine uptakes in pregnancy will need to be improved to make testing no longer necessary [71–73]. Other companies such as MinervaX (minervax.com) and Pfizer have also been developing GBS vaccines [77]. The Pfizer vaccine is hexavalent [82] and it is currently in a phase 1 trial due to have been completed by March 2020 [80]. The South Africa based Biovac Institute and PATH, an international health organisation, are developing a multivalent vaccine funded by the Bill and Melinda Gates Foundation (https://path.azureedge.net/media/documents/PATH_GBS_factsheet_new_template_081418_FINAL.pdf).

Summary

Group B Streptococcus, a common commensal in the gut of humans and in the lower genital tract in women, remains an important cause of neonatal mortality and morbidity. The incidence of early onset disease has fallen markedly in countries that test women for carriage at 35–37 weeks of pregnancy and then offer intrapartum prophylaxis with penicillin during labour. Countries that do not test, but instead employ a risk factor approach, have not seen a similar fall. There are concerns about the effect on the neonatal microbiome of widespread use of antibiotic prophylaxis during labour, but so far the effects seem minor and temporary. Vaccination against GBS would be acceptable to most women and GBS vaccines are in the early stages of development.

Declaration of Competing Interest

The authors do not have any other conflicts of interest to declare.

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