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Disease burden due to Group B *Streptococcus* in the Indian population and the need for a vaccine – a narrative review

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***Abstract*:** *Streptococcus agalactiae*, a Gram-positive bacterium, causes invasive infection known as Group B streptococcal disease (GBS). It is a leading cause of neonatal death and complications prior to delivery. The burden of GBS is unknown in India despite the high incidence of preterm and stillbirths. In this study, we performed a narrative review of the available literature (published in the last 10 years) on the epidemiology of GBS, using PubMed and Google Scholar, to understand its impact in India and evaluate potential strategies to prevent the disease in the high-risk population, that is, neonates. The review showed that the incidence of early- and late-onset GBS in neonates (per 1000 live births) was in the ranges of 0.090–0.68 and 0.0–0.07 respectively. The overall case fatality rate reported in only one study was 0.63. In pregnant women, the prevalence of GBS colonization was 2–62% and its transmission to their newborns varied from 6.7% to 11.1%. The serotype distribution of GBS is unclear, but some studies reported the distribution of types Ia, Ib, II, III, V, VII among pregnant women in India. The associated risk factors for GBS colonization in pregnant women are unclear but a few studies suggest the role of age and multigravida, while the risk factors in neonates include preterm birth, prolonged rupture of membrane (⩾18 h), maternal fever, obstetric complications, and prolonged labor >18 h. Screening of GBS is not a routine practice in India and intrapartum antibiotics prophylaxis is limited to only in risk conditions to prevent neonatal disease transmission. A few studies also suggest that high birth rate, poor detection methods, and financial constraints limit routine GBS screening in a developing country such as India. Hence, maternal vaccination is the most promising strategy to prevent neonatal GBS and Pfizer's hexavalent GBS conjugate vaccine (GBS6) is being developed for GBS neonatal disease.

Keywords: Group B streptococcal disease, epidemiology, India, maternal vaccination

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Introduction

Group B *streptococcal* infection, or Group B streptococcal disease (GBS), is caused by *Streptococcus agalactiae*. This Gram-positive bacterium harmlessly lives in the gastrointestinal and genitourinary tracts of healthy human adults.[1] At any given time, 10–30% of all healthy adult women are carriers of this bacterium, which is present in their vagina and/or rectum.[2] GBS is surrounded by a bacterial capsule and is sub-classified into 10 serotypes (Ia, Ib, II–IX) depending on the immunologic reactivity of its polysaccharide capsule.[3,4]

In 2017, the first global study of GBS published by the London School of Hygiene & Tropical Medicine estimated the overall incidence risk of GBS in infants to be 0.49 (95% confidence interval, 0.43–0.56) per 1000 live births. The incidence risk for GBS in infants was highest in Africa (1.12), middle ranged in Latin America and the

Caribbean (0.49), and lowest in Asia (0.30). The incidence was found to be highest in Southern Africa (2.00) and lowest in Southeast Asia (0.21).[5] Another review study, by Kwatra *et al.*,[6] conducted between 1997 and 2015, supported the above findings and highlighted the estimated overall mean prevalence of GBS recto-vaginal colonization to be 17.9%, with the highest prevalence rates in Africa (22.4%), followed by the Americas (19.7%) and Europe (19.0%).

GBS can cause serious illness and sometimes death. The population at risk includes pregnant women, the fetus, newborns, and adults with chronic illnesses (e.g. diabetes mellitus, obesity, and cardiovascular disease);[7] however, neonates are at the highest risk of infection by GBS.

Symptoms of GBS in newborns appear like any other common health problem, including fever, irritability or lethargy (limpness or difficulty in waking up the baby), difficulty in breathing, and bluish skin. When symptoms have appeared since the day of birth, it is known as early-onset GBS.[8] Sometimes these symptoms may appear after the first week or through the first three months of life in babies and that is known as late-onset disease. The early- as well as the late-onset GBS is often associated with neurologic sequelae, including sight or hearing loss and cerebral palsy.[8,9]

In newborns, the bacterium spreads through intrapartum transmission.[10] Early-onset GBS occurs from transmission during or before the delivery, causing severe illness during the first week of life. Late-onset GBS occurs due to transmission from environmental or caregiver sources and in some cases from maternal mastitis, causing symptoms to appear between the first week and first three months of life.[11] The disease often results in sepsis (infection of the blood), pneumonia (infection in the lungs), and meningitis (infection of the fluid and lining around the brain and spinal cord),[12] where meningitis is more common with late-onset GBS than with early-onset GBS.[13] In pregnant females, it may also cause amnionitis, urinary tract infection, and stillbirth.[14]

Various risk factors for early-onset disease have been well described in resource-rich/high-income countries. Some of the risk factors as listed by Centers for Disease Control and Prevention (CDC)[15] include reporting positive for GBS colonization late (35–37 weeks) in pregnancy, GBS in urine during the current pregnancy, early/preterm delivery (before 37 weeks of pregnancy), fever during labor, prolonged rupture of membranes [having a long time between water breaking and delivery ($\geqslant$18 h)], birth of a previous infant with GBS and human immunodeficiency virus (HIV) infection in mothers.[16] Risk factors for late-onset GBS are not understood well, unlike those for early-onset disease. But some of the studies have identified different risk factors for late-onset GBS which include premature birth of less than 37 weeks, exposures to colonized parents and siblings, medical equipment used in supporting a preterm neonate,[13] and maternal mastistis.[11] Late-onset disease is found to be more common among babies who are born prematurely (before 37 weeks of pregnancy), babies with low birth weight as well as whose mothers tested positive for GBS, and HIV infected mothers.[16]

Prevention measures for GBS in newborns (early-onset disease) include universal screening and risk-based approach. In the former case, all pregnant women are screened between 35 and 37 weeks of pregnancy whereas in the latter case, risk-based strategy is used to identify neonates at high risk of early-onset disease and screening is limited to certain high risk conditions. While some guidelines recommend universal screening to prevent the disease in neonates, because of limited resources and poor laboratory support, it is difficult for low-income countries to adopt same. Pregnant women who test positive for the bacterium are further given antibiotic therapy during labor to prevent disease transmission.

The World Health Organization (WHO) recommends the administration of intrapartum antibiotic prophylaxis (IAP) intravenously for pregnant women with GBS colonization to prevent early onset neonatal GBS.[17] The CDC recommends the use of antibiotic therapy during labor and not before labor in pregnant women with positive GBS status as the bacterium can quickly grow back.[15] According to the CDC, pregnant women testing positive for GBS have 1 in 200 chance of transmitting the disease to their newborn if not treated with an antibiotic.[18] This risk decreases to 1 in 4000 if an antibiotic is given during labor.[19]

Administration of IAP reduces the vertical transmission of GBS bacteria colonized in the maternal vaginal area to the baby by reducing the colony count at time of delivery. It also provides

protection to newborns by circulating an effective level of antibiotic in the amniotic fluid so that they can have antibiotic in their system during deliver and early life.[20] Penicillin is the drug choice for IAP. It is considered safe and effective in preventing of spread of GBS bacteria to newborns during birth. The treatment is given intravenously.[15] For babies with severe illness, other procedures, in addition to antibiotics, may be needed. However, the drug may be associated with side-effects or allergic reactions.[20] Resistance to clindamycin or erythromycin has also increased over the past 20 years. Studies conducted in 2006–2009 in the US found the *in vitro* resistance level of GBS isolates against erythromycin was 25–32% and against clindamycin was 13–20%.[21] A large systematic review of women with preterm pre-labor rupture of membranes (PPROM) has reported the benefits of using penicillin and erythromycin in terms of prolonging pregnancy and reducing neonatal morbidity, including neonatal infection. It has been observed that the administration of penicillin, ampicillin, or cefazolin prophylaxis for more than 4 h before delivery to GBS-colonized women delivering before 37 weeks increases the effectiveness by 78% in preventing early-onset GBS.[22]

Prevention of late-onset disease in newborns is still a cause of concern. Antibiotic therapy does not prevent late-onset disease. A prevention strategy is yet to be identified for the prevention of late-onset disease.[20] Immunization of pregnant women promises to reduce the burden of GBS neonatal disease[23] since maternal antibodies against type-specific GBS capsular polysaccharides (CPSs) are found to be protective. Currently, Pfizer is developing a GBS conjugate vaccine (GBS6) (under phase II clinical trial) for the prevention of GBS neonatal disease.

Due to limited studies, the systematic review of GBS burden in India could not be conducted. Hence, this study provides a narrative review of epidemiology, risk factors, treatments and recommendations/guidelines for GBS infection in India.

Methodology

Relevant studies were identified using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (http://scholar.google.com/) with the following search strings:

- "Group B Streptococcus OR *Streptococcus agalactiae* AND Epidemiology AND India"
- "Group B Streptococcus OR *Streptococcus agalactiae* AND Prevalence AND India"
- "Group B Streptococcus OR *Streptococcus agalactiae* AND Incidence AND India"
- "Group B Streptococcus OR *Streptococcus agalactiae* AND Disease Burden AND India"
- "Group B Streptococcus OR *Streptococcus agalactiae* AND Statistics AND India"
- "Group B Streptococcus OR *Streptococcus agalactiae* AND Treatment AND India"
- "Group B Streptococcus OR *Streptococcus agalactiae* AND Serotypes AND India"
- "Group B streptococcus OR Streptococcus agalactiae AND newborns AND India"
- "Group B streptococcus OR Streptococcus agalactiae AND neonates AND India"
- "Group B streptococcus OR Streptococcus agalactiae AND early onset AND India"
- "Group B streptococcus OR Streptococcus agalactiae AND late onset AND India"

Manual search was also done by reviewing the bibliographies of relevant studies. Only the studies done on humans were included. The databases were accessed up to year 2020 to check for the published articles/reports.

Results

This study provides a narrative review of the burden of GBS in the India and evaluates serotype distribution, risk factors, and guidelines available in India for screening, treatment, and prophylaxis of GBS infection in a high risk population.

Epidemiology of GBS infections in India

Disease burden

Neonatal GBS. The disease burden of GBS in India can be determined through the statistics on incidence, prevalence, and mortality. Two studies[24,25] showed that the incidence of early-onset GBS (per 1000 live births) in India ranged from 0.09 to 0.68 while that of late-onset disease was 0.0–0.07. The overall case fatality rate was reported in only one study (0.63) and was due to early-onset GBS.[25] According to a global study, India ranked 1 with estimated numbers of 31,000 infant GBS cases and 13,000 deaths in 2015.[26]

Colonization of GBS in pregnant women. GBS spreads through intrapartum transmission in newborns. Studies also identified the prevalence of GBS colonization amongst the Indian population in pregnant women that varied from 2% to 62% (Table 1). A meta- analysis published in 2020 (1981–2019) reported that the estimated prevalence of recto-vaginal colonization in pregnant Indian women was 7.8% when culture methods were used and 11.6% when immunological methods (antigen detection) was used. A study included in this meta-analysis also reported a prevalence of 62% when polymerase chain reaction (PCR) was used for GBS detection.[27] Transmission of GBS colonization from pregnant women to their newborns was also reported in two studies; the range varied from 6.7% to 11.1%.[28,29]

Serotypes. In India, the distribution pattern of GBS serotypes is unclear. A study conducted by Chaudhary *et al.*[37] from August 2015 to April 2016 studied serotype distribution of GBS isolates in 45 pregnant women and reported highest prevalence of serotype III (22.2%) followed by type V (20%), II (20%), Ia (13.3%), VII (6.7%), Ib (4.4%) and non-typeable (13.3%).[37] A carriage study conducted by Johri *et al.*[41] in 250 samples collected from 30 subjects (both men and women; 10–83 years old) identified Ia (23%) and III (20%) as the most widespread serotypes, followed by type II (14%), VII (13%), V (7%); 23% of the isolates were not typeable. This suggest that a multivalent vaccine targeting all major serotypes would be able to confer maximum protection against GBS infection.[41]

Recommendation/guidelines. The National Guidelines for Infection Prevention and Control in Healthcare Facilities, India, adapted from WHO, recommends a risk-based approach for prophylaxis of GBS infection. Routine intrapartum antibiotic administration is not recommended. IAP is recommended only in women with GBS localization for prevention of early neonatal GBS infection; routine vaginal cleansing with chlorhexidine during labor is not advised.[42] For prophylaxis, routine antibiotic administration is recommended only in risk conditions enumerated in Table 2. Routine IAP is not recommended in other cases, as specified in the Table 2.

In India, IAP is not routinely recommended and is given only in women with GBS localization to prevent early neonatal GBS infection. Women who are unaware of their GBS status are given IAP only when risk factors such as preterm labor (<37 weeks), premature rupture of membranes (PROM) (>18 h), fever during labor or chorioamnionitis, history of previous baby with GBS infection, bladder or kidney infection due to GBS are present. In such cases, ampicillin [2 g intravenous (i.v.) initial dose followed by 1 g i.v. 4–6 h until delivery] is the first choice if the patient is not allergic to penicillin. If allergic, alternative antimicrobials used for prophylaxis include cefazolin (2 g i.v. followed by 1 g every 8 h until delivery) or vancomycin (1 g i.v. every 12 h until delivery).[43]

A cross sectional study conducted by Vinod *et al.*[39] in 2018 on antibiotic susceptibility of GBS among antenatal women in a tertiary care center observed that all of the 11 isolates were sensitive to penicillin, gentamycin, ampicillin, vancomycin, and clindamycin. The majority of isolates were either resistant or had moderate sensitivity to erythromycin respectively. Resistance was observed for chloramphenicol, cotrimoxazole, ciprofloxacin, ceftriaxone, and tetracycline. Another prospective study, performed by Sharmila *et al.*,[30] reported that all the GBS isolates from pregnant women were sensitive to penicillin or clindamycin while 14.3% were resistant to erythromycin and 71.4% were resistant to tetracycline.

Risk factors. Several risk factors are found to be associated with GBS colonization. An observational cross-sectional study conducted by Dechen *et al.*[44] on pregnant women in Sikkim showed that age and number of pregnancies (*gravida*) were positively correlated with GBS infection but were not statistically significant. Dechen also reported PROM and preterm labor in 24% and 64% respectively of the GBS culture-positive mothers.[44] No correlation between blood group or socioeconomic status and GBS infection was observed in a study by Mhaskar *et al.*[45] Another study, by Khatoon *et al.*,[35] showed significant association of GBS infection with increasing age, gravidity (age >30 years, $p < 0.012$; *gravida* >3, $p < 0.03$), and higher socioeconomic status ($p < 0.007$) while no association was found between GBS colonization and level of education, urban/rural area, and gestational age. In neonates, a prospective cross-sectional study conducted by Shah *et al.*[46] at Lady Hardinge Medical College

Table 1. Prevalence of GBS among pregnant women in India.

Author	Study design	Year	Study population	Sample size	Prevalence of GBS colonization (%)	Detection method
Sharmila *et al.*[30]	Prospective observational cohort study	2006–2008	Pregnant women	*N* = 300	2.33%	Antibiotic susceptibility testing by Kirby–Bauer disc diffusion method
Patil *et al.*[31]	Prospective cross sectional study	2007–2008	Pregnant women	*N* = 905	12.15%	Not provided
Das *et al.*[32]	Observational study	–	Pregnant women	*N* = 50	2%	Antibiotic susceptibility testing by Kirby–Bauer disc diffusion method
Konikkara *et al.*[33]	Observational study	January to June 2008	Pregnant women	*N* = 50	Culture test: 16% Antigen test: 22% PCR: 62%	Standard culture method Antigen detection method PCR assay
Uday *et al.*[28]	Prospective cross-sectional study	2009–2012	Pregnant women	*N* = 350	2.57%	Antibiotic sensitivity testing by Kirby–Bauer disc diffusion method
Arif *et al.*[34]	Descriptive study	2012–2014	Pregnant women	*N* = 100	4%	Antibiotic sensitivity testing by Kirby–Bauer disc diffusion method
Khatoon *et al.*[35]	Observational cross-sectional study	2011–2012	Pregnant women	*N* = 300	2%	Not provided
Doddaiah *et al.*[36]		2014–2015	Pregnant women	*N* = 160	14.38%	CHROMagar method
Chaudhary *et al.*[37]	Prospective cohort study	2015–2016	Pregnant women	*N* = 300	15%	Not provided
Santhanam *et al.*[29]	Observational study	2012–2013	Pregnant women	*N* = 305	In 5% blood agar: 2.6% In enriched media: 7.6%	Not provided
Shettian *et al.*[38]	Prospective study	–	Antenatal women	*N* = 350	1.4%	Not provided
Vinod *et al.*[39]	Cross sectional study	–	Pregnant women	*N* = 126	Rectal colonization = 5.5% Vaginal colonization = 3.17%	Standard methods Antibiotic sensitivity testing by Kirby–Bauer disc diffusion method
Goel *et al.*[40]	Single centric study	–	Pregnant women	*N* = 450	Recto-vaginal colonization = 3.3%	CHROMagar method

GBS, Group B streptococcal disease; PCR, polymerase chain reaction.

and Kalawati Saran Children's Hospital, New Delhi on 1050 neonates observed various maternal and neonatal risk factors for GBS and they are documented in Table 3.

A study carried out in a tertiary care hospital showed that amongst the 40 children (1–59 months old) diagnosed with GBS, ultra-late onset disease (after 3 months of age) and

Table 2. Guidelines for recommendation of intrapartum antibiotic prophylaxis to prevent maternal peri-partum infection.

Routine IAP is recommended in the following conditions	Routine IAP is not recommended in the following conditions
i. Preterm pre-labor rupture of membranes; ii. Women undergoing manual removal of the placenta; iii. Women with a third- or fourth-degree perineal tear; iv. Women undergoing elective or emergency Caesarean section (IAP given prior to skin incision).	i. During the second or third trimester for all women; ii. In preterm labor with intact amniotic membranes; iii. With premature rupture of membranes at (or near) term; iv. Women with meconium-stained amniotic fluid; v. Women undergoing operative vaginal birth (Caesarean section); vi. Women with episiotomy; vii. Women with uncomplicated vaginal birth.

IAP, intrapartum antibiotic prophylaxis.

Table 3. Risk factors for early-onset invasive Group B *Streptococcus* disease.[46].

Risk factors	Percentage of neonates/mothers with risk factor (%)
Preterm birth	22.1
Respiratory distress at birth	18.5
PROM (⩾18 h)	19.3
Intrapartum antibiotics	2.9
Presence of foul-smelling meconium-stained liquor	8.3
Maternal fever	2.8
Other obstetric complications during pregnancy	26.7
Prolonged labor >18 h	7.5

PROM, premature rupture of membranes.

late-onset disease occurred in 75% and 25% of children respectively. Complications in both of these groups during hospitalization included seizures, increased intra-cranial pressure, and ventilator support. State of coma and death were also observed in the ultra-late onset disease. On follow-up after 6 months, the ultra-late onset disease group reported seizures, monoparesis, and sixth and seventh cranial nerve palsies with hydrocephalus; the late-onset disease group reported only seizure while half of the patients did not report any complication and recovered completely. No significant difference was observed between the two groups.[47]

Management of neonatal GBS infection. In India, neonatal sepsis or early-onset GBS is prevented by combining IAP and infant antibiotic prophylaxis. However, benefit–risk assessment of routine neonatal prophylaxis has not been largely investigated. Since signs of early onset GBS are observed in the first 24 h, it is advised to observe and regularly assess general well-being, feeding, heart rate, respiratory rate, and temperature of the newborns who are at high risk of GBS infection; only those presenting clinical symptoms should be evaluated and treated with antibiotics. Routine blood test to guide evaluation is not advised. In newborns at risk of sepsis or with established early-onset disease, penicillin and gentamicin are the first-line antibiotics. A study performed in a tertiary care perinatal center in Vellore found GBS isolates from blood cultures of 10 babies; all isolates were found to be penicillin sensitive. Nine of these neonates survived when treated with penicillin for 10–14 days.[48] Another study performed on newborns with early-onset GBS showed that IAP helped in lowering early-onset GBS sepsis as it was observed that factors such as PPROM and PROM >18 or 24 h were not found to be significant after initiating IAP.[29] However, in order to establish an optimal strategy suitable for the Indian population, there is a need to perform comparative study of the preventive approaches.

Screening. In India, GBS screening is not a part of routine pregnancy health examination. Many women in India still give birth at home and investigation of ill neonates, preterm births and stillbirths is not performed in many rural and even institutionalized settings. These factors contribute to the underestimation of the true prevalence of GBS infection in India. According to a worldwide survey, pregnant women in India have the highest incidence of GBS colonization. This also increases the chances of transmitting the infection

to the newborns. Hence, proper screening procedures should be made mandatory especially in patients who are at increased risk of GBS infection. In developing countries such as India, while it is difficult to perform universal screening due to logistic and financial constraints, it may prevent many infant deaths due to GBS.

For effective screening, the employed culture method should be both specific and sensitive. A recent study showed that bacteriological swabs plated in selective enriched media increased the detection from 2.6% to 7.6% when compared with using standard agar medium.[29] In addition, newer techniques such as antigen testing and molecular methods such as PCR have shown to increase the sensitivity of detection.[33] Hence, choice of screening procedure helps in better detection of GBS colonization in pregnant women and may prevent further complications and transmission in neonates.

Discussion

There is controversy on the significance of GBS in India. A global meta-analysis published in 2017 by the London School of Hygiene reported low incidence of GBS in Southeast Asia.[5] However, another study, conducted in 2015, reported that India ranked first with estimated numbers of 31,000 infant GBS cases and 13,000 deaths.[26] Another study, by the WHO in 2017, estimated highest GBS colonization in pregnant women in India (2.5 million),[49] which is a major source of transmission in early-onset GBS in neonates,[50] which are the primary target group. Hence, this review was conducted to identify the disease burden of GBS in newborns as well as the presence of GBS colonization in pregnant women to identify the risk of neonatal GBS in the Indian population.

In the current review, we found that early-onset GBS has a higher incidence than late-onset GBS. However, case fatality rate (0.63) was reported in only one study. The low incidence observed in the studies could be attributed to under-reporting or ineffective screening technique. A global meta-analysis conducted in 2012 estimated an overall GBS incidence of 0.53 cases per 1000 live births in infants aged 0–89 days and suggested underreporting as the primary reason for the lower incidence, highlighting the need for quality studies.[51] The current review showed that prevalence of GBS colonization in pregnant women varied from 2% to 62% and its transmission to their newborns varied from 6.7% to 11.1%. The wide difference in the prevalence reported could be attributed to the method employed for detection. A study by Konikkara *et al.*[33] reported that the sensitivity of GBS detection in women increased to 62% when molecular methods like PCR are used as compared with 16% and 22% when standard culture based and antigen testing methods were used respectively. Similar observation was also made by the author in a recent meta-analysis conducted by Ashary and colleagues.[27] As per the WHO, the disease colonization in pregnant women was reported to be highest in India (2.5 million) followed by China (1.9 million), Nigeria (1.1 million), the US (0.9 million), and Indonesia (0.8 million), while the highest burden of disease was found in Africa, accounting for 54% of the estimated cases and 65% of all fetal/infant deaths.[49] Despite these statistics, only a few cases of GBS are reported, which can be attributed to a high number of home births, inadequate or conventional methods of screening, and financial constraints.

Serotype distribution of GBS was unclear and studies reported type I, II, III, V, VII GBS colonization. Similar observations were made in a global meta-analysis which reported that over 90% of GBS cases in infants are caused by serotypes Ia, Ib, II, III, and V.[51] The global study of GBS published in 2015 reported a similar result, with five serotypes accounting for 97% of invasive isolates in all regions (Table 4). Prevalence of serotype III was higher globally, accounting for 47% of the early-onset GBS cases and 73.0% of late-onset GBS cases while serotype Ia, Ib, and V were frequently isolated in 21.8%, 8.0%, and 10.6% of the early-onset GBS cases respectively, and 14.2%, 5.3%, and 4.0% of the late-onset GBS cases.[5] Risk factors responsible for GBS colonization in Indian women were not clearly identified but suggested the role of age and multigravida; contradictory results were reported for socioeconomic status. In neonates, preterm birth, prolonged rupture of membrane ($\geqslant$18 h), maternal fever, obstetric complications, and prolonged labor ($>$18 h) were the common risk factors associated with GBS colonization.

Table 4. Maternal GBS vaccines in development.

Vaccine candidate	Vaccine construct	Status	Program status
CPS-CRM_{197}[52]	Multivalent CPS conjugate	Preclinical	Clinical program started in 2017
GBS vaccine[52]	Trivalent CPS (serotypes Ia, Ib, III) conjugated to CRM197, unadjuvanted	Phase II	Completed safety and immunogenicity in pregnant women. Study completed.
–	Pentavalent (Ia, Ib, II, III, V) CPS-CRM197	Preclinical	–
–	Pilus proteins	Preclinical	–
–	Polyvalent CPS conjugate	Discovery	Program started in 2017
GBS-NN vaccine/ MVX13211[52]	N-domains of Rib and Alpha C surface proteins, unadjuvanted or alhydrogel-adjuvanted	Phase I	Safety and immunogenicity in non-pregnant women. Study completed.
–	Multivalent CPS conjugate	Preclinical	Clinical program started in 2017
GBS CRM_{197} conjugate vaccine[53]	Trivalent (Ia, Ib, and III)	Phase I/II	Started at 2010. Study completed.
GBS6[54]	Multivalent GBS polysaccharide conjugate	Phase I/II	Study started in 2017. Further clinical trials will be required.
GBS vaccine[55]	Multivalent GBS vaccine	Phase I/II	Program starts in 2019. Not completed.
CPS-CRM_{197}[56]	Trivalent glycoconjugated composed of CPS Ia, Ib, and III	Phase II	Study started in 2011. Safety and immune response in pregnant women. Study completed.
Trivalent GBS vaccine[57]	CRM197-conjugated GBS CPS of serotypes Ia, Ib, and III	Phase II extension	Study started in 2016. Safety and immunogenicity of a second dose of the investigational trivalent GBS vaccine. Study completed.

CPS, capsular polysaccharide; GBS, Group B streptococcal disease.

To date, there are no standard protocols for the screening of maternal GBS colonization in India. Detection is mostly based on conventional culture techniques whereas advanced technologies like PCR are rarely used. Many births still occur in home settings and many GBS cases go unreported. The 2010 CDC guidelines recommend prenatal GBS screening at 35 0/7 weeks of gestation.[58] The most updated guideline from the American College of Obstetricians and Gynecologists (ACOG) now recommends universal GBS screening between 36 0/7 and 37 6/7 weeks of gestation. As per the Indian Council of Medical Research guidelines, GBS positive status is treated with intrapartum antibiotic, while in those in which GBS status is unknown, IAP is limited to high risk conditions, that is, PPROM, women undergoing manual removal of the placenta, women with a third- or fourth-degree perineal tear, or those undergoing elective or emergency Caesarean section. These risk conditions in the Indian guidelines are in line with the updated ACOG guidelines but do not include GBS colonization status in a previous pregnancy as a risk factor.[59]

Therapeutic advances

Alternative prevention strategies

Vaccines. Maternal immunization promises to help reduce the burden of the disease. It is thought to raise effective antibodies in pregnant women,

providing protection to the mothers and, when they cross the placenta, offering protection to the infants during the delivery and the following months. However, concerns regarding vaccination in pregnancy are often focused on the potential risks of vaccines to the fetus. Studies suggest that benefits of vaccines to mothers and infants are far more than risks of associated adverse events. Therefore, maternal vaccination is being considered as the most suitable strategy to prevent neonatal GBS infection. The optimal time for vaccine administration is considered to be in the early third trimester to eradicate the risk of disease in premature babies (which account for approximately 30% of GBS cases).[60]

Several studies have suggested that maternal vaccination could be a suitable effective strategy to prevent GBS infection. In 1976, Baker and Kasper confirmed that vaccination is a possible and effective prevention strategy for GBS in newborns. The study concluded that maternal CPS-specific antibodies, transferred to the newborn by transplacental transmission, could confer protection to babies against GBS infections.[61]

Different vaccines' development strategies have been identified to help with the prevention of GBS. The first generation of GBS vaccines involved unmodified type-specific polysaccharides. In human trials, purified native type Ia, II, or III polysaccharides were injected in healthy adult volunteers, including pregnant women. The results demonstrated the vaccine to be safe and well tolerated;[62] however, there was a need to improve the immunogenicity.

The second generation of GBS vaccines was based on the generation of glyco-conjugates, as polysaccharide vaccines were seen to have an improved immunogenicity when conjugated to protein carriers. Studies found that conjugation of a highly immunogenic protein to CPS antigens induced a strong and long-lasting immune response against the polysaccharide.

Conjugate vaccines prepared with GBS type-specific CPS (Ia, Ib, II, III, V) were coupled to tetanus toxoid (TT). In comparison with unconjugated polysaccharide, phase I and II clinical trials in healthy women showed that these monovalent conjugate vaccines have an improved immunogenicity and consistency with memory response, along with the ability to induce functionally active serotype-specific antibodies, which, in the presence of complement, could opsonize and induce killing of GBS by human peripheral blood leukocytes *in vitro* assays.[63–66]

However, the need for multivalent conjugate vaccines was identified as a broadly effective vaccine against the most common disease-causing strains circulating worldwide. In 1996, a study confirmed the safety and immunogenicity of a tetravalent vaccine formulation in healthy adults, where vaccination showed good tolerability, higher IgG titers in subjects with pre-existing anti-capsular antibody to GBS.[67] In 2003, a bivalent vaccine containing II–TT and III–TT glyco-conjugates was tested in humans. However, the immune response did not statistically differ from the antibody responses to monovalent vaccine, with no significant interference between the two single vaccines.[68]

Vaccination in adults. Elderly and immune-compromised populations are also at risk for GBS. Vaccination in these target groups needs to be introduced. However, only one clinical study targeting the elderly has been published, where type V CPS–TT (V–TT) conjugate vaccine was administered to healthy adults (65–85 years old). The results showed that glycoconjugate V–TT vaccine elicited specific antibodies against type V CPS, which could mediate opsonophagocytic killing of type V GBS strain *in vitro*. The data confirms the possibility of eliciting an effective immune response *via* vaccination in the elderly, with a need for additional studies.[69]

The global study conducted in 2015 estimates that a maternal GBS vaccine with 80% efficacy and 90% coverage could prevent 107,000 (Uncertainity Range, 20,000–198,000) cases of fetal and infant death. However, no vaccines are currently available to help mothers protect their newborns, although development of such vaccines is in progress.[52]

Vaccines in development. During the 2015 WHO Product Development for Vaccines Advisory Committee meeting, GBS was identified as a high priority for the development of a vaccine for maternal immunization due to the major public health burden posed by GBS in low- and middle-income countries.[70] Currently, a number of CPS

conjugate vaccines as well as protein-based GBS vaccines are under development.

A number of virulence factors expressed by GBS are involved in colonization, adherence, invasion, and immune evasion and hence these could be used as potential vaccine candidates. One of the most well-studied virulence factors of GBS is its unique sialic acid-rich CPS which inhibits complement deposition and protects the bacteria from opsonophagocytosis by immune cells. This further contributes to the evasion of host immune defense mechanisms.[55] Moreover, the conjugate vaccines enhance immunogenicity by covalent conjugation of a protein carrier, such as TT or CRM_{197}. Nowadays, the most advanced vaccine candidates are hexavalent vaccines including serotypes Ia, Ib, II, III, IV, and V, which are now in phase II trials.[54] Immunogenicity and safety of these candidates has been demonstrated in non-pregnant and, more recently, pregnant women.

Still, there are several obstacles to research on, and ultimately deployment of, GBS vaccines in low- and middle-income countries, which includes infrastructure challenges, limited financial resources, health systems deficiencies, and limited regulatory experience for product licensure. Public–private partnership initiatives and innovative financing mechanisms can help to overcome these challenges. Table 4 summarizes the status of current vaccine candidates in development.

Studies also confirm that other prevention strategies, including oral antibiotic treatment or treatment taken before labor and delivery, are not effective in preventing GBS in babies. Use of disinfectants like chlorhexidine in washing the birth canal does not reduce the risk of the spread of GBS bacteria to babies.[20]

Need for GBS vaccine in India. While IAP remains the mainstay for prevention of GBS infection, it is not feasible in developing countries because of deficiencies in pregnancy health examinations and care, home birth, high birth rate, inadequate screening procedures, logistic and financial constraints, and poor assessment for a clinical risk factor based approach. Maternal active vaccination for women of childbearing age remains the most practical approach to protect both maternal and neonatal health as well as prevent adverse outcomes such as maternal deaths, preterm births/stillbirths. According to a worldwide estimate, maternal vaccination has a higher impact than IAP as it affects more outcomes, that is, maternal sepsis, fetal, and late-onset infant invasive infection (7–89 days). In addition, maternal vaccination not only avoids extensive antenatal care and screening procedures but may also provide higher coverage as compared with IAP.[26] According to the worldwide report, IAP prevents an estimated 29,000 (UR, 0–51,000) cases of early-onset GBS while maternal vaccination (with 80% efficacy and 90% coverage) could prevent 229,000 (UR, 114,000–507,000) infant and maternal GBS cases, 41,000 (UR, 8000–75,000) stillbirths, and 67,000 (UR, 12,000–123,000) infant deaths.[26]

Since several serotypes of GBS have been recognized, a multivalent vaccine would be a suitable approach to extend protection. Several vaccines being developed may provide a cost-effective option for patients belonging to the lower socioeconomic strata, high therapeutic coverage and help reduce the disease burden. Unfortunately, no vaccines are currently available for routine use in India. Until then, IAP-based prevention of early-onset GBS is the only effective approach to reduce the overall burden of GBS infection.

Conclusion

GBS remains a leading cause of neonatal and maternal infections. Several factors limit the prevention of the disease in the neonates. Limited access to the healthcare system hinders the implementation of routine IAP in India. Due to limited studies, the burden of GBS has not been properly evaluated in India but shows the presence of the disease in newborns as well as GBS colonization in pregnant women, which indicates high risk of disease transmission to newborns. Hence, there is a need for the development and deployment of maternal GBS vaccination for prevention as well as to reduce the overall burden of the disease.

Author contributions

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