REVIEW ARTICLE

Group B Streptococcal Disease

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SUMMARY

Group B streptococcus commonly colonizes the human gastrointestinal and genitourinary tracts and is the single most common bacterial cause of invasive infection among newborns in the United States. Intrapartum antibiotic prophylaxis is currently used to reduce the risk of group B streptococcal disease among pregnant persons and newborns. No strategies are currently available to prevent disease in later infancy or among nonpregnant adults. Vaccines against group B streptococcal disease that consist of capsular polysaccharides linked to protein antigens are in development and may provide a means of prevention for all at-risk populations.

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CME

Group B streptococcus (*Streptococcus agalactiae*) infects persons across the age spectrum, but newborns, young infants, and persons older than 65 years of age account for a disproportionate burden of disease. Invasive disease is defined by isolation of group B streptococcus from a normally sterile site. The incidence of group B streptococcal infection across age groups in the United States is tracked by the Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance system; summary data for 2020–2022 are shown in Table 1.[1-3] Infants younger than 1 year of age have the highest rates of group B streptococcal infection. Group B streptococcus is the single most common pathogen causing invasive infection among all newborns in the United States and the second most common among infants born preterm.[5,6] The global burden of perinatal group B streptococcal infection is also substantial. Worldwide in 2020, group B streptococcus caused approximately 400,000 infections among infants, 50,000 to 100,000 infant deaths, 40,000 infections among pregnant persons, and 40,000 to 50,000 stillbirths.[7] Efforts to prevent perinatal infection in high-income countries have been successful but have contributed to intrapartum antibiotic exposure in approximately 1 in 2 newborns.[8,9] Multivalent conjugate polysaccharide vaccines against group B streptococcus are in development and have the potential to change the landscape of disease, particularly in low- and middle-income countries. This review describes the microbiologic and epidemiologic features, pathogenesis, treatment, and prevention of group B streptococcal disease.

MICROBIOLOGIC, IMMUNOLOGIC, AND VIRULENCE FEATURES

Group B streptococcus is a facultative gram-positive diplococcus that grows under both aerobic and anaerobic conditions. Group B streptococcal organisms were classified in 1933 as group B by Rebecca Lancefield, who used acid extracts and serum from rabbits injected with formalin-killed bacteria to distinguish hemolytic streptococcal strains.[10] The group B streptococcus genome was mapped in 2002; approximately 50% of group B streptococcus genes are homologous to genes of group A streptococcus and *S. pneumoniae*.[11] The group B antigen is a polysaccharide structure that is linked to cell-wall peptidoglycan; it does not elicit a protective antibody response in humans.[12]

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Ten capsular polysaccharide antigens define group B streptococcus serotypes Ia through IX; these immunologically distinct antigens are extensively characterized with respect to their structure, genetic features, role in virulence, and immunity.[12] The streptococcus capsule is a major determinant of virulence that resists bacterial uptake and killing by host white cells and possibly promotes intestinal colonization.[13-15] The capsular polysaccharides are composed of different combinations of repeating carbohydrate units, with a common terminal sialic acid residue. Sialic acid plays a key role in immune evasion by group B streptococcus by inhibiting complement deposition on the bacterial surface and inhibiting killing by means of the alternative pathway of complement. Therefore, neutrophil-mediated killing of group B streptococcus requires a capsular-specific antibody and activation of the classical complement pathway.[12,16] Serotype-specific capsular antibody is protective against infection, and maternal antibody levels correlate with newborn protection from infection, making the group B streptococcus capsule the primary target for vaccine development.[14,17,18]

Multiple group B streptococcus surface proteins have also been implicated in disease pathogenesis, with roles in cell adhesion, organ colonization, epithelial invasion, immune evasion, and cytotoxicity. Notable factors contributing to the virulence of group B streptococcus include the alpha-like proteins associated with cell invasion, pilus proteins associated with cell adhesion, hypervirulent group B streptococcus adhesin present in hypervirulent clonal complex 17, and β-hemolysin–cytolysin, which mediates the hemolysis observed with the growth of group B streptococcus on blood agar plates.[12,19,20] Virulence-factor expression is regulated by multiple two-component regulatory signal transduction systems that function in response to environmental conditions such as pH, oxygen content, and temperature.[21] Several proteins have been investigated as vaccine targets; a vaccine based on the alpha-like surface proteins has been studied in a phase 1 clinical trial.[22]

GROUP B STREPTOCOCCAL INFECTION

Group B streptococcus is isolated from a variety of species. Before the recognition of human disease, bovine group B streptococcus strains were identified in the late 19th century as a cause of mastitis in dairy cows.[23] The name *S. agalactiae* (from the Latin for "without milk") derives from the observation that group B streptococcal udder infection results in decreased milk production. Group B streptococcus can infect and kill farmed fish, particularly freshwater tilapia.[23,24] Among humans, group B streptococcus can colonize healthy adults with no clinical consequences but may cause illness in newborns, young infants, pregnant persons, and older adults.

DISEASE IN NEONATES AND YOUNG INFANTS

In the United States, neonatal group B streptococcal disease was first recognized in the 1960s; by the 1970s, the frequency of group B streptococcal infection had eclipsed that of other prevalent neonatal pathogens with a rapidity that has never been fully explained.[25-27] Neonatal group B streptococcal infection is categorized as early-onset disease when it occurs from birth to 6 days of age and as late-onset disease when it occurs from 7 to 89 days of age. These definitions align with the distinct characteristics of each type of group B streptococcal infection and differ from the 3-day time frame that is applied to other pathogens in most neonatal cohort studies.[28] Very-late-onset disease is defined as occurring among infants 3 months of age or older.

Maternal rectovaginal group B streptococcal colonization is the most important risk factor for neonatal early-onset disease. Group B streptococcus is neither a permanent nor a populous member of the human gastrointestinal and genitourinary flora. At any given time, 20 to 30% of pregnant persons in the United States are colonized with group B streptococcus, and approximately 18% are colonized worldwide (with geographic variation).[7,29] Factors associated with maternal group B streptococcal colonization in the United States include younger age, obesity, sexual activity, and tobacco smoking.[29-32] Maternal group B streptococcal colonization status (colonized or not colonized) can change over the course of pregnancy, and a rectovaginal culture for group B streptococcus performed at 36 weeks' gestation or later correlates best with colonization status at the time of childbirth.[29,30] The pathogenesis of early-onset disease involves ascending group B streptococcal colonization from the maternal gastrointestinal and lower genitourinary tracts to the upper genital tract, uterine compartment (including amniotic fluid),

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Table 1. Incidence of Group B Streptococcal Disease in Selected U.S. Populations.*

Population	Incidence
Newborns (0–6 days of age)	0.20 per 1000
Infants (7–89 days of age)	0.25 per 1000
Pregnant persons	0.12 per 1000
Age	
<1 yr	49.0 per 100,000
1–17 yr	0.2 per 100,000
18–49 yr	4.0 per 100,000
50–64 yr	14.0 per 100,000
65–84 yr	22.0 per 100,000
≥85 yr	39.0 per 100,000
Overall U.S. population	9.0 per 100,000

* Summary statistics are from the Centers for Disease Control and Prevention Active Bacterial Core Surveillance reports[1-3] except for data on pregnant persons (from Phares et al.[4]).

and ultimately colonization of the fetus and newborn. Fetal and neonatal mucosal and skin colonization, as well as aspiration or swallowing of infected amniotic fluid, can promote transition to invasive disease. In the absence of intrapartum antibiotic prophylaxis, approximately half the infants born to colonized parturient persons are colonized at surface sites, and invasive disease develops in 1 to 2%.[29,33,34] Table 2 shows additional independent risk factors for early-onset disease, including factors that support pathogenesis (e.g., longer duration of rupture of membranes), provide baseline vulnerability (e.g., preterm birth with poor neonatal immune defenses), or provide evidence that infection is developing (e.g., maternal fever). The pathogenesis of late-onset disease is less well described. Infants can acquire group B streptococcus from nonmaternal sources, but maternal group B streptococcal colonization and preterm birth are the strongest predictors of late-onset disease.[29,35,36] Infant oropharyngeal and gastrointestinal colonization are important factors in late-onset pathogenesis, and late-onset disease has been associated with maternal group B streptococcal mastitis.[37] Whether infected breast milk is a source of group B streptococcal infection or whether infants with heavy colonization seed breast milk with group B streptococcus remains unclear, although group B streptococcus antibodies in breast milk may play a role in the prevention of colonization and infection in infancy.[38]

Group B streptococcal disease in the United States is described in a CDC 2006–2015 report of 1277 cases of early-onset and 1387 cases of late-onset disease.[39] Most cases of early-onset disease (75%) are recognized on the day of birth, and overall 94 to 95% occur within 48 hours after birth. Infants born preterm (<37 weeks' gestation) account for 10 to 11% of births in the United States but 27 to 28% cases of early-onset disease. Meningitis complicates approximately 10% of cases of early-onset disease.[39] Infants with early-onset disease may present with nonspecific signs of illness that range from relatively subtle findings (e.g., tachypnea, poor feeding, and skin mottling) to severe sepsis syndromes that may include metabolic acidosis, pneumonitis, surfactant deficiency, persistent pulmonary hypertension, or systemic hypotension. The U.S. case-fatality rate (4 to 6%) has remained unchanged over the past 30 years.[39,40] Most deaths occur in preterm infants (19% mortality) rather than term infants (2% mortality).[39] A report of 82 cases of early-onset disease in eight European countries (2008–2010) found that results were similar to results in the United States with respect to preterm birth, clinical presentation, and mortality.[41]

Patients with late-onset disease in the United States present at a median of 34 days of age (interquartile range, 20 to 49).[39] More than 40% of cases occur among preterm infants; differences in group B streptococcal colonization, levels of maternally derived antibodies, and immunoprotective responses may contribute to preterm vulnerability. Late-onset disease is complicated by meningitis in approximately 30% of cases, and less commonly by pneumonia, septic arthritis, osteomyelitis, and peritonitis. Unlike early-onset disease, late-onset disease commonly manifests with fever, but the frequency of other signs of systemic illness are similar. The U.S. case-fatality rate for late-onset disease is approximately 5 to 6%, with greater incidence among preterm infants and in cases complicated by meningitis (approximately 8 to 10%).[39] Analysis of 71 late-onset cases in European centers yielded findings similar to those in the United States with respect to age at onset, preterm birth, clinical presentation, incidence of meningitis, and mortality.[41] Very-late-onset disease occurs approximately 10 times less often as late-onset disease; limited data

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suggest a higher risk among infants with underlying medical conditions.[4,42,43]

Neonatal and infant deaths from group B streptococcal infection are observed at higher rates in low- and middle-income countries than in high-income countries, particularly when the presence or absence of skilled birth attendants is taken into account.[7] In all settings, both term and preterm survivors of group B streptococcus infection may have permanent neurologic injury, particularly when infection is complicated by meningitis.[41,42,44] Extremely preterm infants fare particularly poorly: a 19-year study of infants born in the United States at less than 27 weeks' gestation and with group B streptococcus infection showed that nearly 80% either had died or had survived with moderate-to-severe neurodevelopmental impairment.[45]

DISEASE AMONG PREGNANT PERSONS

Group B streptococcal infection may cause asymptomatic bacteriuria, urinary tract infection, or pyelonephritis during pregnancy. Even after appropriate treatment, pregnant persons with these conditions are considered to be colonized with group B streptococcus at the time of childbirth. The incidence of invasive group B streptococcal disease is higher among pregnant persons than among the general population of adults 18 to 49 years of age (Table 1). Globally, the rate of invasive disease among pregnant persons is estimated to be 29 cases per 100,000 deliveries (95% confidence interval, 15 to 47).[7] According to CDC surveillance for 1999–2005, group B streptococcal disease in parturient persons involved bacteremia in half the cases of infection; group B streptococcus was also isolated from the uterus, placenta, amniotic fluid, and peritoneal fluid, with associated clinical syndromes that included sepsis, endometritis, chorioamnionitis, and pneumonia.[4] Group B streptococcus may be isolated from maternal or fetal tissues in cases of spontaneous abortion or stillbirth. Determination of the cause of stillbirth is often incomplete, but studies suggest that worldwide, 20,000 to 100,000 stillbirths each year are attributable to in utero group B streptococcal infection.[7] Group B streptococcal colonization is also inconsistently associated with preterm birth, although effect estimates have wide confidence intervals, and many studies suffer from unresolved confounding.[7,46]

Table 2. Risk Factors for Invasive Group B Streptococcal Disease.

Population and Risk	Risk Factors
Newborn early-onset disease (0–6 days of age)	Maternal group B streptococcal rectovaginal colonization Group B streptococcal bacteriuria or urinary tract infection during pregnancy Preterm gestational age at birth (<37 wk) Intrapartum maternal fever ≥100.4°F (38°C) Prolonged rupture of membranes Previous infant with group B streptococcal disease
Infant late-onset disease (7–89 days of age)	Maternal group B streptococcal rectovaginal colonization Preterm gestational age at birth (<37 wk)
Pregnant persons	Rectovaginal colonization Intrapartum or postpartum fever ≥100.4°F (38°C)
Other adults	Age ≥65 yr Obesity Functional or surgical splenectomy Diabetes mellitus Cancer Chronic cardiovascular, gastrointestinal, hepatic, neurologic, or renal disease Consumption of raw freshwater fish

DISEASE AMONG NONPREGNANT ADULTS

Group B streptococcal bacteremia and organ-specific infections may occur among nonpregnant adults. Worldwide, the disease burden among adults is estimated to be approximately 3 cases of invasive group B streptococcal disease per 100,000 persons, with variations according to geography and age: the highest rates overall are found in North America (5.9 per 100,000 persons) and among persons 65 years of age or older (19.4 per 100,000 persons).[47] The incidence of group B streptococcal disease among adults 19 years of age or older in the United States is shown in Table 1. In the United States, CDC surveillance for 2008–2016 showed an increasing incidence of group B streptococcal disease among nonpregnant adults and changes in the risk profile of persons with infection.[48] By 2016, approximately 28,000 cases of invasive disease were estimated to occur annually among nonpregnant adults, with men affected more often than women. Persons with underlying medical conditions accounted for 95% of cases, with obesity and diabetes each present in approximately half the cases and cancer and cardiovascular disease present in approximately 15% of cases. Nearly all patients were hospitalized, 83% had bacteremia, 27% were admitted into intensive care, and 5 to 6% died. Clinical syndromes included skin, soft tissue, bone, and joint

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infections; occult bacteremia; and pneumonia.[48] The vulnerability of older persons to invasive group B streptococcal disease is not well understood. The incidence of group B streptococcal colonization among adults 65 years of age or older and pregnant persons is similar (20 to 25%), as is the serotype distribution.[49] The presence of coexisting conditions in many older adults suggests a role for decreased immune defenses, particularly neutrophil function. Deficits in mobility, skin integrity, and oral hygiene may also contribute to vulnerability to infection among older adults.[49]

TREATMENT AND PREVENTION OF GROUP B STREPTOCOCCAL DISEASE

TREATMENT

Group B streptococcus remains almost universally susceptible to β-lactam antibiotic agents. Among 6340 invasive group B streptococcus isolates collected in the United States from 2015 through 2017, fewer than 1% harbored genes that affected penicillin susceptibility.[50] In contrast, 56% of group B streptococcus isolates carried genes associated with macrolide and lincosamide resistance, correlating with 2022 surveillance data that revealed that 52% of the isolates had resistance to clindamycin and 62% had resistance to erythromycin.[3,50] The best available treatment for infections is penicillin G, with ampicillin an acceptable alternative. Neonatal bacteremia and uncomplicated meningitis are treated with intravenous antibiotic therapy for 10 days and 14 days, respectively.[28] Complicated central nervous system infections and site-specific infections may result in longer periods of therapy and surgical intervention. Severe sepsis in newborns may also lead to mechanical ventilation, pressor support, or treatment with inhaled nitric oxide (or a combination of these); extracorporeal membrane oxygenation is used to treat full-term infants in whom conventional therapy has failed. Infants with meningitis are monitored for seizure activity and receive treatment with antiepileptic drugs as indicated. Group B streptococcal infection may recur despite adequate antibiotic therapy. Recurrence is associated with persistent group B streptococcal colonization at mucosal surfaces; poor immune response to infection may also contribute to colonization, particularly among preterm infants and adults who are immunocompromised.[51-53] The addition of rifampin to standard antibiotic treatment does not consistently result in mucosal decolonization among infants.[51] Adult patients and families of infants with infection should be counseled about the approximate 1 to 5% risk of recurrent disease.

PREVENTION OF NEONATAL EARLY-ONSET DISEASE

Current prevention efforts focus on the use of intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease. Both the administration of oral antibiotics to persons with group B streptococcal colonization during pregnancy and the administration of penicillin prophylaxis to newborns have failed as strategies to eradicate group B streptococcal colonization and prevent neonatal infection.[40] Intrapartum administration of intravenous ampicillin, however, can reduce the incidence of both neonatal colonization and infection.[33] The best use of intrapartum antibiotic prophylaxis has been debated, and recommendations issued by the American College of Obstetrics and Gynecology (ACOG) and the American Academy of Pediatrics (AAP) in 1992 differed from each other.[54,55] Consensus guidance subsequently published by the CDC, ACOG, and AAP in 1996 recommended two potential approaches.[40] The first approach was administration of intrapartum antibiotic prophylaxis on the basis of the presence of clinical risk factors for neonatal group B streptococcal disease. The second approach was to administer intrapartum antibiotic prophylaxis on the basis of maternal group B streptococcal colonization identified by prenatal rectovaginal or urine culture. Results of subsequent active surveillance studies showed greater effectiveness of the prenatal culture–based approach, and revisions to prevention guidance in 2002, 2010, and 2019–2020 have consistently recommended prenatal culture–based administration of intrapartum antibiotic prophylaxis.[28,29,40,56,57] Intrapartum rapid nucleic acid amplification testing is used in some centers when group B streptococcal colonization status is unknown at the time of childbirth.[29] A summary of current recommendations is shown in Table 3. Intrapartum antibiotic prophylaxis has been associated with a reduction by a factor of 10 in the incidence of neonatal early-onset disease in the United States (Fig. 1). Maternal group B streptococcal colonization status and appropriate intrapartum antibiotic prophylaxis are key considerations in rec-

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ommended multivariate models and algorithms for risk assessment in neonates.[28,58] The effectiveness of intrapartum antibiotic prophylaxis to prevent group B streptococcal infection is attributed to three downstream effects: a decrease in culture-detectable group B streptococcus in the rectovaginal flora, concentration of β-lactam antibiotics in the amniotic fluid, and transfer of β-lactam antibiotics across the placenta into fetal circulation. With the administration of ampicillin or penicillin, each of these effects occurs rapidly (within 1 to 2 hours after administration), and results in cord-blood antibiotic levels above the minimum inhibitory concentration for prevention of group B streptococcal infection.[28,33] In parturient persons with penicillin allergy, cefazolin, clindamycin, and vancomycin are alternatives, with the choice based on the circumstances. Although cefazolin can be considered adequate prophylaxis against group B streptococcus, clindamycin and vancomycin are not as effective in preventing early-onset disease.[28,29,59,60] Because most persons who report penicillin allergy do not have severe IgE-mediated hypersensitivity, ACOG currently recommends that a test for penicillin allergy be performed during pregnancy to confirm the need for an alternative agent.[29]

Table 3. Indications for Intrapartum Antibiotic Prophylaxis against Group B Streptococcus.*

Group B streptococcus–positive status in current pregnancy, as indicated by one of the following:†
Positive prenatal rectal or vaginal culture
Bacteriuria (asymptomatic or associated with urinary tract infection)
Positive intrapartum nucleic acid amplification testing
Unknown group B streptococcus status in current pregnancy and any of the following:
Intrapartum maternal fever ≥100.4°F (38°C)
Rupture of membranes ≥18 hr earlier
Preterm onset of labor (gestation <37 wk)
Preterm rupture of membranes (gestation <37 wk)
History of positive result on group B streptococcus test in previous pregnancy‡
Group B streptococcal disease in previous infant

* Recommendations are adapted from the American College of Obstetricians and Gynecologists.[29]
† In parturient persons who are group B streptococcus–positive with planned cesarean birth before onset of labor and with intact membranes at time of delivery, antibiotic prophylaxis for group B streptococcus is not indicated, regardless of gestational age of the neonate at birth.
‡ In this case, the parturient person and the provider may use shared decision making to determine the benefit of administering intrapartum antibiotic prophylaxis, because the risk of group B streptococcus colonization in the current pregnancy is elevated if colonization occurred in a previous pregnancy.

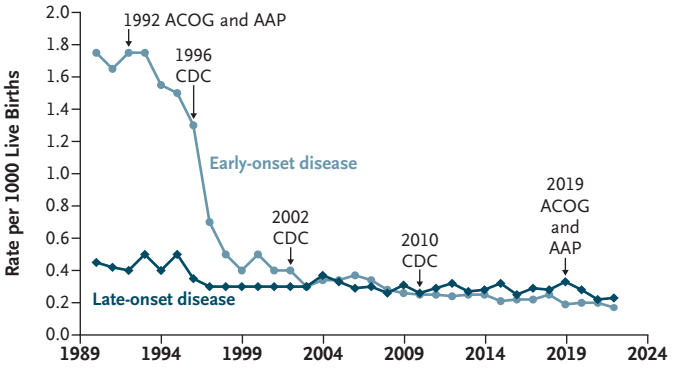

Figure 1. Incidence of Infant Early-Onset and Late-Onset Group B Streptococcal Disease in the United States, 1990–2022.

Data for 1990–1996 are from Schrag et al.[65] and for 1997–2022 are from Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance reports (https://www.cdc.gov/abcs/reports/). AAP denotes American Academy of Pediatrics, and ACOG American College of Obstetricians and Gynecologists.

LIMITATIONS OF PERINATAL PREVENTION STRATEGIES

Concerns persist regarding intrapartum antibiotic prophylaxis as a strategy to prevent neonatal group B streptococcal disease, and international use varies. In low- and middle-income countries, routine administration of intravenous antibiotic agents during labor is impractical. Some high-income countries, such as those in the United Kingdom, reject the universal use of intrapartum antibiotic prophylaxis administered on the basis of prenatal screening on the grounds that it is costly and confers more risk than benefit.[61] Intrapartum antibiotic prophylaxis does not prevent late-onset disease (Fig. 1) or all early-onset disease: 40% of cases of early-onset disease now occur among infants born to persons with negative prenatal cultures and no indication for intrapartum antibiotic prophylaxis.[39] Prophylaxis against surgical-site infection in cesarean deliveries, prophylactic antibiotics against intraamniotic infection, and intrapartum antibiotic prophylaxis against group B streptococcus in total expose approximately 50% of newborns in the United States to antibiotics before birth.[8,9] Intrapartum antibiotic prophylaxis is meant to alter the microflora that is passed from mother to

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newborn, and studies show that changes in infant gut microbiota persist for weeks to months after birth.[62] Although evolving evidence links development of the infant gut microbiota with a number of chronic health conditions, the enduring effects of intrapartum antibiotic prophylaxis against group B streptococcus remain uncertain. One retrospective cohort study of 223,431 children showed differences in growth and increases in the prevalence of childhood obesity among children exposed to intrapartum antibiotic prophylaxis, with the effects enduring up to 10 years after birth.[8,63] In contrast, in a different cohort of 14,046 children, intrapartum antibiotic prophylaxis against group B streptococcus was not associated with pediatric asthma, eczema, food allergy, or allergic rhinitis.[64]

PREVENTION OF DISEASE IN OTHER POPULATIONS

Intrapartum antibiotic prophylaxis against group B streptococcus has been associated with lower rates of maternal peripartum disease.[65] Intrapartum antibiotic prophylaxis has not appreciably affected the incidence of late-onset disease in infants (Fig. 1), probably because it only temporarily suppresses maternal rectovaginal group B streptococcal colonization.[33] In many cases of late-onset disease, the mothers had previously received adequate intrapartum antibiotic prophylaxis.[35] Strategies to prevent late-onset disease in neonates and specific approaches to the prevention of disease in nonpregnant adults are lacking.

VACCINES

The protective effect of serotype-specific antibodies directed against the group B streptococcus capsule has prompted the development of a vaccine to prevent invasive group B streptococcal disease. Maternal immunization is the strategy of vaccinating the pregnant person to induce production of IgG antibodies for transfer across the placenta to the fetus and thus the newborn. This strategy can provide protection from infection at birth and after birth during time periods in which young infants cannot be effectively vaccinated. Maternal immunization is currently recommended to protect infants from pertussis, tetanus, influenza, coronavirus disease 2019 (Covid-19), and, most recently, respiratory syncytial virus (RSV) disease.[66,67] Baker and colleagues showed that immunization of pregnant women with serotype III polysaccharide elicited antibodies that were transferred across the placenta, and serum specimens that were isolated from their newborns at 1 month and 2 months of age had opsonic activity against serotype III group B streptococcus[68]; however, this study and subsequent studies showed the overall poor immunogenicity of polysaccharide vaccines, leading to a focus on glycoconjugate vaccines linking group B streptococcus capsular polysaccharide molecules to proteins such as tetanus or diphtheria toxoids. Results of phase 1 studies in healthy nonpregnant adults, pregnant persons, and older adults subsequently showed that glycoconjugate vaccines were safe and elicited higher antibody levels than polysaccharides alone.[69]

Development of a vaccine for group B streptococcus is currently supported, from a variety of perspectives, by the World Health Organization, the CDC, the Gates Foundation, pharmaceutical companies, and academic centers. A randomized, placebo-controlled, phase 2 trial of a hexavalent glycoconjugate vaccine was conducted in South Africa (2019–2020).[70] The vaccine contained polysaccharides from the six serotypes that cause 98% of group B streptococcal disease in infants worldwide. The trial enrolled 360 pregnant persons, confirmed short-term safety, and defined a dose associated with the highest antibody response. Transplacental transfer antibody ratios (the ratio of antibody concentration in cord blood to antibody concentration in maternal blood) ranging from 0.4 to 1.1 were observed, with variation according to vaccine dose and serotype. The vaccine research group also conducted a seroepidemiologic study involving 17,752 pregnant persons to estimate the concentration of capsular polysaccharide antibody required for protection against disease in infants. Both studies used a standardized, multiplex immunoassay adopted by an international consortium on group B streptococcus to quantify IgG antibodies. Together, these studies identified an antibody level associated with 75% protection against disease in infants and showed that vaccination could induce antibodies at this potentially protective level at birth, although the proportion of infants reaching this level varied among serotypes.[70]

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KEY POINTS

GROUP B STREPTOCOCCAL DISEASE

- Group B streptococcus commonly colonizes the human gastrointestinal and genitourinary tracts; it causes disease primarily in newborns, young infants, pregnant persons, and adults older than 65 years of age with coexisting conditions.
- Group B streptococcus is the single most common bacterial cause of invasive infection among newborns in the United States, and worldwide it causes an estimated 400,000 infant infections and 50,000 to 100,000 infant deaths each year.
- Ten serotypes of group B streptococcus are defined on the basis of surface polysaccharide structures. Serotype-specific antibodies to these capsular polysaccharides can provide protection from invasive infection.
- Intrapartum antibiotic prophylaxis is currently used in the United States to reduce the risk of group B streptococcal disease among pregnant persons and newborns. No strategies are currently available to prevent disease in later infancy or among nonpregnant adults.
- Multivalent glycoconjugate vaccines against group B streptococcal disease that consist of capsular polysaccharides linked to protein antigens are in development and may provide a means of prevention for all at-risk populations.

Further testing, regulatory approval, and clinical use of group B streptococcus vaccines face multiple hurdles. With regard to vaccine use in pregnant persons, clinical trials will need to determine the timing of vaccine administration during gestation to maximize protection of newborns against both early- and late-onset group B streptococcal disease. Timing will also need to account for vaccines currently recommended during pregnancy, including tetanus–diphtheria–acellular pertussis, influenza, Covid-19, and RSV vaccines.[66,67] Conditions such as malaria and human immunodeficiency virus infection can impair vaccine immunogenicity and placental antibody transfer and will need consideration.[71,72] The most urgent issue with regard to vaccine licensure is the need to determine an end point for phase 3 studies.[73] Although the total worldwide burden of neonatal group B streptococcal disease is considerable, the current incidence of disease is such that an estimated 40,000 to 60,000 participants would be needed for a vaccine trial with clinical efficacy as the primary end point.[73] A trial based on a serologic correlate of disease protection as the end point may be possible, with licensure conditional on mandatory surveillance for vaccine effectiveness and safety.[73] Additional studies will be needed to determine whether the correlate of protection identified in the recent phase 2 hexavalent vaccine trial is the appropriate surrogate end point for phase 3 perinatal studies[74] and to determine protective antibody concentrations for use in nonpregnant adults.

CONCLUSIONS

Group B streptococcus is an opportunistic human pathogen that primarily causes disease among newborns, young infants, pregnant persons, and older adults. The worldwide burden of disease is substantial, and the only current prevention strategy is the administration of intrapartum antibiotics during labor in persons who have group B streptococcal colonization or are otherwise at high risk for transmitting infection to the neonate. Although this approach is effective in reducing perinatal disease, it has contributed to widespread antibiotic exposure among newborns, is not feasible for use in low- and middle-income countries, and does not prevent disease later in infancy. There are no effective strategies to prevent group B streptococcal disease in adults. Glycoconjugate vaccines have been developed, and phase 3 trials will be needed to determine the efficacy and safety of the vaccines for use in various at-risk populations.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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