Preventing Newborn Infection with Maternal Immunization

Steven Black,1 Immaculada Margarit,2 Rino Rappuoli2*

Group B streptococcal disease is a common cause of bacterial sepsis in newborns and is often fatal. To protect these babies, a vaccination program must target pregnant women for immunization so that the resulting antibodies can be passively delivered from the mother to the fetus. Scientists met in Siena, Italy, to discuss potential approaches to maternal immunization for the prevention of perinatal group B streptococcal disease.

Group B streptococcal disease is the most common cause of bacterial sepsis and meningitis in newborns in developed countries and a common cause in the developing world; the disease is often fatal and frequently causes severe sequelae in survivors (1). Group B streptococcal infections are unusual in that the majority of cases occur in newborn infants who acquire the pathogen from their mothers at birth (2). Therefore, development of an effective vaccine for maternal immunization could eliminate neonatal mortality and severe morbidity associated with this disease.

Before the introduction of conjugate vaccines—which are created by binding a poorly immunogenic polysaccharide antigen to a carrier protein to build an effective immunogen—the majority of cases of bacterial meningitis and sepsis in children were caused by Haemophilus influenzae type b (Hib), pneumococcal, and meningococcal species. Routine vaccination with Hib-, pneumococcal-, and meningococcal-saccharide conjugates has nearly eliminated these diseases (1, 3, 4). To further accomplish total control of meningococcal disease, a protein-based vaccine against serogroup B meningococcus was recently approved by the European Medicines Agency (5).

Although Group B streptococcus (GBS) has been recognized as the major cause of infant bacterial meningitis and sepsis in developed countries since the 1970s (6–9), it is the only remaining major cause of bacterial sepsis and meningitis in children for which no vaccine is commercially available yet. A protective role for capsular polysaccharide-specific antibodies was demonstrated several years ago in animal models of infection (10) and in humans (11). A conjugate GBS vaccine is now in clinical trials in order to assess safety and immunogenicity. Here, we report on a symposium held in Siena, Italy, in which participants discussed (12). The classic presentation of early-onset disease (EOD) includes overwhelming respiratory distress, cardiovascular instability, pneumonia, sepsis, and meningitis, often ending in death. EOD often appears during the first hours after birth, with most cases occurring within 24 to 48 hours and the remaining within the first 7 days of life. Risk factors for infection are prolonged rupture of membranes (rupture of the amniotic membrane at least 18 hours before delivery of an infant), prematurity, maternal fever, GBS infection in a previous child, and black race (13, 14).

GBS also causes late-onset disease (LOD), which presents between 1 week and 3 months of life and peaks in frequency at about 1 month of age. LOD can be acquired from the mother by colonization of the infant during birth, and case reports have also identified breast milk as a source of infection. Nosocomial transmission has been reported as well (15). The majority of EOD cases present as sepsis, whereas meningitis is more frequent for LOD (16), and in some geographical settings, the number of such cases can equal or exceed the number of cases presenting as sepsis (17, 18).

As with EOD, prematurity appears to be an important risk factor for LOD, and incidence is higher among black infants. Apart from timing of colonization, the factors that influence whether an infant will develop EOD or LOD are unknown.

Despite early antimicrobial treatment and improvement in neonatal intensive care in many countries, up to 10% of GBS infections are lethal, and 25 to 35% of surviving infants with meningitis experience permanent neurological sequelae (19). Mortality in patients with EOD increases with prematurity, reaching 24.1% of the cases in infants younger than 24 weeks gestation, then decreasing to 13.9% in infants between 24 and 37 weeks and to 5.7% in those older than 37 weeks gestational age (17).

GBS also causes maternal infections, including bacteremia, chorioamnionitis, urinary tract infections, endometritis, and septic abortion, and morbidity and mortality in the elderly and in immunocompromised adults (16).

Recently it has been demonstrated that selected strains of GBS lacking the hemolysin repressor CovR/S accelerate the failure of the amniotic barrier and allow GBS to penetrate the chorioamniotic membrane.

Fig. 1. Mapping neonatal disease. The estimated number of cases of GBS infection per 1000 live births in infants <90 days of age is indicated in different colors. Countries in gray do not have incidence data available. Adapted from data reviewed by Edmon et al. (21).
Table 1. Serotype survey. Shown is the potential coverage (percent) of a trivalent GBS vaccine in various countries. Data are extrapolated from (16) and (21).

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Early-onset disease</th>
<th>Late-onset disease</th>
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<tbody>
<tr>
<td></td>
<td>USA</td>
<td>Germany</td>
</tr>
<tr>
<td>la</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>lb</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td>58</td>
</tr>
<tr>
<td>Trivalent (la+lb+III)</td>
<td>65</td>
<td>80</td>
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barrier and gain access to the fetus (20). This provides a pathophysiologic basis for the previously demonstrated ability of GBS to cause maternal chorioamnionitis, as well as to gain access to the fetus and cause EOD.

GLOBAL EPIDEMIOLOGY
Perinatal GBS disease is a global problem, although surveillance data to document the true disease burden have been difficult to obtain (Fig. 1) (21). Factors that likely contribute to underestimation of cases include the lability of the organism in the laboratory, the small volumes of blood available for cultures from infants, use of nonautomated culture methods, poor surveillance, and barriers to health care access, especially in developing countries (22).

When women with vaginal GBS deliver, about 50% of their infants become colonized as well (23). Nearly 2% of these colonized infants go on to develop early-onset GBS disease. The incidence of EOD in the United States has declined from 1.7 cases per 1000 live births in the early 1990s to 0.35 cases per 1000 live births in 2005, after implementation of universal antenatal culture screening and antibiotic prophylaxis (16). Conversely, the incidence of LOD (0.4 cases per 1000 live births) has remained unchanged over the past 20 years (24). In many preterm infants, EOD may not be immediately recognized because its early symptoms can be mistaken for those of hyaline membrane disease. In the UK, the incidence of LOD is 0.24 cases/1000 live births (17). Among infants with GBS meningitis, 13% of survivors have severe disabilities, and an additional 17% have moderate disabilities (25).

Because of a paucity of reliable surveillance data, there is only limited evidence that suggests that the disease burden in developing countries is higher than that in the developed world. A recent meta-analysis and global review (21) revealed that only a few studies met preestablished inclusion criteria. Zero incidence of early-onset perinatal GBS infection was reported in India, where surveillance was poor, whereas incidence in South Africa is approximately five times higher than that observed in the UK or the United States (26). In countries that use screening and intrapartum prophylaxis, EOD has been greatly reduced, but LOD incidence has remained untouched by this intervention. It is likely that if robust surveillance data were available, the incidence rates in developing countries would be similar to those in the United States before the use of screening and intrapartum prophylaxis.

VACCINOLOGY
In 1976, Baker and Kasper noted a correlation between the absence of type-specific capsular maternal antibody and susceptibility to GBS infection (11). This suggests that placental transfer of maternal antibody for a specific serotype is associated with protection (27). This observation led to the early consideration of maternal vaccination as a possible means of protecting infants from disease. In the 1970s and 1980s, pure polysaccharide vaccines were considered, but when these were evaluated in adults, they were insufficiently immunogenic, with an overall response rate of 63% (28). Recognizing the success of polysaccharide conjugate vaccines for Hib, scientists have turned their attention to the development of a conjugate vaccine for maternal immunization.

Vaccines have now been developed against GBS serotypes Ia, Ib, II, III, and V by conjugating the capsular polysaccharides from GBS with tetanus toxoid. For each GBS serotype, functional activity has been demonstrated in vitro for vaccine-induced antibodies (29). In vitro functional testing correlated well with standard enzyme-linked immunosorbent assay testing (30). In phase 1 clinical trials, these vaccines were well tolerated in adults, with no serious adverse events reported. In another phase 1 trial, a type III tetanus toxoid conjugate vaccine was administered safely to healthy pregnant women. In separate phase 2 evaluations, GBS type Ia and type V vaccines were administered to seronegative women, who responded with a robust response of at least 1 μg/ml increase in type-specific antibody 1 month after receipt of vaccine. By 1 year after vaccination, antibody levels had declined to approximately half the peak level. A comprehensive review describing the above-mentioned trials and their results was published in 2011 (31).

Until recently, all studies of conjugate GBS vaccines had been conducted in academic settings. Recognizing that involvement of a commercial vaccine company would be required to make protection against group B streptococcal disease a practical reality, Novartis began the development of a conjugate GBS vaccine that contains CRM197 conjugates for GBS serotypes Ia, Ib, and III. Preclinical studies of this vaccine in pregnant mice revealed 73 to 93% protection against a lethal challenge in their offspring. This vaccine is now in phase 2 clinical trials (31), with a phase 3 efficacy trial being planned. Ongoing preliminary analyses indicate that all regimens and dosages have been well tolerated and immunogenic in both nonpregnant and pregnant women. The potential coverage (in percent) of such a trivalent vaccine is shown in Table 1, based on available epidemiological data for the United States, Germany, the UK, South Africa, and Malawi (16, 17).

Another GBS vaccine, which contains serotypes Ia, Ib, II, III, and V, as well as a combination of pilus proteins broadly represented in the GBS population (32, 33), is in the preclinical development stage.

MATERNAL IMMUNIZATION
Although maternal immunization has been extraordinarily successful in the prevention of neonatal tetanus and immunization of pregnant women is now routinely
Table 2. Needs assessment and recommendations.

<table>
<thead>
<tr>
<th>Working group</th>
<th>Needs and recommendations</th>
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<tbody>
<tr>
<td>GBS epidemiology and vaccine need in developed countries</td>
<td>• Standardize surveillance data throughout Europe</td>
</tr>
<tr>
<td></td>
<td>• Raise awareness of GBS disease</td>
</tr>
<tr>
<td>GBS epidemiology and vaccine need in developing countries</td>
<td>• Standardize surveillance worldwide</td>
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<tr>
<td></td>
<td>• Arrange PCR or culture-free testing</td>
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<tr>
<td></td>
<td>• Set up studies to assess true disease burden</td>
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<tr>
<td>Moving forward with a maternal immunization platform</td>
<td>• Collect epidemiology data to drive decision-making</td>
</tr>
<tr>
<td></td>
<td>• Evaluate the impact of maternal immunization on natural infection and response to vaccines in infants</td>
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<td></td>
<td>• Assess duration of protection provided to infants by maternal immunization</td>
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<tr>
<td></td>
<td>• Study correlates of protection to estimate extent of achievable protection in infants</td>
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<tr>
<td></td>
<td>• Educate mothers, providers, and public health officials about the need for vaccination and vaccine safety</td>
</tr>
<tr>
<td>Optimal phase 3 trial design for a GBS vaccine in pregnant women</td>
<td>• A trial should simulate real-world use of vaccine to assess potential impact</td>
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<td></td>
<td>• Define optimal time in pregnancy to vaccinate</td>
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<tr>
<td></td>
<td>• Assess impact not only on GBS disease but other pregnancy outcomes such as prematurity</td>
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<td></td>
<td>• Identify sites with large disease burden but adequate laboratory facilities</td>
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recommended in the United States for prevention of influenza in both the infant and mother, data on the safety and effectiveness of maternal immunization from randomized clinical trials are rare, and most data come from observational studies and administrative databases (34). Recently, a randomized comparative trial of an influenza vaccine versus a pneumococcal polysaccharide vaccine demonstrated the safety and effectiveness of both of these vaccines in pregnant women (35). In 2011, the U.S. Advisory Committee on Immunization Practices added the adult booster vaccine Tdap (against tetanus, diphtheria, and pertussis) to the list of vaccines that should be routinely administered during pregnancy in order to prevent neonatal and young infant deaths and hospitalizations associated with these diseases. No concerning patterns of pregnancy outcomes have been reported. Last, data on a more limited number of pregnant women showed that pneumococcal and meningococcal polysaccharide vaccines are safe and immunogenic (36).

All of the above-mentioned vaccines were shown to be effective and safe in non-pregnant adults before their use in pregnancy. In contrast, for GBS neonatal sepsis the primary target population for a GBS vaccine is pregnant women, and one could not rely on demonstration of safety and effectiveness in nonpregnant women to evaluate and license this vaccine. However, the knowledge that we have gained through extensive use of tetanus toxoid and, more recently, the influenza vaccine is reassuring on two counts. First, infrastructure now exists in many countries to vaccinate pregnant women, and this infrastructure should be easily adaptable to a new GBS vaccine program. Second, the extensive experience with influenza and tetanus vaccines has demonstrated that vaccination of pregnant women is both safe and efficacious in preventing neonatal disease.

**CURRENT LANDSCAPE AND THE FUTURE**

Perinatal group B streptococcal disease is a global problem (Fig. 1), and epidemiological data from many countries are either of poor quality or unavailable. Therefore, creating disease awareness and prioritization of infant GBS disease as a public health problem in much of the world will require basic work to demonstrate the epidemiology of GBS in those settings.

In the absence of an available vaccine, the United States began, in 2002, routine universal prenatal GBS screening with administration of intrapartum antibiotic prophylaxis for women who test positive. A recent review of this program indicated that 85% of pregnancies are now screened and that 98% of these women have results available at delivery, with more than 80% of these women receiving appropriate antibiotic prophylaxis (37). There are, however, gaps with this program. Only a minority of preterm infants, who are at higher risk for GBS disease, received screening before delivery, and only slightly more than half of these women received intrapartum antibiotic prophylaxis before delivery. In addition, although antibiotics resistance has not been an issue to date, if ampicillin-resistant GBS strains become prevalent, this will adversely impact the viability of intrapartum prophylaxis programs because ampicillin is the mainstay of these programs. Currently, in the United States more than 60% of EOD cases occur in women who tested negative for GBS colonization when screened and hence did not receive antibiotic prophylaxis. Because screening normally occurs weeks before delivery, these cases of EOD may result from new colonization and are not preventable with the current screening program. Perhaps the biggest drawback is that this screening approach has no impact on late-onset GBS disease.

Last, the logistical coordination required to implement such a screening and follow-up system is only available in a few developed countries, leaving the rest of the world without a viable approach for prevention of GBS disease. Therefore, alternative approaches are needed, such as maternal vaccination, which would have broad applicability without the logistical constraints of prenatal screening and antibiotic prophylaxis.

Symposium participants reached a consensus: Perinatal group B streptococcal disease remains a substantial global health problem. Recommendations of the working groups as to how to best approach this problem are summarized in Table 2. The success of prenatal maternal immunization programs for tetanus and influenza as well as the potential for future availability of immunogenic conjugate vaccines make this an ideal time to move forward with the development of a GBS vaccine.

**SUPPLEMENTARY MATERIALS**

www.sciencetranslationalmedicine.org/cgi/content/full/5/195/195ps12/DC1

Table S1. Novartis patents pertaining to GBS vaccine development.
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