Easing the Burden: Characterizing the Disease Burden of Neonatal Group B Streptococcal Disease to Motivate Prevention

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In this issue of *Clinical Infectious Diseases*, Weisner et al. [1] describe the incidence and characteristics of invasive disease due to group B streptococci (GBS) among neonates in England and Wales. GBS emerged as a leading infectious cause of neonatal morbidity and mortality in the United States and several other industrialized countries in the 1970s for reasons that remain speculative. Although clinicians now have >30 years of experience with neonatal GBS disease, debates about the need for prevention and the pros and cons of intrapartum prophylaxis remain lively in many countries. Additionally, although conjugate vaccine formulations appear to be promising, obstacles to vaccine licensure continue to loom large.

A first question for countries or institutions considering prevention policies is whether the disease burden is sufficient to warrant local or national prevention guidelines. Surveillance for invasive GBS disease has played a key role in motivating prevention in several countries. The United States, Canada, Spain, Belgium, and Australia all documented rates of early-onset (age at onset, 0–6 days) GBS disease of >1 per 1000 live births in the era before intrapartum prophylaxis [2–5]. Other European countries, such as Finland and Sweden [6, 7], have reported lower baseline rates of GBS disease. The United Kingdom appears to fall in this category, although the study by Weisner et al. [1] does not discuss whether intrapartum prophylaxis for GBS prevention was used at the time of UK surveillance and, if so, to what extent. Rates in the developing world remain largely characterized because, in many settings, causes of illness and death early in life go undiagnosed. A recent multinational study of vaginal GBS carriage rates among pregnant women in several developing countries, the United States, and Europe found high variability in carriage rates, ranging from 7% to 22% [8]. Invasive early-onset disease rates in Soweto, South Africa, in 1997–1999 were similar to preprevention rates in the United States [9]. These findings are consistent with US data suggesting that carriage rates among African Americans are higher than among whites.

In addition to establishing that the disease burden is sufficient to warrant prevention guidelines, identifying effective and feasible prevention strategies plays a key role in motivating development of national guidelines. To date, intrapartum antimicrobial prophylaxis is the only available intervention with demonstrated efficacy against invasive early-onset GBS disease. In terms of selecting candidates for chemoprophylaxis, a recent multistate observational study in the United States showed that late antenatal culture-based screening for GBS was >50% more effective than identifying at-risk women on the basis of obstetric risk factors during labor (e.g., fever, preterm delivery, and prolonged membrane rupture) [10]. Implementation of intrapartum chemoprophylaxis strategies has led to marked decreases in the incidence of early-onset GBS disease in several countries (reviewed in [11]). Additionally, there is no compelling evidence to date that widespread implementation of GBS prophylaxis has resulted in increased sepsis due to antibiotic-resistant gram-negative bacteria among neonates, although continued monitoring of incidence and resistance trends in both GBS and non-GBS pathogens remains important [11].

Intrapartum alternatives to antimicrobial prophylaxis have not yet been established. Among possible candidates, vaginal disinfection with the microbicide chlor-
maternal GBS vaccine was ranked by scientific progress in vaccine development, a form of multivalent vaccine with coverage against infections (age at time of onset, 7–89 days) that have not decreased during the era of intrapartum prophylaxis [15]. Results of phase I and II testing of conjugate vaccine formulations suggest that vaccines can induce antibody responses at levels that are likely to be protective [16]. The relatively small number of GBS serotypes associated with disease facilitates development of a multivalent vaccine with coverage against circulating strains. Weisner et al. [1] suggest that a 5-valent vaccine would cover 85% of the serotypes associated with invasive disease in the United Kingdom. These findings are similar to evaluations of serotype distribution in Canada and the United States. Although the need for multivalent vaccines poses a technical challenge, it is a much smaller challenge than that associated with the creation of pneumococcal conjugate vaccines, which have been produced for studies in 7–13-valent formulations. In part because of the scientific progress in vaccine development, a maternal GBS vaccine was ranked by a recent Institute of Medicine Report as among the “most favorable” vaccines for development in the 21st Century [17]. Unfortunately, however, Phase III licensure trials appear to be as distant as ever, primarily because of the lack of strong pharmaceutical backing and liability concerns associated with testing a vaccine in pregnant women.

As countries such as the United Kingdom consider adopting prevention strategies, data such as those presented by Weisner et al. [1] may help guide choice of a prevention strategy. Although there is strong evidence supporting the effectiveness of late antenatal screening for GBS carriage and intrapartum prophylaxis for carriers, the costs and logistical challenges of this strategy may be less attractive to authorities in countries with lower baseline disease rates. In developing countries, both the late antenatal culturing component and the intrapartum prophylaxis component may not be feasible. A pivotal randomized trial evaluating the effectiveness of chlorhexidine vaginal wipes for preventing neonatal GBS sepsis could provide these countries with a feasible alternative that may even have the potential for implementation in the home-birth setting.

Development and licensure of an adolescent or maternal GBS vaccine is likely the most effective and sustainable long-term prevention strategy for a wide range of hospital settings and countries. If immunity does not wane rapidly, a single vaccine series may be sufficient to protect women throughout their childbearing years. Although adolescent vaccination strategies would alleviate concerns about vaccination during pregnancy and might prevent adverse outcomes due to GBS infection during early pregnancy, in many settings, maternal vaccination strategies may be easier to implement because of increased contact with the health care system for prenatal care. Maternal vaccination might also be a feasible strategy in developing countries. Initiatives such as the Global Alliance for Vaccine and Immunizations are breaking new ground in supporting and accelerating the introduction of new vaccines in developing countries. Moreover, many developing countries already have a strong track record in successful delivery of tetanus toxoid vaccine during pregnancy to prevent neonatal tetanus [18].

The United Nations recently set millennium development goals of reducing the maternal mortality ratio by three-fourths and the child mortality among children <5 years of age by two-thirds during 1990–2015, with reductions in infant mortality rates as one of the success indicators (http://www.un.org/millenniumgoals/). Neonatal GBS infections and other maternal-newborn infections transmitted primarily during the intrapartum period hold unique promise for prevention. Identification of affordable, feasible interventions for use in developing countries and renewed efforts to support progress towards licensure of a GBS vaccine could be important contributions toward achievement of these goals.

References


