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Review

Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine

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ABSTRACT

Group B *Streptococcus* (GBS) emerged as the leading cause of newborn infection in the United States in the 1970s. In the 1980s clinical trials demonstrated that giving intrapartum intravenous ampicillin or penicillin to mothers at risk was highly effective at preventing invasive GBS disease in the first week of life (early-onset). In 1996, the first national guidelines for the prevention of perinatal GBS disease were issued; these recommended either antenatal screening for GBS colonization and intrapartum antimicrobial prophylaxis (IAP) to colonized women, or targeting IAP to women with certain obstetric risk factors during labor. In 2002, revised guidelines recommended universal antenatal GBS screening. A multistate population-based review of labor and delivery records in 2003–2004 found 85% of women had documented antenatal GBS screening; 98% of screened women had a colonization result available at labor. However, missed opportunities for prevention were identified among women delivering preterm and among those with penicillin allergy, and more false negative GBS screening results were observed than expected. The incidence of invasive early-onset GBS disease decreased by more than 80% from 1.8 cases/1000 live births in the early 1990s to 0.26 cases/1000 live births in 2010; from 1994 to 2010 we estimate that over 70,000 cases of EOGBS invasive disease were prevented in the United States. IAP effectiveness is similar and high among term (91%) and preterm (86%) infants when first line therapy is received for at least 4 h. However, early-onset disease incidence among preterm infants remains twice that of term infants; moreover disease among infants after the first week of life (late-onset disease) has not been impacted by IAP. The US experience demonstrates that universal screening and IAP for GBS-colonized women comprise a highly effective strategy against early-onset GBS infections. Maximizing adherence to recommended practices holds promise to further reduce the burden of early-onset GBS disease. Yet there are also inherent limitations to universal screening and IAP. Some of these could potentially be addressed by an efficacious maternal GBS vaccine.

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1. History of group B streptococcal disease and prevention interventions

The bacteria group B *Streptococcus* (GBS) emerged as the leading cause of infection in newborns in the United States in the 1970s. Case series reported fatality rates as high as 50%, with pneumonia and meningitis the leading clinical syndromes. Early-onset GBS infections (onset within the first week of life) result predominantly from vertical transmission of GBS from colonized mothers during the intrapartum period whereas infections from one week to 90 days of age (late-onset infections) result primarily from transmission after birth, either from the mother or other sources. Before prevention efforts were implemented, early-onset disease incidence was markedly higher than late-onset incidence (2–3 cases per 1000 live births vs. 0.3 cases/1000 live births); late-onset infections present more often with meningitis and the associated sequelae.

In the 1980s clinical trials demonstrated that giving intrapartum intravenous ampicillin or penicillin to mothers at risk for transmitting GBS to their newborn was highly effective at preventing invasive early-onset GBS disease. One trial with ampicillin was stopped early due to overwhelming efficacy [1]; a trial of penicillin showed a potential efficacy of 80% [2] and a large observational study of penicillin for women with antenatal GBS colonization showed a significantly reduced incidence in the penicillin group compared to a control cohort that received intrapartum antibiotics only for maternal infection (0.5/1000 vs. 1.0/1000 live births) [3].

Despite its proven efficacy, intrapartum antibiotic prophylaxis (IAP) was not rapidly adopted in the United States, primarily due to the challenge of how best to identify women that should receive prophylaxis. IAP for all delivering women was not considered acceptable due to the high number needed to prophylax to prevent a single case. Clinical trials used different criteria to limit prophylaxis to higher risk groups such as prenatal or intrapartum maternal GBS colonization (detected using a range of methods) and in some instances additional risk factors for early-onset disease including preterm labor or prolonged rupture of membranes.

2. Development and evolution of GBS prevention policy

Prevention of early-onset GBS disease crosses clinical specialty boundaries because a maternal intervention is needed to protect newborns from disease. In 1992 the American Academy of Pediatrics promoted an IAP strategy that focused on maternal screening for GBS colonization, with an emphasis on colonized women with either preterm delivery or prolonged membrane rupture [4]. During the same time period the American College of Obstetricians and Gynecologists advocated an approach that did not require antenatal screening for GBS colonization, but relied on monitoring for specific obstetric risk factors such as preterm labor, preterm premature membrane rupture, intrapartum fever, or prolonged membrane rupture [5]. In 1996, the first consensus guidelines for the prevention of perinatal GBS disease were issued by the Centers for Disease Control and Prevention, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists [6–8]. Because evidence was not available to identify the most effective strategy for determining which women should receive IAP, these guidelines recommended either late antenatal screening cultures for GBS colonization ("the screening based approach") or assessment for obstetric risk factors during labor ("the risk-based approach") as equally acceptable alternatives. Some years after the issuance of these guidelines, a multistate, retrospective cohort evaluation found that screening was greater than 50% more protective than the risk-based approach, largely because of its ability to detect colonized women without risk factors (18% of all delivering women), high effectiveness of IAP among this group of women, and better implementation of IAP for women with documented GBS colonization [9].

In light of these findings, revised national guidelines were published in 2002 recommending universal late antenatal screening for GBS colonization, and the use of intrapartum risk-based criteria only when GBS colonization status is unknown [10,11]. In 2010, updated guidelines were issued [12]. Universal screening and IAP for women colonized with GBS remained at the foundation of prevention, but the 2010 recommendations refined guidance for laboratory processing of antenatal GBS specimens, management of women with threatened preterm delivery or preterm premature rupture of membranes, and management of newborns to ensure early identification and treatment of early-onset GBS disease.

In all iterations of US prevention guidelines, intravenous penicillin was the first line IAP agent recommended with intravenous ampicillin an acceptable alternative. While minor modifications to penicillin dosing were introduced in 2010 to be consistent with available formulations, all guidelines have recommended a high loading dose followed by lower subsequent doses and a 4-hourly dosing schedule. For penicillin allergic women, initial guidelines recommended clindamycin or erythromycin for prophylaxis. However, due to increasing resistance among group B streptococci to these agents [13], and the poor ability of erythromycin to penetrate the amniotic fluid, the guidance was revised in 2002 to recommend cefazolin as the agent of choice for penicillin-allergic women at high risk for anaphylaxis. Currently, for this small subset of penicillin-allergic women not eligible for cefazolin, clindamycin is recommended if the GBS colonization isolate is susceptible to both clindamycin and erythromycin, and otherwise vancomycin is recommended [12]. None of the antibiotics recommended for GBS prevention in penicillin-allergic women were evaluated in clinical trials. They were chosen based on expert opinion regarding safe intravenous agents appropriate for pregnant women, and available pharmacokinetic and pharmacodynamics data. Cefazolin, which has similar performance characteristics to penicillin and ampicillin including the ability to achieve high intra-amniotic concentrations [14] is expected to be more effective against GBS than either clindamycin or vancomycin.

3. Implementation of prevention, 1996–2002

Successful implementation of an intrapartum prophylaxis strategy is complex and requires strong collaboration between obstetric, clinical laboratory and newborn care providers. Implementation involves two key steps: (1) ascertainment of whether a woman has an indication for IAP; (2) administration of appropriate IAP to women with indications.

Shortly after issuance of the first consensus guidelines, having a newly established hospital policy for GBS prevention was associated with stronger implementation of prevention efforts and reduced incidence of early-onset GBS disease [15]; as IAP use became more widely accepted, provider-level practices became more important than institutional policies. A multistate, population-based review of labor and delivery records of births in 1998 and 1999 found that among women managed by the risk-based approach (women with unknown colonization status on admission for delivery), 61% of women with an indication received IAP (50% of women with preterm delivery, 76% of women with intrapartum fever, and 79% of women with prolonged membrane rupture). In contrast among women managed by the screening-based approach, 89% of GBS colonized women received IAP [9].

4. Implementation of prevention in the era of universal screening

The key steps to successful prevention under a universal screening strategy include reaching a high proportion of women for antenatal screens; correct specimen collection and processing; and implementation of appropriate IAP to women with indications. A large, multistate review of births in 2003 and 2004, shortly after issuance of the first universal screening recommendations, documented rapid, widespread uptake of screening [16]: 85% of women had documented antenatal GBS screening, and 98% of screened women had a colonization result available in the labor and delivery record. Because screening is only recommended at 35–37 weeks' gestation, a majority (50.3%) of women delivering preterm did not have an antenatal screening result; failure to adhere to the recommendation to screen these women on admission for threatened preterm delivery was the most common missed opportunity for screening among preterm deliveries [16]. Among womnen delivering at term, 89.3% were screened. Factors associated with failure to screen among mothers delivering at term included black race, Hispanic ethnic group, previous delivery of a live infant, history of drug use, and inadequate prenatal care. However, these sub-populations were associated with only a very small portion of the remaining disease burden [16]. The largest portion of cases among term deliveries (61%) occurred among women who had been screened, and who had a negative GBS colonization result. While false negative results are expected due to test limitations and acquisition of GBS between the time of screening and delivery, this same multistate review estimated that more false negative prenatal GBS test results were occurring than would be expected, suggesting room for improvement in prenatal specimen collection and processing methods [16].

The proportion of women with an indication for IAP who received it increased from 73.8% in 1998/1999 to 85.1% in the universal screening era. Failure to receive IAP when indicated was most common among women delivering preterm with unknown GBS colonization status: approximately half of women delivering preterm had unknown colonization status and only 63.4% of these received IAP. Administration of inappropriate IAP agents to penicillin allergic women (69.9% of women who should have received cefazolin received clindamycin instead) also represented a key missed opportunity for prevention [16].

Case series of infants with early-onset GBS disease during the era of universal screening and widespread IAP use can also provide insight on missed opportunities for prevention. A study of 54 early-onset GBS cases from a large health care system in Utah in 2002–2006 found few missed opportunities for prenatal screening among term cases (93% were screened), but did describe 7 cases (13%) in which GBS-colonized mothers received no or suboptimal IAP, including 2 penicillin-allergic mothers who received clindamycin despite a lack of antibiotic susceptibilities [17]. In a multi-center study of neonatal sepsis conducted in 2006–2009 that included 159 cases of early-onset GBS disease, 63% of the mothers of term infants with GBS disease had not been screened prenatally, and only 66–76% of mothers of cases with an indication for GBS prophylaxis received IAP [18]. Another multi-center investigation of missed opportunities for prevention among early-onset GBS cases in 2008–2009 found at least one missed opportunity for optimal prenatal screening or use of IAP in 177 (57%) of 309 cases [19]. Thus, while the US GBS prevention strategy has been well implemented at a population level, important gaps in adherence have been noted.

5. Impact of IAP and universal screening on perinatal GBS disease

Despite the high incidence of early-onset GBS disease in the pre-prevention era, monitoring disease trends was complicated by the fact that even large hospitals had only a small number of invasive cases annually. This necessitated surveillance in a large catchment area. To this end, in 1990 the Centers for Disease Control and Prevention in collaboration with state partners launched multistate invasive group B streptococcal disease surveillance as part of the Active Bacterial Core surveillance (ABCs)/Emerging Infections Network. In recent years the surveillance includes selected areas of 10 states and approximately 10% of US live births.

In the period of widespread IAP use, the incidence of invasive early-onset GBS disease in ABCs decreased by more than 80% from 1.8 cases/1000 live births in the early 1990s to 0.26 cases/1000 live births in 2010 (Fig. 1). Using the estimated national cases based on ABCs surveillance in 1993 as a benchmark annual disease burden in the absence of prevention, from 1994 to 2010 we estimate that over 70,000 cases of EOGBS invasive disease were prevented in the United States. In contrast, IAP did not lead to reductions in incidence or changes in clinical presentation or severity of late-onset invasive GBS disease during this same period [20] (Fig. 1).

When invasive early-onset GBS disease trends were stratified by gestational age, declines were evident in both preterm and term populations (Fig. 2a). When further stratified by race, the incidence

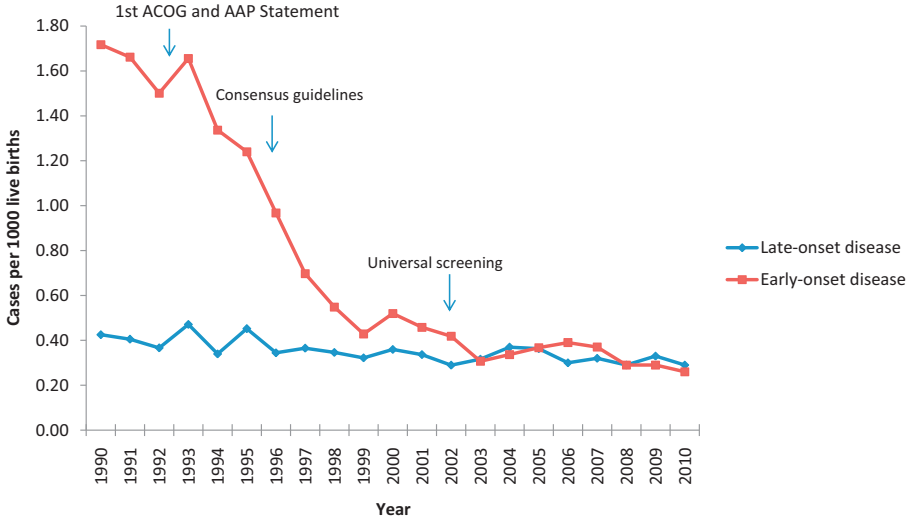

Fig. 1. Incidence of invasive early and late-onset group B streptococcal disease, Active Bacterial Core surveillance, United States, 1990–2010.

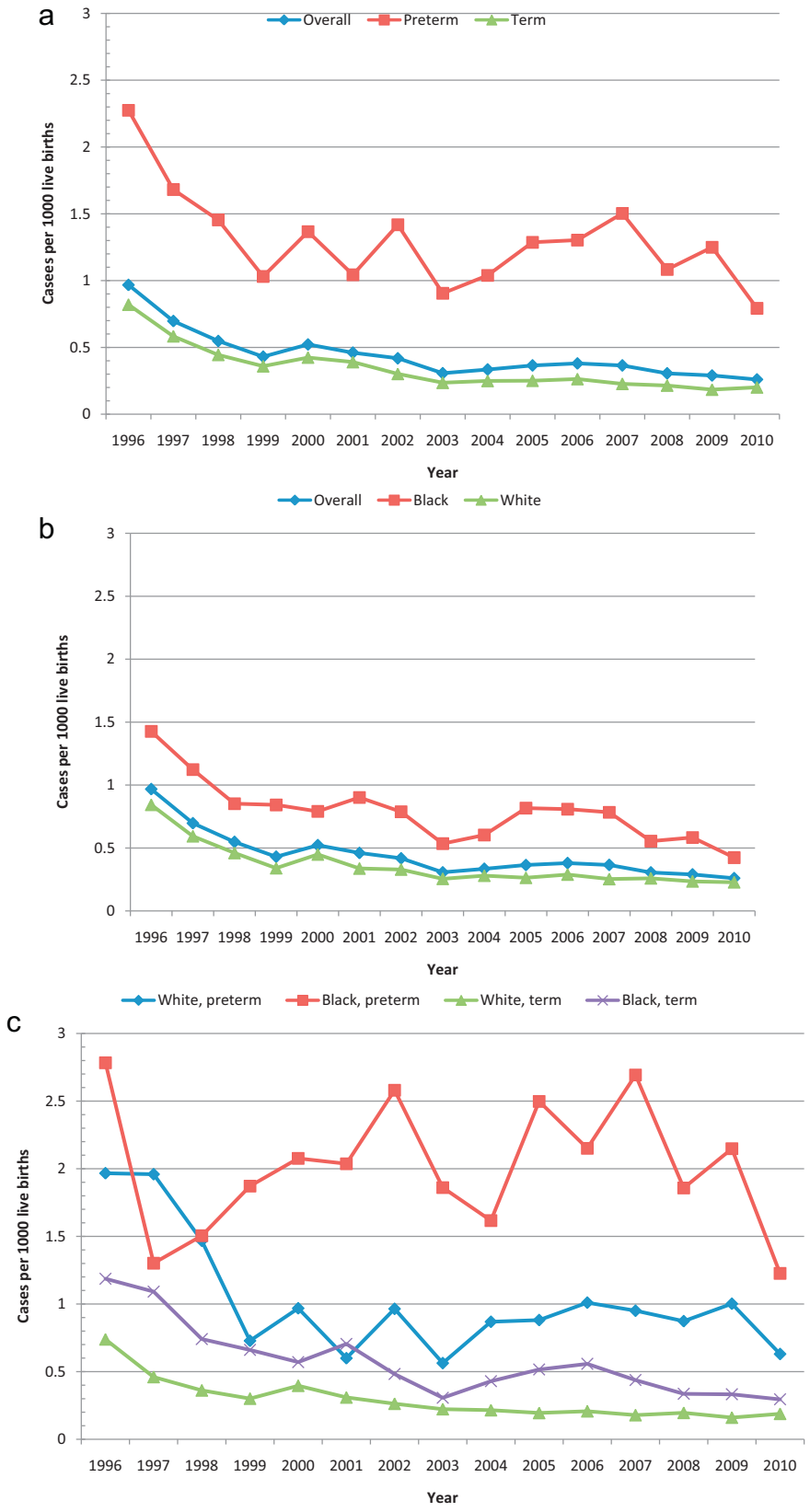

Fig. 2. (a) Incidence of invasive early-onset group B streptococcal disease by gestational age, Active Bacterial Core surveillance, 1996–2010. (b) Incidence of invasive early-onset group B streptococcal disease by race (Black vs white), Active Bacterial Core surveillance, 1996–2010. (c) Incidence of invasive early-onset group B streptococcal disease by gestational age and race, Active Bacterial Core surveillance, 1996–2010.

among black term infants was approximately twice the incidence of white term infants, and the incidence among black preterm infants was similarly approximately twice that of white, preterm infants (Fig. 2b and c). The reasons for this disparity in incidence by race, controlling for gestational age, remain uncharacterized and although incidence has declined significantly among both black and non-black newborns in the IAP era, the disparity in rates has persisted.

The impact of an antibiotic intervention such as IAP may not be limited to GBS, but may also positively or negatively affect other pathogens causing neonatal sepsis. *Escherichia coli*, the second leading cause of invasive early-onset sepsis in the US after GBS, is the pathogen of most concern, particularly due to its high prevalence of beta lactam resistance. A series of case-only studies shortly after IAP became widespread reported associations between IAP exposure and ampicillin-resistant *E coli* infection [21–23]. However, case-only data can lead to erroneous conclusions because they exclude all the early-onset cases successfully prevented by IAP [24]. A case-control evaluation of factors associated with *E. coli* invasive early-onset sepsis and with ampicillin-resistant *E. coli* invasive early-onset sepsis found that IAP was not significantly associated with increased risk of either, nor was it effective at reducing risk of infection [25]. Multicenter surveillance by the National Institute for Child Health and Development's Neonatal Research Network reported an increase in the incidence of invasive early-onset *E. coli* sepsis among very low birthweight infants from 1991–1993 to 1998–2000, but then reported stable rates from 1998–2000 through 2002–2003, as well as no significant change in the proportion of isolates resistant to ampicillin [26,27].

Because newborn blood culture sensitivity is low, particularly when the mother has received intrapartum antibiotics, invasive disease represents only a fraction of all neonatal sepsis. A recent analysis of neonatal sepsis trends using national hospital discharge data and a case definition that included clinical as well as culture-confirmed sepsis based on ICD codes, found a −3.6% annual average percent change in sepsis rates among term infants since 1996, the year the first consensus IAP guidelines were issued [28]. Among preterm infants there was a smaller average annual percent decline in the sepsis rate from 1988 to 2006. The observed reduction in all-cause clinical sepsis, which includes early and late onset sepsis due to all pathogens, mirrored invasive early-onset GBS disease trends, These findings provide evidence that declines in early-onset GBS disease are robust and that culture-negative sepsis or sepsis due to other pathogens has not simply replaced invasive early-onset GBS sepsis in the IAP era [28].

6. IAP effectiveness

Direct IAP effectiveness estimates are helpful as a complement to disease trend data, and also provide a context for comparing IAP to other possible prevention strategies such as a GBS vaccine. A case-control analysis of the effectiveness of IAP among mother with obstetric risk factors reported an adjusted effectiveness of 86% (95% confidence interval, 66–94%) against invasive early-onset GBS disease, with slightly lower point estimates for the subgroup of mothers with intrapartum fever and mothers who received less than 2 h of an IAP regimen before delivery [29]. A recent analysis of a multistate cohort of births using propensity score matching found a similarly high effectiveness against invasive early-onset GBS disease for at least 4 h of bet a lactam IAP among both term (91%, 95% CI +63%, +98%) and preterm (86%, 95% CI, +38%, +97%) infants. Shorter durations of beta lactam IAP (≤2 to <4 h: 38%, 95% CI −17%, +69%; <2 h: 47%, 95% CI −16%, +76%) and clindamycin IAP (22%, 95% CI −53%, +60%) had notably lower effectiveness [30].

7. Maximizing the impact of IAP in the United States

From a review of ABCs invasive early-onset GBS cases that occurred in 2008–2009, we estimated that optimal implementation of prenatal screening and intrapartum prophylaxis could have prevented 31–43% of cases, suggesting that further reduction of the burden of early-onset GBS disease is achievable under current prevention strategies [19]. While the evaluation of laboratory practices for the processing and testing of prenatal screening specimens from the mothers of the cases in that study is on-going, it is likely that better adherence to recommended laboratory practice could further reduce the remaining disease burden.

Based on these findings, the incidence of early-onset GBS disease, which has remained stable at around 0.3 cases per 1000 live births in recent years, could therefore potentially be reduced to 0.2 cases per 1000 live births or even lower. In order to achieve optimal adherence to prevention guidelines, however, tools are needed to facilitate implementation. Based on input from laboratories, CDC and the American Society for Microbiology has developed sample standard operating procedure documents that include the recommended laboratory methods for processing and testing prenatal screening specimens (http://www.cdc.gov/groupbstrep/lab/sops.html). CDC and partners are also currently developing web-based applications (apps) for clinicians; an obstetric app guides decisions regarding intrapartum antibiotic use, and a neonatal app provides recommendations aimed at prompt detection and treatment of early-onset GBS disease. Plans are underway to incorporate this kind of point of care guidance into electronic medical records to further reduce the risk of human error and improve adherence to GBS prevention guidelines.

8. Global experience with IAP

Beyond the US, several industrialized countries have implemented IAP policies. Some (e.g., Spain, Canada, Australia) have adopted indications for prophylaxis similar to the US, and have documented declines similar to the United States [31,32]. Countries and single hospitals that have adopted risk-based approaches have also documented declines [24]. A recent systematic review of neonatal GBS disease globally found that early-onset GBS disease incidence in countries that used IAP (0.23.1000 live births) was significantly lower than in countries that did not use IAP (0.75/1000 live births) [33]. However, in many of the world's poorest countries, intravenous IAP is not feasible or safe. Antenatal screening for GBS colonization and having the results available to guide management during labor also requires a level of coordination and access to care that is not often possible in resource-poor settings. For hospital-based deliveries, a risk-based IAP strategy is used in some settings. In one evaluation of a risk-based policy in a large public hospital in Soweto, South Africa, administration of IAP to women with indications was low, suggesting barriers to IAP -based prevention even in middle income settings [34].

9. GBS vaccine considerations in the setting of widespread IAP

With a trivalent (serotypes 1a, 1b and III) GBS conjugate vaccine currently undergoing Phase II trials in pregnant women (clinicaltrials.gov identifiers NCT01446289, NCT01412801, NCT01193920) it is reasonable to consider factors that might influence the decision to introduce maternal GBS vaccination in a country such as the US where widespread IAP is already in place.

Compared to a serotype-specific maternal vaccine, IAP has certain advantages. First, it is effective against all GBS serotypes; in the US serotypes Ia, Ib and III account for approximately 58% of invasive

early-onset cases [35]. Secondly, IAP effectiveness among preterm infants is similar to that among infants delivered at term. A GBS vaccine may theoretically afford lower protection in preterm deliveries because of incomplete transfer of maternal antibody, insufficient time to mount maternal immune response, or inadequate opportunity for vaccination before delivery. Finally, IAP coverage among women with indications is now high (approximately 85% based on multistate surveillance in 2003–2004) in the US. Although national efforts are in place to strengthen the maternal immunization platform in the US, based on recent experiences with influenza and pertussis-containing vaccines, it might be difficult for a maternal vaccine to achieve a similarly high coverage [36].

However, even with optimal implementation, there are inherent limitations to universal screening and IAP. Because of the timing of screening and the transient nature of GBS colonization, even perfect adherence to recommended specimen collection and laboratory processing techniques would not prevent all false negative prenatal screening results. In addition, precipitous deliveries can impede the ability to provide an adequate duration of intrapartum prophylaxis before delivery. Intrapartum antibiotics are also ineffective at preventing manifestations of GBS in infants other than early-onset disease. The incidence and disease burden (approximately 1100 cases annually) associated with invasive late-onset GBS disease in the United States are substantial compared to other newborn conditions where vaccines have been considered [20]. In fact, the incidence of invasive late onset GBS disease is now higher than that of early-onset GBS disease in the ABCs surveillance catchment population, and the US, based on national estimates (http://www.cdc.gov/abcs/reports-findings/survreports/gbs10.html). GBS has also been implicated as a cause of stillbirth [37]; although the burden of fetal loss due to GBS is unknown, it is a manifestation of GBS disease not impacted by intrapartum antibiotics that could theoretically be affected by a GBS vaccine. Some studies have also reported an association between maternal GBS colonization and preterm delivery, although it is unknown whether the link is causal [38]. If GBS conjugate vaccines were effective at preventing colonization with vaccine associated serotypes, as a Phase II trial of a type III conjugate vaccine suggested [39] and as has been observed for other conjugate vaccines [40], it is hypothetically possible that maternal GBS vaccination might contribute to a reduction in preterm deliveries. Maternal vaccination may also potentially be a simpler strategy to implement than universal screening and IAP, particularly as the maternal immunization platform is strengthened. Because of the many factors influencing the impact of IAP and a theoretical GBS vaccine, and the potential combination of maternal GBS vaccination and IAP, cost effectiveness assessments may also prove helpful in comparing prevention strategies.

Finally, a prevention strategy reliant on antibiotic prophylaxis is vulnerable to the emergence of antimicrobial resistance among GBS or other newborn pathogens. GBS resistance to clindamycin and erythromycin has already affected IAP options for penicillin allergic women. The evolution of clinically meaningful resistance among GBS to the beta lactams would jeopardize IAP effectiveness and also affect treatment of invasive infections. Historically GBS are pan-susceptible to beta lactams. In recent years a small number of clinical isolates have been characterized as having decreased susceptibility that is just at the threshold of the minimum inhibitory concentration breakpoints and is of unclear clinical significance [41,42]. These isolates have been characterized to have the same modifications to the penicillin binding protein genes as have been seen in *Streptococcus pneumoniae* where beta lactam resistance is now common [41,42]. The US ABCs monitors for isolates with increasing MICs to beta lactams and to date they remain exceedingly rare and do not appear to be increasing.

10. Conclusions

The experience in the United States has shown that universal screening and IAP for GBS-colonized women comprise a highly effective strategy against early-onset GBS infections that has been very well implemented at the population level. There are shortcomings, however, with the current GBS prevention efforts. Some of the limitations can be overcome by maximizing adherence to recommended practices, and there is room to further reduce the burden of early-onset GBS disease through improved implementation. Yet there are also inherent limitations to universal screening and IAP, some of which could potentially be addressed by an efficacious maternal GBS vaccine. While there could be added value of a GBS vaccine to prevention efforts for early-onset disease in the United States, barring the emergence of widespread resistance among GBS to beta lactam antibiotics, the true public health value of a GBS vaccine likely depends on the ability of such a vaccine to protect against manifestations of GBS disease that are not impacted by currently available prevention strategies, such as late-onset disease, still-birth and perhaps even preterm delivery. A GBS vaccine holds even greater promise for countries where IAP and universal screening are not feasible or can only be implemented at a minimal level. Resource-poor settings with an established burden of invasive GBS disease could undoubtedly benefit from an efficacious GBS vaccine. The role of a GBS vaccine in the US—where the existing early-onset disease prevention strategy is safe, effective and widely accepted—will depend on multiple factors in addition to vaccine performance.

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