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Discussion

Ethical considerations for designing GBS maternal vaccine efficacy trials in low-middle income countries☆

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ABSTRACT

Many in the scientific community agree that a randomized, placebo-controlled trial would offer the most scientifically rigorous study design for establishing the efficacy of a Group B *Streptococcus* (GBS) vaccine administered to pregnant women for the prevention of invasive GBS disease in young infants. There are compelling reasons to conduct such a trial in low-middle income countries (LMICs) with a high burden of disease, such as South Africa, and to adopt an *add-on* trial design in which participants are randomized to receive the GBS vaccine or placebo in addition to the locally available standard of care. Yet there is a longstanding debate about whether trials in LMICs should offer participants the worldwide best available standard of care. In this article, we examine both the risk–benefit profile and the potential for exploitation with an add-on trial design in the context of the locally available standard of care in South Africa. Our analysis suggests that providing the local standard of care to participants in this case may be not only more scientifically valuable but also more ethically acceptable than attempting to provide the worldwide best available standard of care in the South African setting. Moreover, the example of GBS in the South African setting can help to elucidate important ethical considerations for determining the acceptability of testing vaccine efficacy in the context of locally available rather than the worldwide best available standard of care in Phase III trials of other new maternal vaccines.

1. Introduction

Many in the scientific community agree that a randomized, placebo-controlled trial would offer the most scientifically rigorous study design for establishing the efficacy of a Group B *Streptococcus* (GBS) vaccine administered to pregnant women for the prevention of invasive GBS disease in young infants [1]. There are compelling reasons to conduct such a trial in low-middle income countries (LMICs) such as South Africa, due in part to the high burden of disease, and to adopt an *add-on* trial design in which participants are randomized to receive the GBS vaccine or placebo in addition to the locally available standard of care. Yet there is a longstanding debate about whether trials in LMICs should offer participants the worldwide best available standard of care [2]. In this article, we examine both the risk–benefit profile and the potential for exploitation with an add-on trial design in the context of the locally available standard of care in South Africa. Our analysis suggests that providing the local standard of care to participants in this case may be not only more scientifically valuable but also more ethically acceptable than attempting to provide the worldwide best available standard of care in the South African setting. Moreover, the example of GBS in the South African setting can help to elucidate important ethical considerations for determining the acceptability of testing vaccine efficacy in the context of locally available rather than the worldwide best available standard of care in Phase III trials of other new maternal vaccines.

2. Background

Despite a 36% decline in global under-5 childhood mortality over the past decade, the number of deaths occurring during the first month of life has remained high [3]. In 2013, 44% of all under-5 child deaths occurred during the first month of life, approximately

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one-third of which were attributable to infectious causes [3]. The potential to reduce neonatal mortality from infectious diseases by immunizing women during pregnancy to provide antibody protection to their newborns is evident from the tetanus vaccination program targeted at pregnant women, which has contributed to a 9.5% year-on-year decline in neonatal tetanus-related deaths in the past decade [4]. The success of maternal vaccination is now being explored for the prevention of other infections affecting neonates and young infants, prompting the development of new vaccines for use in the third trimester of pregnancy in expectant mothers to provide passive immunity to their newborns.

Ongoing efforts have been aimed at developing a maternal vaccine against GBS, which remains the leading cause of neonatal sepsis and meningitis in many countries [5]. Asymptomatic vaginal colonization of GBS occurs in roughly 12–27% of pregnant women worldwide [5]. In addition to being a possible cause for stillbirth and maternal intrauterine infection, it results in 50% perinatal transmission to newborns, leading to early onset (EOD; 0–6 days of age) invasive disease in 1–2% of colonized newborns [6]. Global case fatality rates reported in a recent meta-analysis range from a mean of less than 1% in Europe to as high as 22% in parts of Africa [7]. South Africa and many other African countries report the highest prevailing incidence of invasive GBS globally [7].

Although effective strategies already exist for prevention of early-onset GBS disease, current approaches are far from optimal. Based on studies showing a more than 80% reduction in preventing early-onset disease (EOD; within 7 days of life), the best possible prevention involves screening pregnant women at 35–37 weeks gestation for recto-vaginal colonization, with targeted intrapartum antibiotic prophylaxis (IAP) given to colonized women during labor [6,8,9]. Yet this strategy has not been effective in preventing late-onset disease (LOD; 7–90 days of life), which represents up to one-third of cases in regions without an IAP program and the majority of disease in settings where screening-based IAP programs exist [6,8].

Moreover, this universal screening strategy, which is the standard of care in some high-income countries, is resource intensive and logistically challenging or impractical in other high-income countries and most LMICs. In addition to citing the low cost-effectiveness of screening all women prior to the onset of labor, countries that have not adopted universal screening have raised concerns about overexposure to antibiotics leading to higher rates of antibiotic resistance, an over-medicalization of labor, uncertainties about the strength of available evidence in the absence of well-conducted randomized trials, and logistical difficulties screening and treating large populations of women delivering at home rather than in a hospital setting [9]. Many countries, including the United Kingdom, have therefore adopted a more targeted risk-based approach in which intrapartum antibiotics are specifically directed to women with established risk-factors for invasive disease in their newborns. These maternal risk-factors associated with EOD include intra-partum fever, rupture of amniotic sac membranes prior to onset of labor or >18 h prior to birth of the child, presence of chorio-amnionitis, history of GBS bacteriuria during pregnancy and preterm labor [10]. Although there is evidence to suggest that universal screening is more effective than the risk-based approach for preventing early-onset GBS disease, the drawbacks of screening have fuelled debate about what recommendations are most appropriate in each country [9].

Both the lack of effectiveness of IAP in preventing late onset disease and the logistical challenges of implementing widespread screening for GBS at 35–37 weeks gestation suggest the need for additional prevention strategies. A conjugate GBS vaccine holds much promise for meeting this need. The vaccine has the potential to reduce the incidence of not only early-onset disease but also late-onset disease. GBS vaccination of pregnant women would ideally become the primary preventative strategy for control of EOD and replace the need for antepartum universal screening and IAP in most cases. However, as optimal transplacental transfer of antibody to the fetus only matures at approximately 34 weeks of gestational age, maternal vaccination may not protect preterm neonates born at earlier gestational ages. Due to the increased risk of invasive GBS disease in premature births, which is partly mitigated by providing IAP to mothers in preterm labor, IAP may still be necessary despite maternal GBS vaccination for some women with EOD risk factors. Nonetheless, an effective vaccine would prevent the vast majority of EOD cases and substantially reduce poor neonatal outcomes attributable to early invasive disease.

The likelihood of maternal GBS vaccination preventing LOD will depend on the magnitude of the antibody response induced by vaccination, transplacental (and possibly breast milk) transfer thereof to the newborn and kinetics of the antibody response in the neonate. As the majority of LOD cases occur within the first month of life, including a median age of 14 days for LOD in South Africa, it is highly plausible that maternal GBS vaccination would protect against EOD and the majority of LOD [11].

Furthermore, vaccination could also provide protection against pregnancy complications and offer direct benefits to mothers. GBS has been implicated as a risk factor for preterm births and stillbirths [12–14]. An effective vaccine could potentially reduce the risk of these poor obstetrical outcomes attributable to maternal GBS colonization. It may also provide direct benefits to pregnant women themselves, as GBS is known to cause urinary tract infections, chorioamnionitis, postpartum endometritis, bacteremia, septic abortion, meningitis, and other serious infections [15]. Thus, demonstrating the efficacy of a GBS vaccine offers maternal and pregnancy-related benefits that could improve outcomes for women and infants in high-income countries as well as LMICs.

The availability of an effective vaccine would be particularly valuable in a middle-income country like South Africa, which has seen a persistently high incidence of invasive GBS disease despite the standard of care being the same targeted risk-based IAP strategy as the standard of care in the United Kingdom. The persistent high burden of disease in LMICs like South Africa relates to the resource constraints of infrastructure to conduct microbiological evaluations and coordinate the return of results to facilities where women actually deliver, which could be unpredictable. Likewise, infrastructure is often lacking to ensure the timely administration of antibiotics for the recommended four hours prior to delivery and to provide any antibiotic coverage for the deliveries occurring outside of health facilities. In a recent cost-effectiveness analysis, Kim and colleagues projected that if a vaccine is 50–90% efficacious and 75% of pregnant women are vaccinated in South Africa, GBS vaccination alone would prevent 30–54% of infant GBS invasive cases compared to the 10% reduction from the current risk-based antibiotic standard of care. In absolute numbers, this would amount to the yearly prevention of 2912–5260 cases and 516–934 deaths attributable to GBS at a high level of cost-effectiveness [16]. Given these projections, a vaccine strategy would be more logistically feasible and sustainable than universal screening. The vaccine would likely only need to be given sometime in the third trimester, could be administered by semi-skilled health workers, and is not subject to the challenges of screening or antibiotic administration. Evidence of the practicality of maternal vaccination is partly based on the experience of maternal tetanus vaccination acceptability and its contribution to reducing neonatal tetanus even in low income settings [17]. A trial demonstrating the efficacy of a GBS vaccine would thus be highly valuable in settings like South Africa.

Phase I/II trials of a trivalent GBS vaccine have now been conducted, and in the absence of a recognized serological correlate of protection acceptable by regulatory authorities for licensure based on safety and immunogenicity, a Phase III trial to determine

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