Editorial
Maternal immunization: An intelligent solution to reduce the hidden burden of group B streptococcus perinatal disease

As a consequence of the significant injection of funds and drive provided by the establishment of the Millennium Development Goals back in the year 2000, child mortality has substantially decreased in the past decade, dropping by >20% from the estimated 9.6 million deaths in 2000 to circa 7.6 million deaths in 2010 [1]. This decreasing tendency has been confirmed in all areas of the world, with the greatest advances in Northern Africa, Eastern and Western Asia and Latin America, although reduction of child mortality has been rather modest in Sub-Saharan Africa. Neonatal deaths (those occurring in the first 28 days of life after having been born alive) have also decreased but at a much slower rate, and thus account for an increasing proportion of child mortality (38.2% in 2000; 40.3% in 2010) and must be further reduced to achieve Millennium Development Goal 4 for child survival [2]. Additionally, stillbirths (delivery or expulsion of a foetus >22 weeks of gestation but with no signs of life) also represent a large and disproportionate burden (2.6 million cases annually) but are seldom counted in the official child mortality statistics [3]. The geographic distribution of both stillbirths and neonatal deaths shows major inequities, with 99% of those occurring in low- and middle-income countries [4]. Undeniably, surviving throughout pregnancy, birth and up until the first 28 days of life in many poor settings has become one of the major challenges occurring in life.

Infectious diseases account for at least 27% of the estimated 3.1 million annual deaths occurring in newborns (826 000 deaths annually [1]), and up to half of all stillbirths [3, 4]. The gram-positive bacterium group B streptococcus (GBS; *Streptococcus agalactiae*) stands out among the major microorganisms responsible for perinatal infections on account of its large burden and associated virulence. Estimates from 2012 describe a global incidence of GBS disease in newborns as high as 0.53 episodes/1000 live births (95% confidence interval 0.44–0.62), with an associated case fatality rate of 9.6% [5], and a wide heterogeneity of burden from country to country. Despite the dearth of reliable microbiologically confirmed studies on the incidence and clinical characterization of GBS disease performed in low-income countries, the scarce available data suggest that the incidence and associated mortality is as of today much higher in Africa than for the rest of the world [5, 6].

GBS disease has traditionally been categorized according to the time of onset of symptoms [7]. Early-onset GBS disease (EOGBS), which can be extremely aggressive, is a vertically transmitted infection, and usually occurs in the first 6 days of life (typically during the first hours after delivery), presenting as sepsis (80–95%), pneumonia (10–15%) or meningitis (5–10%), or more rarely joint and bone involvement [8, 9]. Late-onset GBS disease (LOGBS) can occur anytime between the end of the first week and 3 months of life, has a more insidious presentation, often includes meningitis and is usually community-acquired, although it can also be transmitted from the mother through breastfeeding [10]. Recent estimates suggest that the incidence and associated case fatality rate of EOGBS would double that of LOGBS [5], but the latter is associated with a high incidence of long-term neurological sequelae [8]. Vertical transmission of GBS to the foetus from a colonized mother primarily occurs after the onset of labour or rupture of the membranes [11]. Thus, the prevalence of maternal gastro-intestinal and/or genital-tract carriage during the period closely related to the delivery has been shown to determine the risk of vertical transmission and subsequent early-onset neonatal infection [12], with ~50% of the children born of colonized mothers becoming also colonized, and ~1% developing symtomatology [13]. A systematic review assessing different studies in Europe showed that GBS vaginal colonization rates ranged from 6.5 to 36%, with one-third of studies reporting rates of ≥20% [14], and it is generally agreed that 20–30% of all pregnant women are colonized globally [13]. Colonization rates in developing countries have been much less studied, but some data from Africa have suggested that the prevalence of maternal carriage of GBS there is similar to that reported in the USA or Europe, where GBS remains the leading infectious cause of morbidity and mortality among newborns [15]. In this continent, studies from Malawi [16, 17], Kenya, Zimbabwe, Mozambique and South Africa [15, 18] indisputably confirm that GBS remains a significant—although highly underestimated—cause of neonatal sepsis and meningitis [19].

In Western countries, the identification of maternal carriers has allowed the adoption of prophylactic antibiotic schemes that have played a major role in the reduction of the incidence of neonatal invasive infections. In the 1980s, the effectiveness of
intrapartum antibiotic prophylaxis in preventing neonatal GBS disease was described [20], and confirmed in a meta-analysis of five randomized controlled trials [21]. In the 1990s, the widespread adoption of intrapartum antibiotic prophylaxis in many countries led to a reduction in neonatal GBS disease of between 50 and 80% [22]. The Centers for Disease Control and Prevention of the USA have recently reissued updated recommendations for the prevention of perinatal group B streptococcal disease [23]. These include the establishment of universal culture-based screening (using vaginal and/or recto-vaginal samples [24]) of all pregnant women at 35–37 weeks’ gestation to optimize the identification of colonized women who should receive intrapartum antibiotic prophylaxis. The effectiveness of such prophylactic schemes has been estimated to be ~86–89% in terms of preventing vertical transmission [25]. Women whose culture results are unknown or who go into labour before swabs being collected should be given intrapartum antibiotics according to the presence of obstetric risk factors for neonatal sepsis (delivery <37 weeks gestation, rupture of membranes for ≥18 h or intrapartum temperature of ≥38°C). Importantly, while the administration of antibiotics for at least 4 h before delivery has been shown to be highly effective in the prevention of EOGBS [23], no effect has been proven in the reduction of LOGBS [5, 22, 26].

Nevertheless, neither screening nor prophylactic antibiotic schemes have been routinely adopted or implemented in the majority of health posts, maternity units or hospitals in developing countries, or even in many middle-income ones. Microbiology facilities are scarce or simply non-existent in most poor settings, and although rapid diagnostic tests for GBS carriage exist, their accuracy remains debatable and they have never been adequately validated in routine practice [27]. Introduction of prophylactic schemes for all high-risk pregnancies, even in the absence of prior screening, has been shown cost-effective [28], and could bypass the dearth of systematic screening practices in many of these resource-constrained countries, but its practical implementation in such settings remains challenging, particularly because most deliveries occur at home or are simply not attended by skilled personnel [29]. Indeed, identifying high-risk mothers and administering the intravenous intrapartum antibiotics they would require following current recommendations, is not as straightforward as may appear from a developed country perspective, and is bound to be problematic in settings where human and technical resources are notably short. Moreover, although GBS remain highly or even fully sensitive to penicillin with low minimum inhibitory concentration [30], emerging resistance to beta-lactams or macrolide antibiotics may further threaten the adequacy of this strategy in the long-term [23]. Additionally, intrapartum prophylaxis as a strategy may only be a partly satisfying solution, as, even if applied perfectly, would fail to solve the problem of LOGBS [22].

So what can be done to diminish the enormous, albeit hidden, toll that GBS disease is taking in newborns from developing countries? As usually occurs with infectious diseases, vaccines are the most cost-effective of all potential preventive strategies [31]. Vertical transmission could thus be theoretically solved with vertical vaccination with an effective and durable GBS vaccine. Importantly, and besides pathology caused in the foetus or newborn, GBS is known to cause preterm delivery, puerperal sepsis [32], or even severe disease in older adults [33, 34], multiplying the potential impact that an effective GBS vaccine could have. Astonishingly, GBS vaccines have been entirely neglected in the Global Vaccine Action Plan [35, 36], the product of the Decade of Vaccines Collaboration, an unprecedented effort that brought together development, health and immunization experts, stakeholders and funders, and which set up the road map for vaccine research, development and innovation for the upcoming decade. Despite this surprising oversight, it seems evident that an effective and durable GBS vaccine could be the next game changer for newborn health.

When thinking of GBS vaccines, it is key to agree which would be the ideal primary population targeted for immunization. As opposed to other illnesses in which vaccination of young infants confers protection throughout childhood, the limited ability of the neonatal immune system to generate protective antibody responses [9], and the restricted window of opportunity in GBS disease (most cases developing in the first hours or days after delivery, and infant disease seldom occurring after the third month of life), renders it pointless to attempt to vaccinate infants. By vaccinating women of childbearing age, however, one could decrease or prevent maternal infection and colonization with GBS strains included in the vaccine, and thus significantly alter the risk of vertical transmission, reduce maternal GBS disease (chorioamnionitis, urinary tract infections or even asymptomatic bacteriuria) that are per se risk factors for preterm delivery and/or neonatal disease, and also protect the foetus through the placental transfer of specific GBS antibodies [30], not only reducing EOGBS but critically also protecting the newborn beyond the risk period for LOGBS [9]. Importantly, such a strategy could also have a significant impact on foetal deaths and stillbirths [37], for which intrapartum antibiotics have little or no efficacy. Moreover, targeting women during antenatal consultations, one of the few universal platforms of contact between populations and the health system, which still retains a high coverage throughout the developing world, could allow the protection of mothers and their offspring irrespective of the place they choose to deliver, bypassing another
INSURMONTABLE OBSTACLE FOR THE PROTECTION OF THE NEWBORN. The precise timing of immunization during pregnancy is also important, particularly if protection needs to be extended from ‘intratrueto’ beyond birth. Indeed, antibody placental transport is minimal before week 34, and potential impact on \( \text{LOGBS} \) would be maximized only if pregnant women were to receive vaccines between week 28 and 32, to allow for a robust immune IgG response and an optimal transfer of antibodies when the placental transport is more efficient [9]. Clinical development of such a vaccine candidate should also clearly define the ideal target product profile. Indeed, such a vaccine would primarily need to have an impeccable safety profile, precisely on account of the ethically challenging need to test and use them in pregnant women [9]. It should ideally require a single dose, be highly immunogenic and not interfere with other pregnancy immunizations already in place, such as the administration of tetanus toxoid or anti-influenza vaccines. It should also be compatible with the concomitant use of drugs commonly used during pregnancy, particularly in the developing world, such as antiretrovirals for the prevention of mother-to-child transmission of human immunodeficiency virus (HIV), or antimalarials for intermittent preventive treatment during pregnancy. Importantly, and as a result of the dramatic increase in \( \text{GBS} \) disease among non-pregnant adults, such a vaccine could also benefit other population groups besides newborns [38].

\( \text{GBS} \) neonatal disease presents, however, certain advantages that make prospects for the development of a \( \text{GBS} \) vaccine more encouraging than for other diseases. Contrary to what occurs with other streptococci infections [39], \( \text{GBS} \) serotype distribution seems to be homogenous across regions globally and has suffered no variation in the past 3 decades [5]. Of the 10 described serotypes causing \( \text{GBS} \) disease [8], capsular polysaccharide type \( \text{III} \) is the major culprit for \( \text{GBS} \) disease, causing close to half of all global cases, closely followed by serotype \( \text{Ia} \) [5]. A pentavalent conjugate vaccine including serotypes \( \text{Ia, Ib, II, III and V} \) could thus prevent >85% of the global and 98% of the African \( \text{GBS} \) neonatal disease [5]. Moreover, and also critical to vaccine development, immune correlates of protection to \( \text{GBS} \) have been proposed from case-control studies of natural infection and thus could be used as surrogates of protection in vaccinated individuals [38, 40]. Replacing morbidity or mortality endpoints in \( \text{GBS} \) vaccine trials by serological ones could drastically reduce their costs and required sample size, critically simplifying the clinical development of such a vaccine, and thus accelerating its future availability.

Further advantages of preventing \( \text{GBS} \) disease by means of maternal immunization would include eliminating the need for \( \text{GBS} \) screening and intrapartum antibiotic therapy. This would surely relieve the understaffed and overstretched health systems in developing countries and reduce the potential side effects of antibiotics such as penicillin anaphylaxis, the incidence of which is not negligible [23]. Additionally, little is known of the impact of the HIV/AIDS pandemic that is devastating sub-Saharan African countries in the risk of transmission and vulnerability to \( \text{GBS} \). Studies have suggested that HIV may boost the risk of bacterial carriage of \( \text{GBS} \) and its vertical transmission, increasing the incidence and possibly also the severity of \( \text{GBS} \)-related neonatal disease, particularly cases of \( \text{LOGBS} \) [5, 41]. An effective vaccine that could protect children born of HIV infected mothers could therefore play even a greater role in areas where HIV is highly prevalent.

A new impetus for \( \text{GBS} \) vaccine development is expunging 4 decades of frustrated efforts in research and development without a significant reward [13, 38, 42]. Initial \( \text{GBS} \) vaccine candidates based on unconjugated capsular polysaccharide-specific antibodies of \( \text{GBS} \) [43] have now been replaced by more successful conjugate vaccines, shown in different clinical trials to be well tolerated and safe when administered during pregnancy, and capable of inducing robust and durable immune responses in the newborn. Efforts have initially focussed on a monovalent vaccine candidates targeting the capsular serotype \( \text{III} \) [44], responsible for over one-third of \( \text{EOGBS} \) and almost two-thirds of \( \text{LOGBS} \) [5, 38], but trivalent conjugate vaccines including three common serotypes (\( \text{Ia, Ib and III} \)) have also been developed, and are currently being tested in phase I and II trials [45]. Importantly, animal studies have compellingly reaffirmed the safety profile of such conjugate vaccine candidates by demonstrating no teratogenic effects on the foetus [46]. Recent advances in understanding the molecular basis of \( \text{GBS} \) virulence, and the description of specific surface proteins present on all bacterial serotypes, will also contribute substantially to the design of better vaccine candidates [47].

The rapid decline of neonatal \( \text{GBS} \) disease in those places that can afford to implement routine screening and prophylaxis, contrasts with the devastating burden that this microorganism still carries in the developing world. Such prevailing inequities must urgently be addressed, and the development of an effective \( \text{GBS} \) vaccine will surely represent a cutting-edge achievement and a public health triumph. In the meantime, estimates of its real hidden burden must be improved worldwide, particularly in low-income countries; diagnostic methods must be simplified and adapted to the reality of the developing world, and intrapartum prophylactic practices strengthened and encouraged until a vaccine is available and implemented. Only then may we be able to start correcting \( \text{GBS} \)’s neglect and unacceptable impact.
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