

Preventing invasive Group B *Streptococcus* (GBS) disease in South African infants: Time for change



Streptococcus agalactiae is an encapsulated Gram-positive coccus that colonises the gastrointestinal and genitourinary tracts. This organism belongs exclusively to Group B in Lancefield's grouping of *Streptococcus* species and therefore is referred to as Group B *Streptococcus* (GBS). Of the ten known serotypes, serotypes Ia and III account for most disease. The greatest burden of invasive GBS disease is seen in infants <3 months of age, although GBS can cause disease in adults and pregnant women. Disease manifesting in the first 6 days of life is referred to as early-onset disease (EOD), whereas late-onset disease (LOD) manifests from day 7 - 89 of life.

Approximately 10 - 40% of pregnant women are colonised, rectally and/or vaginally, with GBS. About 30 - 70% of newborns become colonised with GBS *in utero* or during delivery, and invasive disease occurs in 1 - 3% (probably from aspiration of infected amniotic fluid or genital secretions).^[1] Most EOD (>90%) manifests at birth, with signs of respiratory distress or sepsis. Furthermore, there is a strong association between GBS disease and stillbirth.^[2] In contrast, LOD occurs through horizontal transmission via the faecal-oral route (the mother is usually the source), through infected breastmilk, or rarely, through nosocomial spread. These infants may develop sepsis, meningitis (~50%), septic arthritis, osteomyelitis or cellulitis.

The global incidence (per 1 000 live births) of invasive GBS disease in infants <90 days of age is estimated to be 0.53 (95% confidence interval (CI) 0.44 - 0.62) with a case fatality ratio of 9.6%.^[3] In South Africa (SA), the high incidence rate has remained largely unchanged at 2 - 3 per 1 000 live births over the last two and half decades,^[4-7] although it is reportedly lower in the Western Cape (0.67 per 1 000 live births).^[8] Of concern, the high incidence is also associated with a high case fatality ratio (13 - 18%) and there is significant neurological impairment among survivors, especially in those with meningitis (24%).^[7]

Worldwide, the highest incidence of invasive GBS disease is reported in SA;^[9] this is likely to contribute to the high neonatal mortality rate and our subsequent failure to reach the targeted goal of reducing under-five childhood mortality (Millennium Development Goal 4). Trends in the incidence of invasive GBS disease in Soweto from 1997 to 2013 have highlighted that

suboptimal implementation of intrapartum antibiotic prophylaxis (IAP) to women identified to be at risk of having infants with EOD, coupled with maternal HIV infection being associated with a two-to-five-fold greater risk of invasive GBS disease in infants, has contributed to the country persistently reporting the high rates of invasive GBS disease.^[6,7] The increased susceptibility to invasive GBS disease in infants born to HIV-infected women is thought to be due to lower maternal protective GBS capsular antibody concentrations and the inefficient transplacental transfer thereof.^[10]

In the USA, the incidence of EOD has declined significantly (>80%) since the early 1990s through effective execution of secondary preventative strategies, i.e. antibiotics administered intravenously 4 hours before delivery to GBS-colonised women who were screened at 35 - 37 weeks' gestation.^[1] This universal screening approach (as recommended by the Centers for Disease Control (CDC)) cannot be readily implemented in most low-to-middle-income countries, where a large proportion of deliveries occur outside health facilities, although this is not the case in SA. In addition, the high cost of screening pregnant women, providing IAP and creating the necessary infrastructure that enables the administration of intravenous IAP at least 4 hours prior to delivery has hampered preventive efforts in low-to-middle-income countries. Furthermore, the CDC recommendation has limitations such as false-negative cultures in colonised pregnant

women, failure to institute IAP for sudden deliveries, the risk of penicillin resistance and the limited effect of IAP on preventing preterm delivery, stillbirths and LOD.^[1]

Currently, most low-to-middle-income countries, including SA and some European countries, practise the less successful risk-based approach to prevent invasive disease, i.e. IAP is only provided to mothers in labour with risk factors such as maternal fever, prolonged rupture of membranes or prematurity. This strategy is also failing in low-to-middle-income countries because risk factors do not identify all women who are at risk of transmitting GBS. Furthermore, healthcare workers may fail to recognise risk factors, and may not provide IAP in busy obstetric units. Other proposed preventive strategies, including chlorhexidine vaginal wipes, do not prevent EOD. Rapid molecular diagnostic tests to detect maternal GBS colonisation during labour is promising but costly, and the struggle for most low-to-middle-income countries remains the timely and effective administration of IAP, thus rendering molecular tests futile in these settings.

The above limitations, as well as the failure to implement these strategies in low-to-middle-income countries, calls for a paradigm shift regarding the future prevention of invasive GBS disease. Vaccinating pregnant women in the second trimester of pregnancy could result in an increase in maternal antibody levels, which in turn may be transferred to the fetus in the last trimester. This strategy

Table 1. Antibiotic therapy in infants with invasive GBS disease

Clinical presentation	Penicillin G (units/kg per day)*	Ampicillin (mg/kg per day)	Duration of antibiotics (days)
Bacteraemia without a focus	75 000 - 150 000	100 - 200	10 - 14
Sepsis	75 000 - 150 000	100 - 200	10 - 14
Pneumonia	75 000 - 150 000	100 - 200	10 - 14
Urinary tract infection	75 000 - 150 000	100 - 200	10 - 14
Cellulitis	75 000 - 150 000	100 - 200	10 - 14
Septic arthritis	75 000 - 150 000	100 - 200	14 - 21
Osteomyelitis	75 000 - 150 000	100 - 200	21 - 28
Meningitis	450 000 - 500 000	200 - 300	21

*The recommended dosing interval for Penicillin G is 8 or 12 hourly, except for meningitis, for which the recommendation is 6 hourly. For early-onset meningitis, the dose of Penicillin G is 250 000 - 450 000 units/kg per day divided every 8 hours for the first week of life. The recommended dosing interval for ampicillin is 6 hourly, except during the first week of life where the recommendation is 8 or 12 hourly. Gentamicin 5 mg/kg/day for 5 days can be used for synergy in cases of meningitis.

has been successfully used for the prevention of tetanus, influenza and pertussis in infants.^[11] A trivalent GBS polysaccharide-protein conjugate vaccine (against serotypes Ia, Ib and III) has completed phase-II evaluation among pregnant women and has the potential to prevent 70 - 80% of all invasive GBS disease. Maternal GBS vaccination is potentially cost effective and easy to implement in low-to-middle-income settings; furthermore, vaccination during pregnancy is becoming more acceptable to the public.

For those infants who require treatment for invasive GBS disease, penicillin remains the drug of choice (Table 1). There is no role for the use of immunoglobulins or dexamethasone in infants with meningitis. Recurrence of invasive GBS disease may occur in 1 - 2% of infants despite adequate treatment.

In conclusion, GBS is the most common cause of neonatal sepsis and meningitis. SA has a very high incidence of invasive GBS disease and the provision of IAP is practically difficult; maternal GBS vaccination is a promising strategy.

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