Case study: Prevention of vertical transmission of bacterial neonatal sepsis: The example of Group B streptococcus

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Description
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 last decade, dropping by over a third from the 9.6 estimated million deaths in 2000 to circa 6.3 million deaths in 2013[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; 44% in 2013) and must be further reduced to achieve Millennium Development Goal (MDG) 4 for child survival[2]. Additionally, stillbirths (delivery or expulsion of a foetus older than 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 accounted for 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 23% of the estimated 2.76 million annual deaths occurring in newborns (626,000 deaths annually[1]), and up to half of all stillbirths[3, 4]. The gram-positive bacterium **Group B streptococcus (GBS; Streptococcus agalactiae)** stands out amongst 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 livebirths (95%CI 0.44–0.62), with an associated case fatality rate (CFR) of 9.6%[5], and a wide heterogeneity of burden from country to country. In spite of 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].

Vertical transmission of GBS to the foetus from a colonized mother primarily occurs after the onset of labour or rupture of the membranes[7]. 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[8], with approximately 50% of the children born of colonized mothers becoming also colonized, and around 1% developing symptomatology[9]. It is generally agreed that 20-30% of all pregnant women are colonized globally[9].
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. The Centers for Disease Control and Prevention (CDC) of the United States have recently reissued updated recommendations for the prevention of perinatal Group B Streptococcal disease[10]. These include the establishment of universal culture-based screening (using vaginal and/or recto-vaginal samples[11]) 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 around 86-89% in terms of preventing vertical transmission[12].

Nevertheless, neither screening, nor prophylactic antibiotic schemes have been routinely adopted or implemented in the majority of health posts, maternities or hospitals in developing countries, or even in many middle-income ones. This highlights the unpreparedness of middle and low-income countries in terms of identifying GBS as a major public health problem, and the lack of strategies put in place to prevent its vertical transmission to the newborn in such settings. So what can we do to improve the situation in these settings?

**Learning objectives**

1. To discuss the knowledge gaps faced by MoH at the national level in terms of the evaluation of GBS associated burden, morbidity and mortality
2. To discuss the practicalities and challenges of diagnosing and preventing GBS disease in the developing world and the necessary strategies that could be put in place
3. To discuss the need for a vaccine

**Readings**

- Excerpts tables/algorithms from the CDC 2010 reviewed guidelines
Bibliography


Prevention of Perinatal Group B Streptococcal Disease
Revised Guidelines from CDC, 2010

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/conted.html
<table>
<thead>
<tr>
<th>Intrapartum GBS prophylaxis indicated</th>
<th>Intrapartum GBS prophylaxis not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Previous infant with invasive GBS disease</td>
<td>• Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
</tr>
<tr>
<td>• GBS bacteriuria during any trimester of the current pregnancy*</td>
<td>• GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)</td>
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<tr>
<td>• Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy*</td>
<td>• Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors</td>
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| • Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:  
  - Delivery at <37 weeks' gestation*  
  - Amniotic membrane rupture ≥18 hours  
  - Intrapartum temperature ≥100.4°F (≥38.0°C)*  
  - Intrapartum NAAT** positive for GBS | • Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age |

Abbreviation: NAAT = Nucleic acid amplification tests

* Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes.

† Optimal timing for prenatal GBS screening is at 35–37 weeks' gestation.

‡ Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 5 and 6.

* If amniocentesis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

** NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture at ≥18 hours, or temperature ≥100.4°F [≥38.0°C]) is present, then intrapartum antibiotic prophylaxis is indicated.
The following are key components of the screening strategy:

- Women with GBS isolated from the urine at any time during the current pregnancy or who had a previous infant with invasive GBS disease should receive intrapartum antibiotic prophylaxis and do not need third trimester screening for GBS colonization (AII). Women with symptomatic or asymptomatic GBS urinary tract infection detected during pregnancy should be treated according to current standards of care for urinary tract infection during pregnancy and should receive intrapartum antibiotic prophylaxis to prevent early-onset GBS disease (AIII).

- All other pregnant women should be screened at 35–37 weeks’ gestation for vaginal and rectal GBS colonization (AII).

- At the time of labor or rupture of membranes, intrapartum antibiotic prophylaxis should be given to all pregnant women who tested positive for GBS colonization (AII), except in the instance of cesarean delivery performed before onset of labor on a woman with intact amniotic membranes.

- For circumstances in which screening results are not available at the time of labor and delivery, intrapartum antibiotic prophylaxis should be given to women who are <37 weeks and 0 days’ gestation, have a duration of membrane rupture ≥18 hours, or have a temperature of ≥100.4°F (≥38.0°C) (AII).

- In the absence of GBS urinary tract infection, antimicrobial agents should not be used before the intrapartum period to eradicate GBS genitorectal colonization, because such treat-
ment is not effective in eliminating carriage or preventing neonatal disease and can cause adverse consequences (DI).

- Intrapartum antibiotic prophylaxis to prevent early-onset GBS disease is not recommended as a routine practice for cesarean deliveries performed before labor onset on women with intact amniotic membranes, regardless of the GBS colonization status of the woman or the gestational age of the pregnancy (CIII). The use of perioperative prophylactic antibiotics to prevent infectious complications of cesarean delivery should not be altered or affected by GBS status. Women expected to undergo cesarean deliveries should undergo routine vaginal and rectal screening for GBS at 35–37 weeks’ gestation because onset of labor or rupture of membranes can occur before the planned cesarean delivery, and under those circumstances GBS-colonized women should receive intrapartum antibiotic prophylaxis (AII).

- Health-care providers should inform women of their GBS screening test result and the recommended interventions (BIII).

The following key changes were made from the 2002 guidelines:

- Guidance regarding cesarean deliveries performed before onset of labor on a woman with intact amniotic membranes is clarified as applying to cesarean deliveries performed at any gestational age (CIII).

- In settings in which NAAT for GBS is available, obstetric providers can choose to perform intrapartum testing of vaginal-rectal samples from women with unknown GBS colonization status and no intrapartum risk factors (temperature of ≥100.4°F [≥38.0°C] or rupture of amniotic membranes ≥18 hours) at the time of testing and who are delivering at term (CII). If an intrapartum risk factor subsequently develops, antibiotic prophylaxis should be administered regardless of the intrapartum testing results (AIII).

- Women with positive intrapartum NAAT results for GBS should receive antibiotic prophylaxis (AII). NAAT testing is optional and might not be available in all settings.
**FIGURE 5. Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm* labor (PTL)**

1. Patient admitted with signs and symptoms of preterm labor
   - Obtain vaginal-rectal swab for GBS culture† and start GBS prophylaxis§
   - Patient entering true labor?¶
     - Yes
       - Continue GBS prophylaxis until delivery**
     - No
       - Discontinue GBS prophylaxis
   - Obtain GBS culture results
     - Positive
       - GBS prophylaxis at onset of true labor
     - Not available prior to labor onset and patient still preterm
     - Negative
       - No GBS prophylaxis at onset of true labor;†† repeat vaginal-rectal culture if patient reaches 35–37 weeks’ gestation and has not yet delivered§§

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* At <37 weeks and 0 days’ gestation.
† If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.
§ See Figure 8 for recommended antibiotic regimens.
¶ Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.
** If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis.
†† Unless subsequent GBS culture prior to delivery is positive.
§§ A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time.
FIGURE 6. Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm* premature rupture of membranes (pPROM)

Obtain vaginal-rectal swab for GBS culture† and start antibiotics for latency§ or GBS prophylaxis¶

Patient entering labor?

Yes

Continue antibiotics until delivery

No

Continue antibiotics per standard of care if receiving for latency or continue antibiotics for 48 hours** if receiving for GBS prophylaxis

Obtain GBS culture results

Positive

GBS prophylaxis at onset of true labor

Not available prior to labor onset

Negative

No GBS prophylaxis at onset of true labor;†† repeat vaginal-rectal culture if patient reaches 35–37 weeks' gestation and has not yet delivered†‡

* At <37 weeks and 0 days' gestation.
† If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.
§ Antibiotics given for latency in the setting of pPROM that include ampicillin 2 g intravenously (IV) once, followed by 1 g IV every 6 hours for at least 48 hours are adequate for GBS prophylaxis. If other regimens are used, GBS prophylaxis should be initiated in addition.
¶ See Figure 8 for recommended antibiotic regimens.
** GBS prophylaxis should be discontinued at 48 hours for women with pPROM who are not in labor. If results from a GBS screen performed on admission become available during the 48-hour period and are negative, GBS prophylaxis should be discontinued at that time.
†† Unless subsequent GBS culture prior to delivery is positive.
†‡ A negative GBS screen is considered valid for 5 weeks. If a patient with pPROM is entering labor and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time.
BOX 2. Procedures for processing clinical specimens for culture of group B Streptococcus (GBS) (see Figure 7)

- Remove swab(s) from transport medium. Inoculate swab(s) into a recommended selective broth medium, such as Todd-Hewitt broth supplemented with either gentamicin (8 µg/ml) and nalidixic acid (15 µg/ml) [TransVag broth], or with colistin (10 µg/ml) and nalidixic acid (15 µg/ml) [Lim broth]. TransVag broth may be supplemented with 9% defibrinated sheep blood to increase the recovery of GBS. As an alternative, swabs may be inoculated into selective enrichment broth that incorporates chromogenic pigments for the detection of beta-hemolytic GBS using color detection. Examples of appropriate commercially available options include StrepB carrot broth or Granada Biphagic broth.
- Incubate inoculated selective broth for 18–24 hours at 35°–37°C in ambient air or 5% CO2.
- For TransVag or Lim broth, subculture the incubated broth to an appropriate agar plate (e.g., tryptic soy agar with 5% defibrinated sheep blood, Colombia agar with colistin and nalidixic acid, or a commercial chromogenic agar). For chromogenic broth, monitor for color change indicative of GBS per product instructions. GBS detection using chromogenic broth is possible only for beta-hemolytic strains, and therefore all broths that are negative (i.e., no color detection) should be subcultured to a sheep blood agar plate with 5% sheep blood or tested for GBS antigen or by DNA probe to further identify nonhemolytic GBS strains.
- Inspect agar plates and identify organisms suggestive of GBS (e.g., narrow zone of beta hemolysis on blood agar, gram-positive cocci, catalase-negative, and/or hippurate-positive). Note that hemolysis can be difficult to observe, so typical colonies without hemolysis should also be further tested. If GBS is not identified after incubation for 18–24 hours, then reincubate plates overnight and examine for suspected GBS colonies.
- Various streptococcal grouping latex agglutination tests or other tests for GBS detection (e.g., GBS Accuprobe) may be used for specific identification, or the CAMP test can be employed for presumptive identification.
- Optional direct broth testing:** Detection of GBS can be determined directly from broth media using latex agglutination, probes or nucleic acid amplification tests (NAAT) such as PCR.

** Before the inoculation step, laboratories may choose to roll the vaginal-rectal swab(s) on a blood agar plate with or without colistin and nalidixic acid or commercially available chromogenic agar (appropriate recommendations include chromID Strept B which might detect both hemolytic and nonhemolytic GBS) or Granada Agar (which detects hemolytic GBS). Source: Tazi A, Raynouard A, Proust H, Dartez F, Raymond J, Pouyet C. Comparative evaluation of chromogenic medium and Granada media for the detection of group B Streptococcus from vaginal samples of pregnant women. J Microbiol Methods 2008;73:265–5. This approach should be taken only in addition to, and not instead of, inoculation into selective broth. The directly inoculated blood agar plate should be streaked for isolation, incubated at 35°–37°C in ambient air or 5% CO2 for 18–24 hours and inspected for organisms suggestive of GBS as described above. If suspected colonies are confirmed as GBS, the selective broth can be discarded, thus shortening the time to obtaining culture results. The directly inoculated chromogenic agar should be streaked for isolation and incubated at 35°–37°C for 18–24 hours. Hemolytic GBS isolates are identified by colored colonies as directed by specific manufacturers’ instructions, and selective broth can be discarded if GBS positive.

** Source: Fenton L, Harper MH. Evaluation of colistin and nalidixic acid in Todd-Hewitt broth for selective isolation of group B streptococci. J Clin Microbiol 1979;9:167–9. Although Trans-Vag medium often is available without sheep blood, direct comparison of medium with and without sheep blood has shown higher yield when blood is added. Lim broth also might benefit from the addition of sheep blood, although the improvement in yield is smaller, and sufficient data are not yet available to support a recommendation.


FIGURE 8. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease*

Patient allergic to penicillin?

No

Penicillin G, 5 million units IV initial dose, then 2.5–3.0 million units every 4 hrs until delivery
or
Ampicillin, 2 g IV initial dose, then 1 g IV every 4 hrs until delivery

Yes

Patient with a history of any of the following after receiving penicillin or a cephalosporin?§
- Anaphylaxis
- Angioedema
- Respiratory distress
- Urticaria

No

Cefazolin, 2g IV initial dose, then 1 g IV every 8 hrs until delivery

Isolate susceptible to clindamycin and erythromycin?**?

No

Vancomycin, 1 g IV every 12 hrs until delivery

Yes

Clindamycin, 900 mg IV every 8 hrs until delivery

Abbreviation: IV = intravenously.

* Broader spectrum agents, including an agent active against GBS, might be necessary for treatment of chorioamnionitis.
† Doses ranging from 2.5 to 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. The choice of dose within that range should be guided by which formulations of penicillin G are readily available to reduce the need for pharmacies to specially prepare doses.
§ Penicillin-allergic patients with a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillin or a cephalosporin are considered to be at high risk for anaphylaxis and should not receive penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. For penicillin-allergic patients who do not have a history of those reactions, cefazolin is the preferred agent because pharmacologic data suggest it achieves effective intraamniotic concentrations. Vancomycin and clindamycin should be reserved for penicillin-allergic women at high risk for anaphylaxis.
¶ If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing (Box 3) should be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If no susceptibility testing is performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis.
** Resistance to erythromycin is often but not always associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin, resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be used for GBS intrapartum prophylaxis instead of vancomycin.
FIGURE 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns

- **Signs of neonatal sepsis?**
  - Yes: Full diagnostic evaluation* Antibiotic therapy†
  - No: Maternal chorioamnionitis?
    - Yes: Limited evaluation§ Antibiotic therapy†
    - No: GBS prophylaxis indicated for mother??
      - Yes: Routine clinical care††
        - Yes: Mother received intravenous penicillin, ampicillin, or cefazolin for ≥4 hours before delivery?
          - Yes: Observation for ≥48 hours†††
          - No: Observation for ≥48 hours†††
        - No: Observation for ≥48 hours†††
      - No: ≥37 weeks and duration of membrane rupture <18 hours?
        - Yes: Observation for ≥48 hours†††
        - No: Either <37 weeks or duration of membrane rupture ≥18 hours?
          - Yes: Limited evaluation§ Observation for ≥48 hours††
          - No: Routine clinical care††

* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).
† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including Escherichia coli and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.
§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.
† Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6-12 hours of life).
?? See Table 3 for indications for intrapartum GBS prophylaxis.
†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.
††† If ≥37 weeks’ gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.
†† Some experts recommend a CBC with differential and platelets at age 6-12 hours.