

THE BURDEN OF INVASIVE NEONATAL GROUP B STREPTOCOCCAL (GBS) DISEASE IN THAILAND AND THE PHILIPPINES

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Abstract. Group B Streptococcus (GBS) is a leading cause of meningitis and sepsis in infancy, but burden of disease data are scarce for Asia. We performed two hospital-based, prospective, descriptive, observational studies using similar protocols in the Philippines and Thailand to evaluate neonatal GBS disease epidemiology. Infants aged <90 days with a GBS-positive culture from normally sterile sites using routine microbiological standards were eligible for inclusion. Awareness of GBS symptoms was raised by informing all women at delivery and follow-up for 90 days post-delivery. Infections were classified as early onset disease (EOD) if they occurred within 6 days of birth and late onset disease (LOD) if they occurred 7-89 days after birth. Due to ethical requirements in Thailand, consent for study participation, including periodic post-discharge telephone calls, was obtained at delivery. Parents in the Philippines gave consent for study participation at case identification. The clinical outcomes of GBS infections were recorded. During the 6-month study period, two cases (one fatal) of EOD were identified among 8,409 live births at the study hospitals in Thailand and three cases (two fatal) of EOD were identified among 11,768 live births reported at the study hospitals in the Philippines. Incidence rates per 1,000 live births were 0.2 (95% CI: 0.0-0.8) and 0.3 (95% CI: 0.1-0.8) in Thailand and the Philippines, respectively. There were no cases of reported LOD. The low number of cases precluded analysis of serotype distribution and case fatality rates. Large epidemiological studies are needed to better understand the factors influencing GBS infection incidence in Asia.

Keywords: Group B Streptococcus (GBS), incidence, neonatal sepsis, Thailand, Philippines

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INTRODUCTION

Group B *Streptococcus* (*Streptococcus agalactiae*) or GBS is a leading cause of bacterial infection in neonates and very young infants, with one report estimating the mean global rate at 0.53 per 1,000 live births (Edmond *et al*, 2012). Infection can result in sepsis, pneumonia or meningitis, with serious consequences including death. There are nine capsular serotypes, with five types (Ia, Ib, II, III and V) responsible for 95% of invasive disease (Edmond *et al*, 2012). Infant GBS disease occurs as a continuum over the first 3 months of life, but has often been categorized as early-onset disease (EOD; occurring between birth and 6 days of age) and late-onset (LOD; occurring between 7 and 89 days of age) (Schuchat, 1998; CDC, 2005; Heath and Schuchat, 2007, Matsubara *et al*, 2013). Substantial variation in disease incidence has been reported by geographic region, which may reflect differences in surveillance methods, healthcare access, antibiotic usage or population differences. Further evaluation of factors underlying this variation is complicated as limited data are available from many regions, including Eastern Europe, Latin America and Asia, (Dagnew *et al*, 2012).

The implementation of intrapartum antibiotic prophylaxis (IAP), to mothers with a positive screening culture for rectovaginal colonization with GBS in late pregnancy, has been associated with a dramatic decline (~80%) in EOD incidence in many developed countries (Schrag *et al*, 2000; Van Dyke *et al*, 2009). However, this intervention has had no impact on LOD incidence and the extensive use of intravenous antibiotics at delivery raises concerns about increased antibiotic resistance (Stoll *et al*, 2011; Lamaghi *et al*, 2013). Furthermore, effective implementation

of culture-based screening and IAP is resource intensive and requires sufficient healthcare infrastructure to implement high rates of screening as well as the administration of IAP >4 hours before delivery. Interventions in less developed countries have therefore relied on risk-based screening approaches with IAP administered to women presenting in labor with clinical factors associated with increased GBS disease risk in the infants (*eg*, maternal fever, prolonged rupture of membranes, previous infant with GBS infection). However, risk-based screening has not been associated with substantial declines in disease incidence (Lopez Sastre *et al*, 2005; Schrag *et al*, 2002; 2013; Lamagni *et al*, 2013).

Future interventions include vaccination against GBS with a trivalent candidate currently in phase 2 development (Chen *et al*, 2013). Implementation of current and future interventions would benefit from availability of local epidemiological data regarding disease burden and serotypes. In light of the lack of epidemiological data for many countries in Southeast Asia, we performed two descriptive observational studies using similar study protocols in the Philippines and Thailand to investigate the incidence, serotype distribution and case fatality of GBS among young infants.

MATERIALS AND METHODS

We conducted two hospital-based, prospective, descriptive, observational studies using similar protocols in government funded tertiary referral centers for neonatal care in Thailand and the Philippines. The hospitals that participated in Thailand were the Queen Sirikit National Institute of Child Health and Siriraj Hospital in urban Bangkok, Thailand (com-

bined 14,000-15,000 births per year). In the Philippines, the participating centers (10,000-11,000 births per year) were the Philippine General Hospital, its satellite site at Ospital Ng Maynila both in Manila and the Governor Celestino Gallares Memorial Hospital, a government funded center in rural Bohol, (6,000 births per year), which serves as the main neonatal referral center for 18 towns on the island of Bohol. Nearly all the deliveries in the urban settings (Bangkok and Manila) occurred in hospitals, while approximately 25% of the deliveries in rural Bohol occurred outside hospitals. In-patient hospital stays after normal vaginal delivery were three days in Thailand and one day in the Philippines. Complicated pregnancies and cesarean sections were followed in the hospital for longer periods post-delivery. All study hospitals employed risk-based antenatal screening for GBS. Case identification for both studies occurred over a 6-months period at individual sites between January 2012 and January 2013. The study in Thailand included a 3-month follow-up of all identified infants of which parents consented to follow-up contact.

Inclusion criteria for both studies included the infant being born in the study hospitals in Manila or Bangkok, or within the study area in Bohol, receiving parental informed consent and GBS disease confirmed by a positive GBS culture in an infant aged <90.

Case definition and identification of GBS infection

All study hospitals followed the same routine standard for identification of GBS cases: cultures were routinely performed, prior to the administration of antibiotics, on infants presenting with any of the following signs or symptoms: not appearing well, irritability, lethargy, hypotonia, temperature instability [hyper-

thermia (>38°C) or hypothermia (<36°C)], poor feeding or weak suck, respiratory distress, apnea, cyanotic spells, glucose instability (hypoglycemia or hyperglycemia), feeding intolerance (vomiting, abdominal distension, diarrhea), poor perfusion, hypotension, shock, seizures, jaundice, thrombocytopenia, or signs of disseminated intravascular coagulation. Cultures were obtained from one or more of the following normally sterile sites: blood cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, marrow, joint fluid, suprapubic bladder aspiration or internal body site (eg, lymph node, brain). The microbiological confirmation of GBS adhered to local standards. All centers used automated (BacT/Alert®; Biomerieux, Marcy, l'Étoile, France or BACTEC®, Becton Dickinson, Franklin Lakes, NJ) and selective culture methods. Group B Streptococcus was confirmed using Gram stain, colony morphology, CAMP and Strepex testing. The date of collection of the first GBS-positive sample was considered to be the onset of disease.

Only infants aged <90 days on admission to the hospital were considered to have met the definition of a confirmed GBS case by a positive culture as described above.

Additional clinical data on the disease episode and outcome were collected after GBS case identification, or retrospectively if subjects were already admitted to hospital at study start. All isolates of confirmed GBS cases were kept at -70°C until sent to a reference laboratory (Respiratory and Meningeal Pathogens Research Unit, Bertsham, South Africa) for serotyping using the Strep-B-Latex® rapid latex agglutination test (Slotved *et al*, 2003).

Case ascertainment in Thailand

Fig 1 shows the case ascertainment

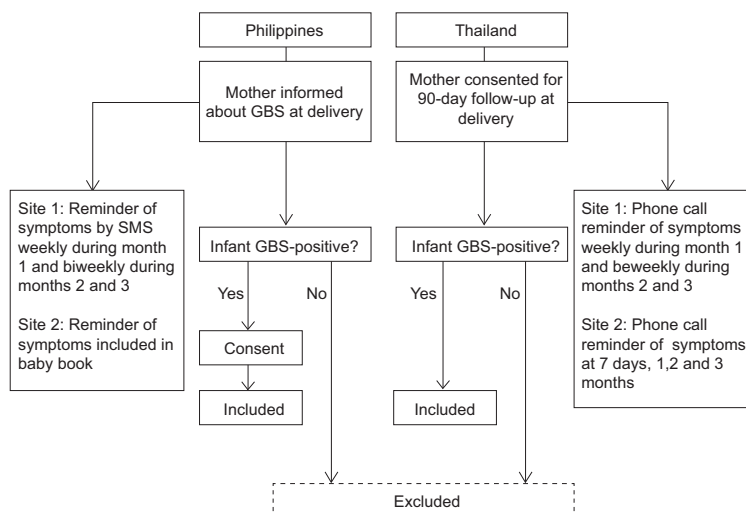


Fig 1—Recruitment and follow-up of subjects in the Philippines and Thailand. Philippines Site1 = Philippine General Hospital and Ospital Ng Maynila; Philippines Site 2 = Governor Celestino Gallares Memorial Hospital; Thailand Site 1 = Siriraj Hospital; Thailand Site 2 = Queen Sirikit National Institute of Child Health.

process. To increase awareness of GBS disease with the intent of increasing case ascertainment, all mothers were informed about the study at delivery. To further facilitate case ascertainment post-discharge, parents were actively reminded about the study and the symptoms of GBS infection by periodic telephone calls for 90 days. Due to ethical requirements, pregnant women in Thailand were asked to consent to the period follow-up calls at the time of delivery when they were first informed about the study. This included consent to participate in the study in case of a GBS positive culture. Therefore, consent at case identification was only necessary, if the woman had not been informed or consented at delivery (*ie*, if the woman delivered in a non-study hospital).

Case ascertainment in the Philippines

Similar to the awareness activities in Thailand, all the mothers at the study

hospitals were informed about the study at delivery. Post-discharge awareness was raised by passive reminders in baby books in rural Bohol, or with active reminders via short SMS messages in Manila. In contrast to Thailand, there was no ethical requirement to obtain consent prior to delivery for these activities; therefore, parents were only approached for consent to participate in the study at the time of GBS infection case identification.

Both study protocols were approved by the appropriate local institutional review boards or ethics

committees. The studies were performed in compliance with good pharmaco-epidemiological practices and local and international regulations.

Statistics

The number of GBS cases by timing of onset of symptoms and serotypes were analyzed descriptively by country and site. The incidence rate was expressed as number per 1,000 live births, and computed overall, by site and country.

$$\{i = \frac{\text{total number of cases admitted from study start to 6 months}}{\text{total number of live births from study start to 6 months}} \times 1,000\}$$

Different denominators for incidence calculation were used for urban and rural settings, due to differences in catchment area and proportions of deliveries occurring outside the hospital. In Bangkok and Manila, the majority of births occur in the hospitals and the denominator was

Table 1
Numbers of eligible live births, enrollment and positive cultures in the Philippines and Thailand.

Site	Philippines		Thailand	
	Manila	Bohol	Bangkok 1	Bangkok 2
Live births	5,970	5,798	3,027	5,382
Consented (eligible) ^a	2 (3)	0 (n/a)	2,022 (3,027)	2,980 (5,382)
Cultures sent	1,283	1,126	n/a	n/a
All positive cultures (GBS)	243 (3)	123 (0)	n/a (1)	n/a (1)

^aOnly mothers of GBS-positive infants were eligible for consent in the Philippines. All mothers seen at delivery were eligible for consent in Thailand. n/a, not available. Manila, Philippine General Hospital and Ospital Ng Maynila; Bohol, Governor Celestino Gallares Memorial Hospital; Bangkok 1, Siriraj Hospital; Bangkok 2, Queen Sirikit National Institute of Child Health.

defined as the total number of live births at the study hospitals. In rural Bohol, the hospital is a neonatal referral center for 18 towns on the island. This, together with a lower proportion of births occurring in hospital in Bohol, meant the denominator was defined as total number of live births in study area, which was extracted from local government statistics. The case fatality ratio (CFR) was expressed as the percentage of confirmed GBS infection cases whose outcome was death. A 95% confidence interval (95%CI) were calculated using the Wilson score method.

RESULTS

Thailand

A total of 8,409 live births occurred at the study hospitals in Thailand during the study period, and 5,002 mothers gave consent to participate via periodic telephone call for 90-days (Table 1). The total number of cultures taken for further investigation was not available. Only two cases of confirmed GBS infection were found, one from each study hospital in Bangkok. The first case occurred in a baby boy, born pre-

term at 33 weeks, who died 14 hours after birth (Table 2), due to infection with GBS serotype III. The second case was a girl born at 35 weeks who had GBS serotype VI infection, from which she recovered and was released from hospital after 10 days. Neither mother had received IAP.

Incidence rates were 0.3 (95% CI: 0.0-1.8) and 0.2 (95% CI: 0.0-1.1) per 1,000 live births, at the Siriraj and Queen Sirikit hospitals, respectively. These gave an overall incidence rate of 0.2 (95% CI: 0.0-0.8) per 1,000 live births for the study hospitals in Thailand. As there may have been differential case ascertainment between mothers who consented to active follow-up and those who did not; incidence calculations were repeated using the denominator of mothers who consented at delivery to study participation and active telephonic follow-up: these incidence rates were higher at 0.5 (95% CI: 0.1-2.8) and 0.3 (95% CI: 0.1-1.9), respectively, with an overall incidence rate for Thailand of 0.4 (95% CI: 0.1-1.5) per 1,000 live births. The overlapping 95% confidence intervals show these two estimates were not significantly different from each other.

Table 2
Reported cases of neonatal GBS disease with confirmation from blood cultures in the Philippines and Thailand.

Site	Philippines*		Thailand	
	Manila	Manila	Bangkok 1	Bangkok 2
Gender	Female	Female	Male	Female
Gestational age at birth	36	37	33	35
Age at onset (in days)	0	0	0	0
Intrapartum antibiotic prophylaxis	No	No	No	Yes
GBS serotype	VI	Ia	III	VI
Outcome	Died	Recovered	Died	Recovered
Length of hospitalization	12 hours	17 days	14 hours	10 days

*No cases identified from Bohol.

Manila, Philippine General Hospital and Ospital Ng Maynila; Bangkok 1, Siriraj Hospital; Bangkok 2, Queen Sirikit National Institute of Child Health.

The Philippines

The total number of live births at the Manila study hospitals and the Bohol catchment area in the Philippines during the study period was 11,768 (Table 1). A total of 2,409 infants aged <3 months presented with clinical symptoms indicative of sepsis for which culture specimens were taken from a normally sterile site. Of these, 366 (15.2%) were culture positive. Of these, three cultures were positive for GBS. All three cases were of EOD in infants from the satellite hospital in Manila, the Ospital ng Maynila Medical Center. The parents of one infant who died with confirmed GBS infection declined to give consent for further data collection and serotyping. The other two babies were female, born at 36 and 37 weeks gestation, and were admitted on the day of birth. Neither mother had received IAP at delivery. One baby died within 12 hours of birth and the other recovered from infection and was released from hospital after 17 days (Table 2). Serotyping of isolates

from both children revealed that the fatal infection was due to GBS serotype VI, while the infant who survived had a GBS Ia infection.

The overall country incidence based on total recorded live births across the study sites in the Philippines was 0.3 (95% CI: 0.1-0.8) per 1,000 live births (Table 3). When calculated with only the 2 enrolled cases the incidence rate was 0.2 (95% CI: 0.1-0.6) per 1,000 live for the Manila sites. The overlapping 95% confidence intervals show the 2 incidences with or without the child rates were not significantly different from each other. No cases of LOD of GBS were detected in Thailand or the Philippines in our study.

DISCUSSION

We performed two observational, hospital-based studies to obtain data on the incidences, case fatality rates and serotype distribution of GBS infection in infants aged <90 days in Thailand and

Table 3
Incidence of neonatal GBS disease per 1,000 live births at the study hospitals or Bohol catchment area.

Site	Philippines*		Thailand	
	Manila	Bohol	Bangkok 1	Bangkok 2
Eligible live births	5,970	5,798	3,027	5,382
Cases	3 ^a	0	1	1
Incidence per site (95% CI)	0.5 (0.2-1.5)	0 (0.0-0.7)	0.3 (0.0-1.8)	0.2 (0.0-1.1)
Incidence per setting (95% CI)	0.5 (0.2-1.5)	0 (0.0-0.7)		0.2 (0.0-0.8)
Incidence per country (95% CI)		0.3 (0.1-0.8)		0.2 (0.0-0.8)

*Incidence rates based on 3 identified cases of GBS disease.

Manila, Philippine General Hospital and Ospital Ng Maynila; Bohol, Governor Celestino Gallares Memorial Hospital; Bangkok 1, Siriraj Hospital; Bangkok 2, Queen Sirikit National Institute of Child Health.

the Philippines, where previous data was scarce. Five confirmed GBS infection cases were detected. The rates of GBS in Thailand and the Philippines were similar: 0.2 (95% CI 0.1-0.8) and 0.3 (95% CI 0.1-0.8) cases per 1,000 live births, respectively. All cases were EOD; no cases were LOD.

These data are consistent with previous data from Thailand and the Philippines, though higher incidence estimates have been reported elsewhere in Asia (Rivera *et al*, 2012). Two previous studies from the Philippines identified a single case of GBS among approximately 1,500 hospital admissions in infants aged <90 days with suspected infection (Gatchalian *et al*, 1999; Quiambao *et al*, 2007), although some high risk groups for GBS (preterm infants) were excluded from the analyses (Quiambao *et al*, 2007). A previous hospital-based study from Bangkok, Thailand, reported an EOD incidence of 0.27 per 1,000 live births in 1996 that fell to 0.10 per 1,000 live births in 2001 (Yossuck *et al*, 2002). Unfortunately, interpretation

of these data are complicated due to lack of clear denominators, incomplete information about laboratory techniques used, IAP implementation as well as potential differences in access to healthcare and GBS diagnosis. The relatively low reported incidence rates in those and our current study may represent a lower population risk, differences in serotype distribution with less pathogenic strains represented or issues with case under ascertainment.

Several factors may have led to inadequate ascertainment of cases in our current studies. We attempted to maximize case ascertainment by increasing disease awareness and the need to return to the hospital given clinical symptoms in the infant. This was facilitated through regular SMS message reminders in the Philippines or telephone calls or messages in Thailand. Successful telephonic follow-up was monitored in Thailand, but approximately half of the enrolled families were lost to follow-up (three consecutive failed phone calls). This may simply represent families

changing contact details without informing the study sites or may mask a trend of population movement in the months after delivery, such as moving to stay with family elsewhere. Such movement could lead to under-estimation of the incidence, especially for LOD cases; none of which were identified in this study.

Despite awareness activities emphasizing the importance of returning to the study hospitals with sick infants, it is possible GBS cases may have presented to other health facilities, especially if families lived in districts outside the immediate study hospital catchment area. In the Manila study hospitals, approximately 10%-20% of births in the study cohort were mothers living in adjacent city districts with alternative healthcare facilities available.

Three of the four EOD cases identified occurred in preterm deliveries and the fourth case was born at 37 weeks gestation. Preterm infants are at a higher risk of developing GBS infection (CDC, 2010). The ascertainment of cases in the preterm gestational age group, more than among term infants, may be due to stricter care and closer observation for preterm infants in the study hospitals.

Approximately 90% of EOD cases of GBS infection present within the first 24 hours of life (CDC, 2010). The proportion of births occurring in the hospital and the timing of maternal/child discharge after delivery could impact EOD case ascertainment rates. In Bangkok, a high proportion (95%) of births occur in hospitals. Also in Bangkok at the study hospitals, normal vaginal deliveries stayed 3 days after delivery and longer if there is a complicated delivery. Although nearly all deliveries in Manila occur in the hospital, the inpatient post-delivery stays at the studied hospitals were shorter (1 day for normal

vaginal deliveries). The study hospital in rural Bohol faced a different challenge: 25% of deliveries occur outside of hospital (UNICEF, 2013), increasing the likelihood that GBS cases manifesting immediately after delivery might not be captured within the hospital based study.

Culture methods used for GBS isolation are reported to influence sensitivity of GBS identification (Dagnew *et al*, 2012). The use of local laboratories may have introduced some variability in the sensitivity of diagnosis despite the provision of a single laboratory manual describing best practice.

Antibiotic prophylaxis is reported to be administered almost universally during cesarean sections in some Southeast Asian hospitals (Festin *et al*, 2009). Higher cesarean section rates are associated with higher risk pregnancies. Three study sites (Philippines General Hospital in Manila, Queen Sirikit Hospital and Siriraj Hospital in Bangkok) were tertiary referral centers with a higher proportion of high risk pregnancies. This was in contrast to the Ospital ng Maynila Hospital in Manila, Philippines with a lower proportion of high risk pregnancies, where all the EOD cases in our study were identified. A better understanding of the use of antibiotics at the time of delivery in Asia, and its effect on neonatal GBS incidence, is needed to evaluate whether antibiotic use could play an important role in the epidemiology of GBS disease.

Some uncertainty about the GBS incidence estimates generated in our current studies remains, reflected by the relatively wide confidence intervals reported. This emphasizes a challenge regarding the assessment of GBS incidence and the need for active surveillance across large birth cohorts. The 6-month study period was

short, and continuing surveillance in these populations would help clarify our findings.

The number of GBS cases identified in our study was too small to draw conclusions concerning case fatality rates and serotype distribution. It is concerning that 2 of the 4 enrolled GBS cases died, highlighting the clear severity of invasive GBS disease in infants. Although too few cases were observed to assess serotype distribution, 2 of the 4 isolates were serotype VI, which comprises only 1% of the global serotype distribution (Edmond *et al*, 2012) but has previously been reported to represent 24.7% of GBS isolates colonizing pregnant Japanese women (Lachenauer *et al*, 1999). Further investigation is needed to assess whether this serotype is more common in Southeast Asia than the rest of the world.

In conclusion, these studies highlight the challenges involved in the surveillance of GBS infection and the need for clearly defined birth cohorts at risk for infection, good healthcare access, robust diagnostics and a good understanding of antibiotic practices. This study confirms GBS infection does occur in diverse global regions and can be a very serious infection in the newborn infant. Limitations in the ability to identify and diagnose sick newborns, continue to challenge robust determination of incidence in such setting.

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Conflicts of interest

The two studies were funded by Novartis Vaccines and Diagnostics. NN-B, HB, MC and IB are employees of Novartis Vaccines and Diagnostics, CN received consultancy fees from Novartis Vaccines and Diagnostics. The other authors did not receive any stipend, allowance, salary or monetary incentives from Novartis. On 2 March 2015 the GSK Group of Companies acquired Novartis Vaccines non-influenza vaccines business including a candidate vaccine for GBS under development, which has not yet completed the necessary trials for licensure.

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