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Neonatal group B streptococcal infection in Australia: a case-control study

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Abstract

Objectives: To determine maternal and neonatal risk factors for, and incidence of, neonatal early-onset group B streptococcus (EOGBS) and late onset (LOGBS) infection in South Australia (SA) and the Northern Territory (NT).

Design: A case–control study with 2:1 matched controls to cases.

Setting: The study included tertiary hospitals in South Australia and the Northern Territory, Australia.

Participants: Retrospective data were collected from a 16-year epoch (2000–2015).

Results: Of a total of 188 clinically suspected or confirmed cases, 139 were confirmed, of which 56.1% (n = 78) were EOGBS and 43.9% (n = 61) were LOGBS. The incidence of clinically suspected and confirmed cases of EOGBS was 0.26/1000 live births in SA and 0.73/1000 live births in the NT, and the incidence of confirmed cases was 0.19/1000 for SA and 0.36/1000 for the NT. The incidence of clinically suspected or confirmed LOGBS was 0.18/1000 live births in SA and 0.16/1000 for the NT. The majority of infants with GBS presented with sepsis, pneumonia, or meningitis.

Developmental delay was the most commonly recorded long-term complication at 1 year old. Risk factors for EOGBS included maternal GBS carriage, previous fetal death, identifying as Aboriginal and/or Torres Strait Islander, and maternal fever in labor/chorioamnionitis.

Conclusions: GBS remains a leading cause of neonatal morbidity and mortality. Adding previous fetal death to GBS screening guidelines would improve GBS prevention. The introduction of maternal GBS vaccination programs should be guided by country-specific disease epidemiology.

INTRODUCTION

Group B Streptococcus (GBS) colonizes approximately 10-30% of pregnant women.(1, 2) While GBS infections rarely lead to maternal death, infections can result in miscarriage or stillbirth of the fetus,(3) and GBS is the most common cause of early neonatal infections worldwide.(4) Neonatal (early onset) GBS infection (EOGBS) is defined as occurring up to 7 days of life and likely develops after aspiration of infected amniotic fluid and/or exposure to GBS colonization of maternal genital tract;(5) late onset disease (LOGBS) occurs from 7 days to 90 days of life, with uncertain pathogenesis but nosocomial sources are implicated in addition to acquisition of the pathogen from the maternal genital tract.(6)

Two major screening approaches have been adopted internationally. The first is based on the stratification of risk for pregnant women at the time of delivery with IAP administered to women in labor with clinical risk factors for the disease. The second is based on the universal screening of pregnant women by vaginal and rectal swabs for GBS with IAP then offered to carriers.(7) Prior to the introduction of intrapartum antibiotic prophylaxis (IAP) for those women at risk of GBS disease, the incidence of EOGBS disease in Australia was 200-300 per 100,000 live births.(8) In Australia, the management strategies of GBS began evolving in late 1970. Australia has no national policy, and states and territories have different guidelines, recommending screening or a risk-based approach, or a combination of the two.(9) Antenatal guidelines have recommended routine GBS screening at 36 weeks gestation in South Australia (SA: population 1.77m, including 42,000 Aboriginal and Torres Strait Islander people) since 2004 and prior to 2009 in the Northern Territory (NT: population 246,500, including 74,500 Aboriginal and Torres Strait Islander people).(10) In Tertiary Hospitals, IAP is recommended for women screened GBS positive during pregnancy, women who have given birth to a neonate with previous GBS sepsis,

pregnant women who are GBS negative or unknown with rupture of membranes (ROM) > 18 hours, and women in preterm labor or with preterm prelabor rupture of membranes (PPROM) who are GBS positive or unknown.(11)

No publicly available data indicates how well the guidelines are followed in South Australia. In the Northern Territory, clinical audits were undertaken in 2009 as part of the ABCD Project in Aboriginal Primary Health Care Centres and identified that low vaginal swabs were performed for 49% of pregnant women in the Top End and 62% in Central Australia. No data is available for the administration of IAP.(12) A retrospective cohort study in the New England local health district, New South Wales (NSW) Australia, between 2006–2016, investigated compliance with GBS screening and IAP. In 2005, they changed GBS management from identifying risk factors to universal screening and provision of IAP. Of the women eligible for routine GBS screening, 69% were screened, and 21.5% of those were positive for GBS. IAP was received by 79% of these women.(9) Despite the introduction of routine maternal GBS screening and IAP and a greater than 80% reduction in the incidence of EOGBS cases in Australia, GBS remains a leading infectious cause of neonatal morbidity and mortality.(2)

There are limited contemporary data regarding the true incidence of GBS in Australia following the introduction of routine maternal screening and IAP. In 2012, a systematic review of the global burden of perinatal GBS infection identified only three studies investigating the incidence of neonatal group B streptococcal infection in Australia.(13) Each of the identified Australian studies confirmed that following the introduction of IAP, the incidence of early-onset neonatal GBS fell.(14-16) The largest, multi-center study reported a reduction in EOGBS incidence from 1.43/1,000 live births in 1993 to 0.25/1,000 live births in 2001.(15) However, little change was reported in LOGBS disease following the introduction of IAP, with 0.94/1,000 prior to the

introduction of IAP and 0.72/1,000 after its introduction. (14) A follow up 2016 systematic review that included three further studies from Australia found that the overall estimated incidence of infant GBS disease was lower (0.49/1,000 live births), than the 2012 systematic review (0.53/1,000) in high-income countries where IAP was predominantly in use.(17) Recently, attention has focused on the potential role of maternal GBS vaccination. Internationally, GBS vaccine development has advanced to phase II trials in pregnant women.(18, 19) Accurate data on the incidence, risk factors, disease burden, and outcomes of GBS in infants is critical to guide cost-effectiveness estimates and local and national policies focusing on a new immunization program targeting this disease. At present neonatal GBS disease is not a notifiable disease, and there are sparse contemporary data on incidence and disease burden in Australian infants. In addition, data on GBS affecting Aboriginal and Torres Strait Islander infants is similarly limited. The current study aimed to identify the true incidence and disease burden of EOGBS and LOGBS infection in SA/NT and identify risk factors predisposing newborns to these infections.

PATIENT AND METHODS

Infants diagnosed with GBS during the period 2000-2015 in all major hospitals with birthing units in SA and NT were included in this study, including: the Women's and Children's Hospital, the Lyell McEwin Hospital, Flinders Medical Centre in SA; and the Royal Darwin Hospital and Alice Springs Hospital in the NT. The study included all tertiary hospitals in the three most populated cities in SA and the NT. It did not include smaller private hospitals and infants born in smaller remote and rural hospitals.

Identification of cases and controls

Clinical cases were identified by searching pathology databases for GBS-positive sterile site specimens from infants aged less than 90 days and identifying cases using the "ICD 10 CODE P36.0: Sepsis of newborn due to streptococcus, group B".

Cases were classified using an adapted case definition from the Ontario Public Health Standards Infectious Disease Protocol case definition(20) with a "confirmed GBS case" defined as an infant with: GBS cultured from a normally sterile site, clinically-compatible signs, and symptoms of invasive disease up to 90 days after birth.

A "clinically suspected GBS case" was defined as clinically-compatible signs and symptoms and a diagnosis of invasive GBS disease in a newborn up to 90 days after birth, whose mother has laboratory confirmation of Group B streptococcus from a lower vaginal or anorectal specimen. Clinically suspected GBS cases were included to ensure completeness of reporting in cases where an infant is treated early with antibiotics before all the appropriate specimens have been taken. Control infants were identified in a 2:1 ratio, with one selected control born as soon as possible before the case and a second control as soon as possible after the case. Control infants were matched for gender and birth weight categories (<1500 grams, 1500–2499 grams, >3000 grams). In smaller Northern Territory hospitals, not all controls could be matched by sex. Potential control infants were excluded if they had clinical evidence of sepsis during the first 90 days of life.

Data collection

Data were collected from medical records by trained medical students, Registered Nurses, and Medical Officers, using a pre-specified data collection form, for all proven and suspected GBS

cases and controls (supplementary material). The lead investigator oversaw data collection. Data were then entered into a Redcap database, where data quality checks were conducted.

HREC approval

Research ethics approval was obtained from the South Australian Aboriginal Health Research Ethics Committee, the Women's and Children's Health Network Human Research Ethics Committee, the Central Australian Human Research Ethics Committee, and the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research.

Sample size and statistical methods

A total of 363,968 (including 30,533 Aboriginal and Torres Strait Islander) live births occurred in SA and the NT over the study period.(21) Based on 2012 data, the Women's and Children's Hospital and Lyell McEwin Hospital sites account for approximately 41% of births in SA, with 4.0% and 3.9% of Aboriginal infants births, respectively. In the NT, the Royal Darwin Hospital and Alice Spring Hospital sites contributed to approximately 67% of all births with 35% and 55% of Aboriginal births, respectively. With a conservative estimate of 0.11 per 1,000 live births for early-onset disease and 0.08 per 1,000 live births for late-onset disease based on the Australian Paediatric Surveillance Unit (APSU) data,(22) we expected approximately 40 early-onset neonatal GBS sepsis cases and 29 late-onset GBS cases over the 16-year study period. This is primarily a descriptive study, and the sample size is not specifically powered to detect differences between groups, but instead, it has been chosen pragmatically based on feasibility. The period 2000-2015 was chosen to make the results relevant to contemporary management procedures.

We assessed the association between clinical features related to EOGBS and LOGBS infection using logistic regression, expressed as odds ratios with 95% confidence intervals. Risk factors for GBS were analyzed using univariate logistic regression. The analysis was performed for 1) EOGBS cases, compared to matched controls, and 2) LOGBS cases, compared to matched controls. The analysis was done using Stata version 17.(23)

RESULTS

INCIDENCE OF GBS

During the 16-year study period, of a total of 188 cases of confirmed or clinically-suspected GBS cases, 139 were confirmed (Table 1). This included 78 cases (56.1%) of EOGBS and 61 cases (43.9%) of LOGBS. There were an additional 49 cases that had clinically suspected GBS disease with a positive maternal swab for GBS (Figure 1). Of the combined confirmed/clinically-suspected cases there were 125/188 EOGBS (66.5%) and 63/188 LOGBS cases (33.5%) in SA/NT.

Using the number of live births identified from the Australian Bureau of Statistics in SA during the study period (302,421), the SA incidence (of clinically suspected and confirmed cases) was 0.26/1,000 live births for EOGBS disease and 0.18/1,000 for LOGBS. There were 61,547 live births in the NT during this period. The estimated incidence (of clinically-suspected and confirmed cases) in the NT was 0.73/1,000 live births for EOGBS and 0.16/1,000 for LOGBS. When only confirmed cases were included, the incidence for EOGBS in SA was 0.19/1,000 live births and for LOGBS was 0.17/1,000 live births, and NT incidence for EOGBS was 0.36/1,000 and for LOGBS was 0.15/1,000 live births.

DISEASE BURDEN

The majority of infants with EOGBS presented with sepsis followed by meningitis and pneumonia. Infants with LOGBS were more likely to present with meningitis, than those with EOGBS, and the opposite was the case for pneumonia. Infants with LOGBS were more likely to require ventilation, and had a longer admission (Table 2). Developmental delay was the most commonly-recorded long-term complication at 1 year of age (Table 2).

During the study period, 10 of 24 neonatal deaths in the study cohort were attributed to GBS infection.

RISK FACTORS

Univariate analysis of risk factors associated with GBS disease included known maternal GBS carriage. For EOGBS, GBS carriage, previous fetal death, maternal chorioamnionitis, prolonged rupture of membranes > 18 hours, and identifying as Aboriginal or Torres Strait Islander were all associated with an increased risk of disease. (Table 3). For those with LOGBS, maternal fever/chorioamnionitis and GBS carriage were associated with a higher risk of LOGBS (Table 4). In the control group, 173/264 (66%) were screened for GBS, with 28/173 (16%) carrying GBS. Of the 28 GBS-positive controls, 13 (46%) received IAP before delivery. In the cases, 93/139 (67%) were screened for GBS, with 40/93 (43%) carrying GBS. Of the 40 GBS-positive cases, 12 (30%) received IAP before delivery.

DISCUSSION

Despite the introduction of GBS screening programs and maternal IAP use, it is clear that the incidence and disease burden of GBS in Australia requires better prevention. The high rates in the NT indicate the importance of preventative strategies, including any future antenatal GBS vaccination program.

While a recent prospective surveillance study conducted in the United Kingdom (UK) over 2014-2015 showed that the incidence of GBS disease was increasing despite national screening and prevention guidelines,(24) previous Australian studies have reported a decrease in the incidence of EOGBS in particular. This difference may be because Australia employs universal-screening vaginal swabs, or a risk-based approach depending on state guidelines, compared to the UK, where only the risk-based screening approach is applied.(25, 26) In the Netherlands, where a risk-based approach is applied, the rising incidence of GBS disease has been attributed to an increase in the number of GBS cases caused by GBS serotype III (clonal complex 17).(7) The incidence of suspected and confirmed EOGBS cases in the NT was higher in this study compared to previous Australian data.(15, 27) A previous surveillance (APSU) study was conducted between 2005-2008 at 12 major public hospitals across Australia,(27) did not include the NT. Further, the authors concluded that clinicians only reported about one-third of actual GBS cases in this time, indicating the importance of having multiple sources of surveillance in national studies.(27)

This study captured both laboratory data and clinician-reported GBS cases and covered a 16-year time frame, thus providing a more reliable estimate of the true incidence of GBS disease. The high incidence of EOGBS in the NT indicates that geographical and socioeconomic factors may predispose to higher infection rates.

Maternal IAP may be a protective factor against neonatal EOGBS disease; with other studies showing that the use of maternal IAP had a negative linear relationship with EOGBS.(28) IAP was not protective against LOGBS. The long-term implications of widespread IAP include disruption of neonatal microbiota, which may increase neonatal risks of associated diseases including coeliac disease and type 1 diabetes, as well as life-long risks for obesity and

asthma.(29) IAP should therefore be administered thoughtfully and according to current guidelines.

The unadjusted EOGBS analysis indicated Aboriginal or Torres Strait Islander infants may be at increased risk of EOGBS as estimated in other Australian studies.(8) Infants in this demographic were more likely to have EOGBS compared to LOGBS; this warrants further evaluation of colonization and GBS strain virulence. Another study conducted in Townsville did not find that Aboriginal newborns were more at risk of neonatal sepsis(30) and a NZ study showed that Maori and Pacific Island infants were similarly not at greater risk of GBS infection.(31)

One potential new direction for the management of this important perinatal complication is maternal GBS vaccination. A GBS vaccination program would likely be acceptable to pregnant Australian women, as there are already successful pertussis and influenza vaccine programs for this cohort and especially where vaccination is primarily to protect the infant.(32) Maternal IAP has made a significant impact in decreasing neonatal morbidity and mortality due to EOGBS, but it has not reduced the incidence or clinical burden of LOGBS.(33) As a result, it is increasingly apparent that a future vaccination program would be the most effective approach to lowering the incidence and disease burden of LOGBS. A study in the UK showed that a GBS vaccination program would prevent about twice as many cases of death and disability in the neonate as microbiological screening, and three times as many as risk factor-based screening.(34) A vaccination program could also contribute by preventing the impact of widespread antibiotic use on bacterial antibiotic resistance (35) and microbiota dysbiosis.(29) Other potential vaccination benefits include the prevention of preterm labor caused by GBS as well as reduced stillbirth rates caused by GBS infection.(35)

Capsular polysaccharide (CPS) serotype III is a major cause of neonatal disease, and is particularly associated with neonatal GBS meningitis.(36) As a result, this serotype is a key target for CPS-protein conjugate vaccines. GBS vaccine development has advanced to phase II trials.(18),(19) Alternatives to CPS-based vaccines include those based on conserved antigenic proteins.(37) Multi-genomic approaches have identified new GBS proteins and may facilitate future GBS vaccine development.(38)

In selecting the optimal vaccine design, it is important to identify the most prevalent GBS serotypes and sequence types in all the regions of the world.(38) Further Australian data on GBS serotypes is required in order to contribute towards vaccine and policy development. Further Australian studies are also necessary to ascertain whether it is economically viable to implement a GBS vaccination program to pregnant women. However, a 2018 UK study clearly established the cost-effectiveness of such a vaccination program when considering the cost and the burden of invasive GBS disease.(39)

This study has some limitations. The study used a retrospective design, where a prospective study of risk factors would ensure more complete data collection. Further, retrospective data collection is associated with a greater risk of missing data, with pertinent information often not included in medical notes resulting in a reliance on the accuracy of clinicians' data entries and the availability of results on pathology databases. Due to the number of cases and missing data, multivariate analysis of risk factors was not able to be conducted, which increases the risk of confounding. Although the majority of controls were matched, the small number of patients identified in the NT made it difficult to match every case for gender and weight category (particularly in the case of very premature or low birth weight infants as these were often

transferred interstate to major tertiary centers for ongoing care). Finally, we did not evaluate which specific GBS strains were responsible for GBS disease burden.

While clinically suspected cases were included in the data collection stage of the study to calculate the incidence of GBS, they were excluded in the analysis of risk factors to ensure the validity of the data. Exclusion of clinically suspected cases when evaluating risk factors ensured a more robust data set in an era of IAP where many infants who clinically have EOGBS disease have negative blood cultures due to the sensitivity of newborn blood cultures being low, which is further compounded by the use of maternal antibiotics in labor.(40) However, by excluding clinically suspected cases from data analysis, this may have influenced the identification of risk factors associated with early onset disease.

CONCLUSION

This study identified that in addition to prior known risk factors, previous fetal death should be considered a risk factor for neonatal EOGBS infection. Aboriginal or Torres Strait Islander infants may be at increased risk of EOGBS. The incidence of EOGBS in the NT appears much higher than the national average and would potentially benefit from a future maternal GBS vaccination program, which may lower both the incidence of EOGBS and LOGBS and potentially lead to disease eradication.

Declaration of interests:

HSM is an investigator on vaccine trials sponsored by Industry. HSM's and MM's institution receives funding for investigator-led studies from Industry (Pfizer, GSK, Sanofi-Pasteur). HSM and MM receive no personal payments from Industry. PTH's Institute receives research funding from Industry (GSK, Minervax, Pfizer) but PTH receives no personal payments. All other authors have indicated they have no potential conflicts of interest to disclose.

Author contribution statement:

MY, HSM, PTH, MM, and MS contributed to study design and protocol. AG, JR, AW, RL, KC, OPQ, RB, LF and JRF identified cases and controls, and collected data. All authors contributed to interpretation of the study results and the manuscript. MY is the primary author of this work.

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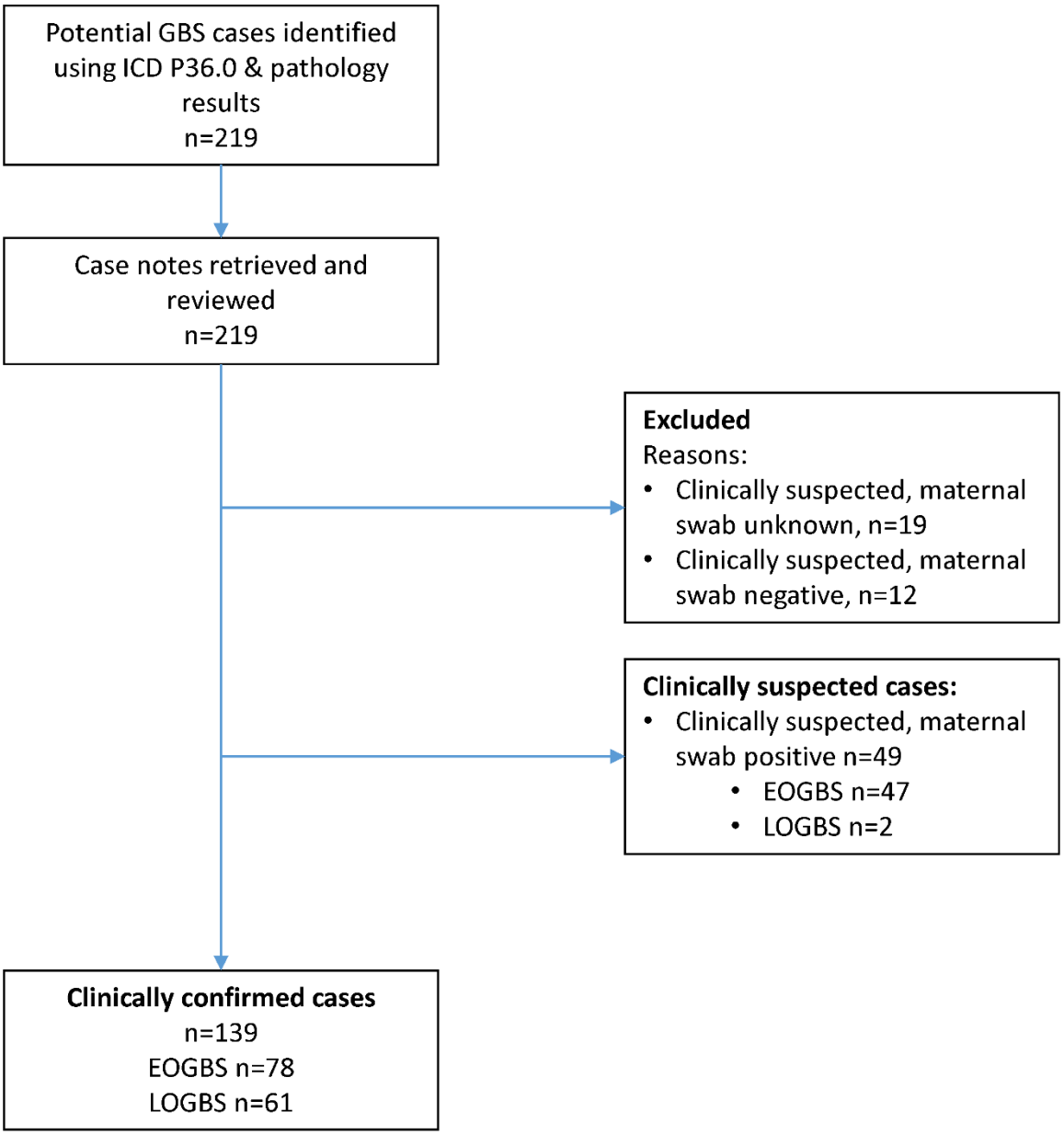
Figure 1 Flow chart of study inclusion



*EOGBS = Early-onset Group B Streptococcus; LOGBS = Late-onset Group B Streptococcus

Table 1: Description of confirmed early and late onset GBS cases and controls in South Australia (SA) and Northern Territory (NT)

Characteristic	EOGBS n/N (%)	LOGBS n/N (%)	Controls n/N (%)
SA Hospitals	56/78 (71.8)	52/61 (85.3)	210/264 (79.6)
NT Hospitals	22/78 (28.2)	9/ 61 (14.8)	54/264 (20.5)
Birth weight			
< 1500g	10/76 (13.2)	31/59 (52.5)	71/264 (26.9)
1500 – 2499 g	11/76 (14.5)	8/59 (13.6)	37/264 (14.0)
≥ 2500g	55/76 (72.4)	20/59 (33.9)	156/264 (59.1)
Sex			
Male	43/78 (55.1)	34/61 (55.7)	140/264 (53.0)
Female	35/78 (44.9)	27/61 (44.3)	124/264 (47.0)

*EOGBS = Early-onset Group B Streptococcus; LOGBS = Late-onset Group B Streptococcus

Table 2. Presenting signs and symptoms, complications, and clinical features of confirmed late-onset group B streptococcal (LOGBS), compared with early-onset group B streptococcal (EOGBS) infection

Presenting signs and symptoms, complications, and clinical features	LOGBS n/N (%)	EOGBS n/N (%)	Odds ratio (95% CI)	P-value
Clinical Presentation(s)				
Sepsis	55/61 (90.2)	66/78 (84.6)	1.67 (0.59 to 4.73)	0.34
Meningitis	16/61 (26.2)	7/78 (9.0)	3.61 (1.38 to 9.45)	0.009
Pneumonia	8/61 (13.1)	26/78 (33.3)	0.30 (0.13 to 0.73)	0.008
Clinical features				
Intensive care or high dependency	37/60 (61.7)	35/75 (46.7)	1.84 (0.92 to 3.67)	0.08
Required intubation or ventilation	41/60 (68.3)	31/75 (41.3)	3.06 (1.50 to 6.24)	0.002
Days in hospital mean days (SD) **	57.6 (41.7)	16.2 (21.1)	RR 3.55 (2.60 to 4.85)	<0.001
Neonatal death due to GBS infection	3/61 (4.9)	7/77 (9.1)	0.52 (0.13 to 2.09)	0.36
CSF culture or PCR positive	10/51 (19.6)	4/58 (6.9)	3.29 (0.96 to 11.25)	0.06
Complications (first year of life)				
Developmental delay	4/61 (6.6)	3/78 (3.9)	1.75 (0.38 to 8.15)	0.47
Microcephaly†	1/61 (1.6)	0/78 (0)		
Cortical blindness†	0/61 (0)	1/78 (1.3)		
Deafness†	2/61 (3.3)	0/78 (0)		
Periventricular Leukomalacia	2/61 (3.3)	1/78 (1.3)	2.61 (0.23 to 29.48)	0.44

† Unable to calculate due to small numbers and wide range of error. ** Note that a negative binomial regression model was fitted & the estimate and CI provided are a Rate Ratio (RR) rather than an Odds Ratio (OR).

Table 3: Maternal and perinatal risk factors for confirmed EOGBS infection using univariate analysis compared with matched controls

Potential risk factors	Cases n (%)	Controls n (%)	Odds ratio (95% CI)	P value
Maternal Age, mean (SD)	29.2 (6.4)	28.5 (5.4)	1.02 (0.97 to 1.07)	0.42
Aboriginal or Torres Strait Islander	18/78 (23.1)	19/149 (12.8)	2.05 (1.01 to 4.19)	0.048
Maternal smoking	18/30 (60.0)	28/56 (50.0)	1.50 (0.61 to 3.69)	0.38
First-time pregnancies	23/76 (30.3)	49/148 (33.1)	0.87 (0.48 to 1.59)	0.67
Multiparous mothers	44/76 (57.9)	82/148 (55.4)	1.11 (0.63 to 1.94)	0.72
GBS carrier	25/58 (43.1)	19/100 (19.0)	3.23 (1.57 to 6.64)	0.001
Previous baby with GBS infection	3/75 (4.0)	1/150 (0.7)	6.21 (0.63 to 60.73)	0.12
Previous fetal death	10/74 (13.5)	5/150 (3.3)	4.53 (1.49 to 13.80)	0.008
Maternal fever/ chorioamnionitis	29/63 (46.0)	10/127 (7.9)	9.98 (4.42 to 22.52)	<0.001
Rupture of membranes ≥ 18 hours	21/76 (27.6)	18/148 (12.2)	2.76 (1.36 to 5.58)	0.005
Antibiotics 4 hrs prior to delivery	5/75 (6.67)	24/150 (16.0)	0.38 (0.14 to 1.03)	0.06
Method of delivery				
Vaginal delivery	54/76 (71.1)	87/148 (58.8)	ref	*<0.001
Caesarean section with labour	19/76 (25.0)	29/148 (19.6)	1.06 (0.54 to 2.06)	0.87
Caesarean section without labour	3/76 (4.0)	32/148 (21.6)	0.15 (0.04 to 0.52)	0.003

* Global p-value, Note: Prematurity could not be assessed as cases and controls were matched by birthweight.

Table 4: Maternal and perinatal risk factors for confirmed LOGBS infection using conditional univariate analysis compared with matched controls

	Cases n (%)	Controls n (%)	Odds ratio (95% CI)	P value
Maternal Age, mean (SD)	27.5 (5.3)	29.2 (6.6)	0.96 (0.91 to 1.01)	0.09
Aboriginal or Torres Strait Islander	6/58 (10.3)	13/109 (12.0)	0.85 (0.31 to 2.37)	0.76
Maternal smoking	8/19 (42.1)	24/37 (64.9)	0.39 (0.13 to 1.22)	0.11
First-time pregnancies	16/48 (33.3)	41/110 (37.3)	0.84 (0.41 to 1.72)	0.64
Multiparous mothers	29/52 (55.8)	55/111 (49.6)	1.28 (0.66 to 2.49)	0.46
GBS carrier	15/33 (45.5)	9/70 (12.9)	5.65 (2.12 to 15.04)	0.001
Previous baby with GBS infection†	1/54 (1.9)	0/113 (0.0)		
Previous fetal death	2/54 (3.7)	3/113 (2.7)	1.41 (0.23 to 8.70)	0.71
Maternal fever/ chorioamnionitis	10/31 (32.3)	9/97 (9.28)	4.7 (1.68 to 12.89)	0.003
Rupture of membranes ≥ 18 hours	9/49 (18.4)	14/110 (12.7)	1.54 (0.62 to 3.85)	0.35
Antibiotics 4 hrs prior to delivery	18/47 (38.3)	32/111 (28.8)	1.53 (0.75 to 3.14)	0.24
Method of delivery				
Vaginal delivery	33/57 (57.9)	47/112 (42.0)	ref	*0.09
Caesarean section with labour	11/57 (19.3)	22/112 (19.6)	0.71 (0.30 to 1.67)	0.43
Caesarean section without labour	13/57 (22.8)	43/112 (38.4)	0.43 (0.20 to 0.92)	0.03

* Global p-value, † Unable to calculate due to small numbers and wide range of error. Note: Prematurity could not be assessed as cases and controls were matched by birthweight.

References

1. Sheehy A, Davis D, Homer CS. Assisting women to make informed choices about screening for Group B Streptococcus in pregnancy: a critical review of the evidence. *Women Birth*. 2013;26:152-157.

2. Clifford V, Garland SM, Grimwood K. Prevention of neonatal group B streptococcus disease in the 21st century. *J Paediatr Child Health*. 2012;48:808-815.

3. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299:2056-2065.

4. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics*. 2011;127:817-826.

5. Le Doare K, Heath PT. An overview of global GBS epidemiology. *Vaccine*. 2013;31 Suppl 4:D7-12.

6. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. *Clin Microbiol Rev*. 1998;11:497-513.

7. Bekker V, Bijlsma MW, van de Beek D, Kuijpers TW, van der Ende A. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. *Lancet Infect Dis*. 2014;14:1083-1089.

8. Australasian Study Group for Neonatal Infections. Early-onset group B streptococcal infections in Aboriginal and non-Aboriginal infants. *Med J Aust,*1995:302-306.

9. Braye K, Foureur M, de Waal K, Jones M, Putt E, Ferguson J. Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district: 2006-2016. *PloS one*. 2019;14:e0214295.

10. Perinatal Practice Guidelines - Routine Care in Normal Pregnancy 2022. Available at: https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs+and+practice+guidelines/womens+and+babies+health/perinatal/perinatal+practice+guidelines/perinatal+practice+guidelines. Accessed 21st October 2022.

11. Perinatal Practice Guidelines - Antibiotics in the Peripartum Period 2022. Available at: https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical

+resources/clinical+programs+and+practice+guidelines/womens+and+babies+health/perinatal/perinatal+practice+guidelines/perinatal+practice+guidelines. Accessed 21st October 2022.
12. Rumbold AR, Bailie RS, Si D, et al. Delivery of maternal health care in Indigenous primary care services: baseline data for an ongoing quality improvement initiative. *BMC Pregnancy Childbirth*. 2011;11:16.
13. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and metaanalysis. *Lancet* 2012;379:547-556.
14. Angstetra D, Ferguson J, Giles WB. Institution of universal screening for Group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. *Aust N Z J Obstet Gynaecol*. 2007;47:378-382.
15. Daley AJ, Isaacs D, Australasian Study Group for Neonatal I. Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and Escherichia coli neonatal sepsis in Australasia. *Pediatr Infect Dis J*. 2004;23:630-634.
16. May M, Daley AJ, Donath S, Isaacs D, Australasian Study Group for Neonatal I. Early onset neonatal meningitis in Australia and New Zealand, 1992-2002. *Arch Dis Child Fetal Neonatal Ed*. 2005;90:F324-327.
17. Madrid L, Seale AC, Kohli-Lynch M, et al. Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. *Clin Infect Dis*. 2017;65:S160-S172.
18. Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children. *Clin Infect Dis*. 2017;65:S200-S219.
19. Madhi SA, Koen A, Cutland CL, et al. Antibody Kinetics and Response to Routine Vaccinations in Infants Born to Women Who Received an Investigational Trivalent Group B Streptococcus Polysaccharide CRM197-Conjugate Vaccine During Pregnancy. *Clin Infect Dis*. 2017;65:1897-1904.
20. Ontario Ministry of Health and Long Term Care, Ontario Public Health Standards Infectious Diseases Protocol 2014. Available at:

http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/infdispro.aspx. Accessed 5th December 2018.

21. Australian Bureau of Statistics, Births, by year and month of occurrence, by state. Available at: https://explore.data.abs.gov.au/vis?tm=birth%20data&pg=0&df[ds]=ABS_ABS_TOPICS&df[id]=BIRTHS_MONTH_OCCURRENCE&df[ag]=ABS&df[vs]=1.0.0&hc[Measure]=Births&pd=2000%2C2015&dq=1..7%2B4.A&ly[cl]=TIME_PERIOD. Accessed 21st February 2022.

22. Gilbert L, Garland S, Gidding H, et al. Neonatal Group B Streptococcal (GBS) Sepsis - Final Report. *APSU Research Report 2007-2008*: Australian Paediatric Surveillance Unit; 2008.

23. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.

24. O'Sullivan C, Lamagni T, Efstratiou A, et al. Group B streptococcal (GBS) disease in UK and Irish infants younger than 90 days, 2014-2015: results from prospective surveillance. *Lancet Infect Dis*. 2018.

25. Rodriguez-Granger J, Alvargonzalez JC, Berardi A, et al. Prevention of group B streptococcal neonatal disease revisited. The DEVANI European project. *Eur J Clin Microbiol Infect Dis*. 2012;31:2097-2104.

26. Hughes RG, Brocklehurst P, Steer PJ, Heath P, Stenson BM. The Prevention of Early-onset Neonatal Group B Streptococcal Disease. . *Green-top GuidelineNo 36*. 2017;124.

27. Ko DW, Zurynski Y, Gilbert GL, Group GBSS. Group B streptococcal disease and genotypes in Australian infants. *J Paediatr Child Health*. 2015;51:808-814.

28. Russell NJ, Seale AC, O'Sullivan C, et al. Risk of Early-Onset Neonatal Group B Streptococcal Disease With Maternal Colonization Worldwide: Systematic Review and Meta-analyses. *Clin Infect Dis*. 2017;65:S152-S159.

29. Matamoros S, Gras-Leguen C, Le Vacon F, Potel G, de La Cochetiere MF. Development of intestinal microbiota in infants and its impact on health. *Trends Microbiol*. 2013;21:167-173.

30. Panaretto KS, Muller R, Patole S, Watson D, Whitehall JS. Is being Aboriginal or Torres Strait Islander a risk factor for poor neonatal outcome in a tertiary referral unit in north Queensland? *J Paediatr Child Health*. 2002;38:16-22.

31. Grimwood K, Darlow BA, Gosling IA, et al. Early-onset neonatal group B streptococcal infections in New Zealand 1998-1999. *J Paediatr Child Health*. 2002;38:272-277.
32. South Australian Perinatal Practice Working Group. Vaccines recommended in pregnancy. Adelaide, South Australia: SA Health; 2015.
33. Larsen JW, Sever JL. Group B Streptococcus and pregnancy: a review. *Am J Obstet Gynecol*. 2008;198:440-448; discussion 448-450.
34. Law MR, Palomaki G, Alfirevic Z, et al. The prevention of neonatal group B streptococcal disease: a report by a working group of the Medical Screening Society. *J Med Screen*. 2005;12:60-68.
35. Burns G, Plumb J. GBS public awareness, advocacy, and prevention--what's working, what's not and why we need a maternal GBS vaccine. *Vaccine*. 2013;31 Suppl 4:D58-65.
36. Baker CJ, Barrett FF. Group B streptococcal infections in infants. The importance of the various serotypes. . *JAMA*. 1974;230:1158–1160. .
37. Lindahl G, Stalhammar-Carlemalm M, Areschoug T. Surface proteins of Streptococcus agalactiae and related proteins in other bacterial pathogens. *Clin Microbiol Rev*. 2005;18:102-127.
38. Johri AK, Paoletti LC, Glaser P, et al. Group B Streptococcus: global incidence and vaccine development. *Nat Rev Microbiol*. 2006;4:932-942.
39. Giorgakoudi K, O'Sullivan C, Heath PT, et al. Cost-effectiveness analysis of maternal immunisation against group B Streptococcus (GBS) disease: A modelling study. *Vaccine*. 2018;36:7033-7042.
40. Schrag SJ, Verani JR. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: experience in the United States and implications for a potential group B streptococcal vaccine. *Vaccine*. 2013;31 Suppl 4:D20-26.

Supplementary material: Neonatal Group B Streptococcal Infection in Australia: A Case control Study

Contents

GBS STUDY: USE THIS FORM FOR INDEX CASES

*BABY URN:*_____

*MOTHERS URN:*_____

Once form completed please delete baby's and mother's URN before sending form to WCH

Instructions: Please answer each question by ticking the appropriate box or writing your response in the space provided.

UK= unknown, NA = Not applicable

DE-IDENTIFIED ID: _____ *(W### for WCH, A### for AliceSprings, D### for Royal Darwin etc)*

Enter the following information

PATIENT DETAILS

1. First 2 letters of first name: ☐☐
2. First 2 letters of surname: ☐☐
3. Date of Birth: ☐☐/☐☐/☐☐
4. Sex: ☐M ☐F
5. Postcode of family: ☐☐☐☐
6. Time Of Birth (24 HR CLOCK): ☐☐ : ☐☐
7. Date of Admission to Neonatal Unit: ☐☐/☐☐/☐☐ & Time Of Neonatal Unit Admission (24 HR CLOCK): ☐☐ : ☐☐
8. Was patient admitted to NICU/HDU? ☐Yes ☐No ☐UK

   If yes, what was the total length of ICU admission: ☐☐Days ☐☐hours
9. Mother's Ethnicity _____ ☐UK Maternal DOB: ☐☐/☐☐/☐☐
10. Transferred from another hospital? Y☐ N☐UK☐ IF YES, SPECIFY WHICH HOSPITAL _____

    Date of Admission at referring hospital: ☐☐/☐☐/☐☐
11. Is the child of ATSI descent? Aboriginal ☐ Torres Strait Islander ☐ Both☐ No☐ UK☐

BIRTH HISTORY

10. Gestational age: Term ☐ Pre-term (<37 weeks) ☐ **If pre-term,** state gestational age _____(weeks) UK☐
11. Mothers Parity PRIOR to delivery of this child: G ___ P ___
12. Birth weight _____ grams (exact weight if known please)
    & Weight category:

☐ < 749g	☐ 750-999g	☐ 1000-1499g
☐ 1500-1999g	☐ 2000-2499g	☐ 2500-2999g
☐ 3000-3499g	☐ >/= 3500g	

13: Method of delivery:

- ☐ Spontaneous vaginal delivery (no instruments)
- ☐ Spontaneous vaginal delivery (with instruments: Vontousse suction cup ☐, forceps ☐, intrauterine scalp electrode ☐)
- ☐ Induced vaginal delivery (no instruments)
- ☐ Induced vaginal delivery (with instruments: Vontousse suction cup ☐, forceps ☐, intrauterine scalp electrode ☐)
- ☐ Caesarian section, WITH labour
- ☐ Caesarian section, WITHOUT labour

14. APGAR SCORE:

	At 1 min	At 5 min	At 10 min
Activity (Muscle Tone)			
Pulse			
Grimace (Reflex Irritability)			
Appearance (skin colour)			
Respiration			

OR if APGAR breakdown not known:

Total score at 1 min: _____
Total score at 5 min: _____
Total score at 10 min: _____

Resuscitation required: Y☐ N☐UK☐; If YES:
Nasopharyngeal suctioning ☐
Bag & Mask Ventilation ☐ CPAP/Neopuff ☐ highest Fio2 reached: _____%
Chest compressions ☐
Intubation ☐

15. Prolonged rupture of membranes (more than 18 hours prior to delivery): Y☐ N☐
    IF YES, LENGTH OF RUPTURE OF MEMBRANES _____ HRS
    IF YES, did mother receive maternal antibiotics during labour? Y☐ N☐DK☐
    Name of MATERNAL antibiotics: ☐U/K

Amoxycillin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Ampicillin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Azithromycin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Benzylpenicillin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Clindamycin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Erythromcyin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Lincomycin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Other: _____	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Other: _____	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐

Was at least one dose of IV Antibiotics given **at least 4 hours** from onset of rupture of membranes prior to baby's delivery?
Y☐ N☐UK☐

DATE OF MOTHERS 1st KNOWN ANTENATAL VISIT: ☐☐/☐☐/☐☐ OR GESTATION IF KNOWN: _____ Weeks

16. GBS SWAB TAKEN OF MOTHER DURING THIS PREGNANCY: Y☐ N☐ UK☐

IF YES, was GBS swab POSITIVE? Y☐ N☐ UK☐

If YES what gestation was swab taken at: ____ weeks OR: DATE swab was taken ☐☐/☐☐/☐☐

IF YES, Where was the SITE of GBS swab:

RECTO-VAGINAL ☐
RECTAL ☐
LOW or HIGH VAGINAL ☐
FROM URINE CULTURE ☐
DON'T KNOW ☐
OTHER _____

17. IF GBS SWAB WAS NOT TAKEN this pregnancy, was this patient known to have a previous positive GBS swab prior to this pregnancy?

Y☐ N☐

If YES what gestation was swab taken at: ____ weeks OR: DATE swab was taken ☐☐/☐☐/☐☐

IF YES to known previous GBS swab, where was SITE of swab:

RECTO-VAGINAL ☐
RECTAL ☐
LOW or HIGH VAGINAL ☐
FROM URINE CULTURE ☐
DON'T KNOW ☐
OTHER _____

18. Any previous delivery of an infant with GBS disease: Y☐ N☐

IF YES:

Infant DOB Date of Birth: ☐☐/☐☐/☐☐ Sex: ☐M ☐F

19. Any previous history of fetal death? Y☐ N☐

IF yes at what age: _____

IF yes, what diagnosis was given _____

20. Any previous history of neonatal death (under 30 days)? Y☐ N☐

IF yes at what age: _____

IF yes, what diagnosis was given _____

MATERIAL HISTORY

21. Past/concurrent medical conditions: ☐ Yes (If yes, specify details below) ☐ No ☐ UK

Previous births <37 weeks: ☐ Yes ☐ No ☐ UK If yes, gestational age at birth _____ weeks (if known)

Asthma: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Cardiovascular disease: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Other respiratory disease: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Co-infection (e.g. influenza, viral RTI): ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Diabetes mellitus: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Obesity ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; BMI _____

Other metabolic: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Immunodeficiency conditions: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Other: ..... ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Other: ..... ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

22. Maternal Smoking status: ☐ Current smoker ☐ Past smoker

23. Any recreational or illicit drugs used during pregnancy, please specify: .....

24. Any other known maternal complications or issues this pregnancy, please specify: .....

25. Any foetal complications identified during this pregnancy (from first/second trimester screening or morphology ultrasounds), please specify: .....

26. Any suspicion of maternal chorioamnionitis during labour? (Maternal Intrapartum Fever, maternal tachycardia, maternal uterine tachycardia, fetal tachycardia, foul smelling amniotic fluid) Yes☐ No☐ DK☐

RECRUITMENT PROCESS

27. How was the patient identified? ICD P36.0 Case Note Audit ☐ Laboratory ☐ Other ☐ specify:_____

NEONATAL CLINICAL DETAILS

Neonatal Initial Presentation:

28. 1st medical presentation or review by clinical staff:

Date: ☐☐/☐☐/☐☐ ☐UK & Time: ☐☐:☐☐ 24hrs ☐UK

29. Place of medical presentation:

Operating theatre ☐ Labour ward ☐ Postnatal ward ☐ Neonatal unit ☐ Emergency Dept ☐ GP ☐ U/K ☐

30. Had the baby had any feeds prior to presentation, if so please specify type and number of days:

☐ Breastfed: Days ____ Hours_____

☐ Formula fed: Days ____ Hours_____

☐ Mixed breast and formula feeds: Days ____ Hours_____

31. Was a Full Blood Count done on the neonate prior to onset of GBS symptoms?

Yes☐ No☐ UK☐ If YES, was this because of:

Hospital protocol for maternal chorioamnionitis: Yes☐ No☐ UK☐

Hospital protocol for mother with positive GBS swab but baby was asymptomatic: Yes☐ No☐ UK☐

Mother had a negative GBS swab but there was some clinical concern regarding the neonate (increased respiratory rate, hypoglycaemia, hypothermia, etc) Yes☐ No☐ UK☐

Mother's GBS status was unknown and there was some clinical concern regarding the neonate (increased respiratory rate, hypoglycaemia, hypothermia, etc) Yes☐ No☐ UK☐

Other, please specify _____

If FBC was taken to screen for GBS disease in the newborn what was the:

Total White cell count _____ (please include units)

Total Neutrophil cell count _____ (please include units)

Total Band count _____ (please include units)

Band Neutrophil Ratio (aka "I/T" ratio) _____(please include units)

Date of FBC: ☐☐/☐☐/☐☐ Time of FBC: ☐☐:☐☐ 24hrs

32. 1st dose of parenteral antibiotics given:

Date: ☐☐/☐☐/☐☐ or ☐ UK Time: ☐☐:☐☐ 24hrs ☐ UK

Given by: ☐ UK ☐ GP at GP clinic ☐ In ED ☐ Inpatient ward

Name and dose of antibiotics: ☐ U/K

Ampicillin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Amoxycillin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Benzylpenicillin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Benzathine penicillin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Cefotaxime, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Ceftriaxone, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Flucloxacillin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Gentamicin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Vancomycin, Dose _____ mg	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Other: _____	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Other: _____	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐

Neonatal Clinical Presentation on Admission:

33. Syndrome/s (tick all that apply):

☐ Meningitis ☐ Septicaemia ☐ Pneumonia

☐ Other invasive disease: .....

34. Vital signs **on presentation**:

Heart rate: Respiratory Rate: Blood Pressure: Temperature: __.__ °C

_____ Max _____ Max _____/_____ Highest

_____ Min _____ Min _____/_____ Lowest

35. **Presenting Signs and Symptoms in neonate *(tick all that apply)***

Temperature instability (< T 36.5°)	☐ Yes ☐ No ☐ UK
Pyrexia (≥ T 37.5°)	☐ Yes ☐ No ☐ UK
Vomiting	☐ Yes ☐ No ☐ UK
Poor feeding	☐ Yes ☐ No ☐ UK
Irritable/unsettled	☐ Yes ☐ No ☐ UK
Abdominal distension	☐ Yes ☐ No ☐ UK
Cyanosis	☐ Yes ☐ No ☐ UK
Respiratory symptoms/ (increased respiratory rate or ↑ work of breathing)	☐ Yes ☐ No ☐ UK
Apnoea	☐ Yes ☐ No ☐ UK
Bradycardia	☐ Yes ☐ No ☐ UK
Poor peripheral perfusion	☐ Yes ☐ No ☐ UK
Hypotension	☐ Yes ☐ No ☐ UK
Unexpected need for resuscitation	☐ Yes ☐ No ☐ UK
Hypoglycaemia	☐ Yes ☐ No ☐ UK
Lethargy	☐ Yes ☐ No ☐ UK
Seizures	☐ Yes ☐ No ☐ UK
Capillary refill time more than 2 seconds	☐ Yes ☐ No ☐ UK
Metabolic and/or respiratory acidosis	☐ Yes ☐ No ☐ UK
Tachycardia	☐ Yes ☐ No ☐ UK
Shock	☐ Yes ☐ No ☐ UK
Persistent foetal circulation (Persistent Pulmonary Hypertension)	☐ Yes ☐ No ☐ UK
DIC	☐ Yes ☐ No ☐ UK

Clinical Information during Acute Hospitalisation

Neonatal Complications:

36. Were there any complications during the acute admission or at follow up: ☐ Yes ☐ No ☐ UK

☐ Pneumonia	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Focal infection involving bones or joints	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Focal infection involving skin and/or soft tissue	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Focal infection of the urinary tract	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Endocarditis	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Meningitis	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Ventriculitis (CNS)	☐ Present at 6 week check up	☐ Present at 1 year check up

☐ Osteomyelitis	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Developmental delay	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Spastic quadriplegia	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Microcephaly	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Seizure disorder	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Cortical blindness	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Deafness	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Periventricular Leukomalacia (on brain imaging)	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Other:.....	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Other:.....	☐ Present at 6 week check up	☐ Present at 1 year check up
☐ Other:.....	☐ Present at 6 week check up	☐ Present at 1 year check up

Neonatal Interventions Received During Hospital Admission

37. **Required Intubation/mechanical ventilation** ☐Yes ☐No ☐UK

If yes:

Method of ventilation:

1) Non-invasive ventilation : ☐CPAP ☐BPAP ☐UK

Episode 1 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %
Episode 2 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %
Episode 3 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %
Episode 4 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %

2) Invasive ventilation

Episode 1 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %
Episode 2 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %
Episode 3 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %
Episode 4 Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐ average FI02 required: __ %

38. **Required nasogastric feeds?** ☐Yes ☐No ☐UK

Fed expressed breast milk exclusively via ng ☐Yes ☐No ☐UK
Fed formula exclusively via ng ☐Yes ☐No ☐UK
Fed a mixture of expressed breast milk and formula via ng ☐Yes ☐No ☐UK

Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐

39. **Required total parental nutrition?** ☐Yes ☐No ☐UK

Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐

40. **Investigations:**

Sterile Sites:

Specimen	*Test*	*Collection Date (dd/mmm/yy)*	*Results*
Blood	Microscopy	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
	Culture:	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
	PCR :	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
Lumbar puncture (CSF)	Culture:	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
	PCR:	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
	Microscopy:	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
LP CSF (old test)	Latex Test for GBS Agglutinins:	__/__/__	☐ Negative ☐ Positive ☐Not Done Others: .....
Urine (old test)	Latex Test for GBS Agglutinins:	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....
Gastric Aspirate (old test)	MCS:	__/__/__	☐ Negative ☐ Positive ☐Not Done ☐ Others: .....

41. **Were there any co-infections?** ☐Yes ☐No ☐UK

Specimen	*Test*	*Collection Date (dd/mmm/yy)*	*Results*

General Follow-up

42. **Medical follow-up**
    Was an outpatient appointment made for follow-up? ☐Yes ☐No ☐UK
    Was a follow-up appointment made to see GP 4 to 6 weeks after discharge from hospital? ☐Yes ☐No ☐UK
43. **Feeding status at discharge**
    Discharged breast feeding ☐Yes ☐No ☐UK
    Discharged on formula feeds ☐Yes ☐No ☐UK
    Discharged on mixture of breast feeding and formula feeds ☐Yes ☐No ☐UK
44. **Discharge weight:** _____ grams

TREATMENT/OUTCOME DETAILS

45. Was patient transferred to another hospital?: ☐Yes ☐No ☐UK
If yes, name of hospital: .....

46. Total Duration of hospital stay (following delivery of infant) : _____ days ____ hours

47. What was the date of discharge or transfer? ☐☐/☐☐/☐☐

48. Outcome at discharge:
    ☐ Alive upon discharge
    ☐ Inpatient death; please specify cause of death .....

ICD-10 DIAGNOSIS CODES

49. Primary code: ☐☐☐☐

50. Secondary codes: ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

GBS STUDY: USE THIS FORM FOR CONTROL CASES

*BABY URN:*_____

*MOTHERS URN:*_____

Once form completed please delete baby's and mother's URN before sending form to WCH

Instructions: Please answer each question by ticking the appropriate box or writing your response in the space provided. UK= unkno
NA = Not applicable

DE-IDENTIFIED ID: _____ *(W#### for WCH, A#### for AliceSprings, D#### for Royal Darwin etc)*

Enter the following information

BEFORE STARTING -→ Did this CONTROL PATIENT present to hospital in the first 90 days of life with sepsis? (As identified per online hospital laboratory records or case notes) ☐ Yes ☐ No ☐ UK

If YES → THIS IS EXCLUSION CRITERIA, DO NOT USE THIS PATIENT AS A CONTROL.

PATIENT DETAILS

1. First 2 letters of first name: ☐☐
2. First 2 letters of surname: ☐☐
3. Date of Birth: ☐☐/☐☐/☐☐
4. Sex: ☐M ☐F
5. Postcode of family: ☐☐☐☐
6. Time Of Birth (24 HR CLOCK): ☐☐ : ☐☐
7. Date of Admission to Neonatal Unit: ☐☐/☐☐/☐☐ & Time of Neonatal Unit Admission (24 HR CLOCK): ☐☐ : ☐☐
8. Was patient admitted to NICU/HDU? ☐ Yes ☐ No ☐ UK
   If yes, what was the total length of ICU admission: ☐☐ Days ☐☐ hours
9. Mother's Ethnicity _____ ☐ UK Maternal DOB: ☐☐/☐☐/☐☐
10. Transferred from another hospital? Y☐ N☐ UK☐ IF YES, SPECIFY WHICH HOSPITAL _____
    Date of Admission at referring hospital: ☐☐/☐☐/☐☐
11. Is the child of ATSI descent? Aboriginal ☐ Torres Strait Islander ☐ Both ☐ No ☐ UK ☐

BIRTH HISTORY

10. Gestational age: Term ☐ Pre-term (<37 weeks) ☐ **If pre-term,** state gestational age _____(weeks) UK ☐
11. Mothers Parity PRIOR to delivery of this child: G ___ P ___
12. Birth weight _____ grams (exact weight if known please)

& Weight category:

- ☐ < 749g
- ☐ 750-999g
- ☐ 1000-1499g
- ☐ 1500-1999g
- ☐ 2000-2499g
- ☐ 2500-2999g
- ☐ 3000-3499g
- ☐ >/= 3500g

13: Method of delivery:

- ☐ Spontaneous vaginal delivery (no instruments)
- ☐ Spontaneous vaginal delivery (with instruments: Ventousse suction cup ☐, forceps ☐, intrauterine scalp electrode ☐)
- ☐ Induced vaginal delivery (no instruments)
- ☐ Induced vaginal delivery (with instruments: Ventousse suction cup ☐, forceps ☐, intrauterine scalp electrode ☐)
- ☐ Caesarian section, WITH labour
- ☐ Caesarian section, WITHOUT labour

14. APGAR SCORE:

	At 1 min	At 5 min	At 10 min
Activity (Muscle Tone)			
Pulse			
Grimace (Reflex Irritability)			
Appearance (skin colour)			
Respiration			

OR if APGAR breakdown not known:

Total score at 1 min: _____
Total score at 5 min: _____
Total score at 10 min: _____

Resuscitation required: Y☐ N☐ UK☐ If YES:
Nasopharyngeal suctioning ☐
Bag & Mask Ventilation ☐ CPAP/Neopuff ☐ highest Fio2 reached: ____%
Chest compressions ☐
Intubation ☐

15. Prolonged rupture of membranes (more than 18 hours prior to delivery): Y☐ N☐
    IF YES, LENGTH OF RUPTURE OF MEMBRANES _____ HRS
    IF YES, did mother receive maternal antibiotics during labour? Y☐ N☐ UK☐
    Name of MATERNAL antibiotics: ☐ U/K

Amoxycillin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Ampicillin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Azithromycin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Benzylpenicillin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Clindamycin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Erythromcyin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐
Lincomycin	Start Date: ☐☐/☐☐/☐☐	End Date: ☐☐/☐☐/☐☐

Other: _____ Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐

Other: _____ Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐/☐☐

Was at least one dose of IV Antibiotics given **at least 4 hours** from onset of rupture of membranes prior to baby's delivery?
Y☐ N☐ UK☐

DATE OF MOTHERS FIRST KNOWN ANTENATAL VISIT: ☐☐/☐☐/☐☐ OR GESTATION IF KNOWN: _____ WEEKS

16. GBS SWAB TAKEN OF MOTHER DURING THIS PREGNANCY: Y☐ N☐ UK☐
IF YES, was GBS Swab POSITIVE? Y☐ N☐ UK☐
If YES what gestation was swab taken at: ____ weeks OR: DATE swab was taken ☐☐/☐☐/☐☐
IF YES, Where was the SITE of GBS swab:
RECTO-VAGINAL ☐
RECTAL ☐
LOW or HIGH VAGINAL ☐
FROM URINE CULTURE ☐
DON'T KNOW ☐
OTHE_____

17. IF GBS SWAB WAS NOT TAKEN this pregnancy, was this patient known to have a previous positive GBS swab prior to this pregnancy? Y☐ N☐
If YES what gestation was swab taken at: ____ weeks OR: DATE swab was taken ☐☐/☐☐/☐☐
IF YES to known previous GBS swab, where was SITE of swab:
RECTO-VAGINAL ☐
RECTAL ☐
LOW or HIGH VAGINAL ☐
FROM URINE CULTURE ☐
DON'T KNOW ☐
OTHER _____

18. Any previous delivery of an infant with GBS disease: Y☐ N☐
IF YES:
Infant DOB Date of Birth: ☐☐/☐☐/☐☐ Sex: ☐M ☐F

19. Any previous history of fetal death? Y☐ N☐
IF yes at what age _____
IF yes, what diagnosis was given _____

20. Any previous history of neonatal death (under 30 days)? Y☐ N☐
IF yes at what age: _____
IF yes, what diagnosis was given _____

MATERNAL HISTORY

21. Past/concurrent medical conditions: ☐ Yes (If yes, specify details below) ☐ No ☐ UK
Previous births <37 weeks: ☐ Yes ☐ No ☐ UK If yes, gestational age at birth ____ weeks (if known)
Asthma: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

Cardiovascular disease: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Other respiratory disease: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Co-infection (e.g. influenza, viral RTI): ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Diabetes mellitus: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Obesity ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; BMI _____
Other metabolic: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Immunodeficiency conditions: ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Other: ..... ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....
Other: ..... ☐Yes ☐ No ☐UK If yes, ☐ resolved ☐ ongoing; Details: .....

22. Maternal Smoking status: ☐ Current smoker ☐ Past smoker

23. Any recreational or illicit drugs used during pregnancy, please specify: .....

24. Any other known maternal complications or issues this pregnancy, please specify: .....

25. Any foetal complications identified during this pregnancy (from first/second trimester screening or morphology ultrasounds), please specify: .....

26. Any suspicion of maternal chorioamnionitis during labour? (Maternal Intrapartum Fever, maternal tachycardia, maternal uterine tachycardia, foetal tachycardia, foul smelling amniotic fluid) Yes☐ No☐ UK☐

NEONATAL CLINICAL DETAILS

General Follow-up

27. **Medical follow-up**
Was an outpatient appointment made for follow-up? ☐Yes ☐No ☐UK
Was a follow-up appointment made to see GP 4 to 6 weeks after discharge from hospital? ☐Yes ☐No ☐UK

28. **Feeding status at discharge**
Discharged breast feeding ☐Yes ☐No ☐UK
Discharged on formula feeds ☐Yes ☐No ☐UK
Discharged on mixture of breast feeding and formula feeds: ☐Yes ☐No ☐UK

29. **Discharge weight:** _____ grams

TREATMENT/OUTCOME DETAILS

30. Was patient transferred to another hospital?: ☐Yes ☐No ☐UK
If yes, name of hospital: .....

31. Total Duration of hospital stay (following delivery of infant): _____ days ____ hours

32. What was the date of discharge or transfer? ☐☐/☐☐/☐☐

Outcome at discharge:
☐ Alive upon discharge
☐ Inpatient death; please specify cause of death .....

ICD-10 DIAGNOSIS CODES

49. Primary code: [ ]

50. Secondary codes: [ ] [ ] [ ] [ ]