GBS STUDY: Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns.

(Thesis by Publication)

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LIST OF ABBREVIATIONS

ATSI	Aboriginal & Torres Strait Islander
APGAR	A score measuring clinical condition of a Newborn infant
APSU	Australian Paediatric Surveillance Unit
BNR	Band neutrophil Ratio
CDC	Centre for Disease Control & Prevention
CPS	Capsular Polysaccharides
GBS	Group B Streptococcus/Streptococcal
EOGBS	Early Onset Group B Streptococcal
HDU	High Dependency Unit
HREC	Human Research Ethics Committee
IAP	Intrapartum Antibiotic Prophylaxis
ICD 10	International Statistical Classifications of Disease -10
ICU	Intensive Care Unit
I/T ratio	Immature Neutrophils (band neutrophils) / Total Neutrophil Ratio
LOGBS	Late Onset Group B Streptococcal
NICU	Neonatal Intensive Care Unit
NT	Northern Territory
PROM	Prolonged Rupture of Membranes
RANZCOG	Royal Australian & NZ College of Obstetrics & Gynaecology
ROM	Rupture of Membranes
SA	South Australia

ABSTRACT

This body of work arose from everyday challenges that paediatricians and neonatologists have working in the field of general paediatrics and neonatology regarding the implementation and use of the universal Group B Streptococcal (GBS) Screening and Management Guidelines. Despite universal screening programs for maternal GBS colonisation in pregnancy that have been instituted across hospitals in Australia, neonatal GBS infection remains the most common cause of infectious neonatal morbidity and mortality. This bacterium can illicit early onset disease occurring in the first week of life of the neonate, or late-onset disease occurring anywhere after the first week of life, up to the first three months causing major mortality and morbidity, often presenting as neurodevelopmental sequelae in affected infants.

In Australia, most of our states and territories have adopted a version of the universal screening approach of pregnant mothers during week 35-37 of their pregnancy, for GBS colonisation. Depending on individual risk factors, maternal antibiotic prophylaxis is offered to mothers in labour in order to prevent neonatal GBS disease. Despite the universal recommendations to screen and manage this disease, the guidelines are often followed sporadically and left up to the clinician's discretion. There is also a concern that the widespread use of maternal antibiotic prophylaxis is increasing worldwide antibiotic resistance of GBS strains and may lead to unwanted health issues in the longer term for the infant (such as increasing atopic and gastrointestinal disease).

The first publication, *'GBS Study Protocol'*, describes the novel study design implemented for the comprehensive collection of retrospective data over a 16-year period across 5 hospitals in South Australia and the Northern Territory. Currently, notification of Group B streptococcal infections in the young infant is not mandatory. As a result, the true incidence of early onset and late onset GBS disease is not known in Australia. This case-control study was designed to measure the true incidence of both early onset and late onset GBS disease over the last 16 years in South Australia (SA) and the Northern Territory (NT) and to identify any maternal and neonatal risk factors for disease (see Appendix for data collection tools).

The second publication, '*GBS Case-Control Study',* reports the outcomes of the case control study. A primary objective of this study was to determine maternal and neonatal risk factors for GBS neonatal infection in the SA and NT between the years 2000 to 2015. A further primary objective is to measure the incidence of GBS neonatal infection in SA and the NT for early-onset GBS disease (disease in the first 7 days of life) and late-onset GBS disease (disease occurring after 7 days to 90 days of life), as well as to comment on the clinical features and burden of GBS disease. The SA incidence of probable and confirmed cases of early onset GBS was found to be 32 per 100,000 live births and of late onset GBS was 17.8 per 100,000 live births; and NT incidence of early onset GBS was 90 per 100,000 live births and 17.8 per 100,000 live births for late onset GBS.

This information will assist in determining whether a future GBS vaccination program should be recommended for pregnant mothers in the future. This large study conducted at five hospital sites, required the participation of several site supervisors and data collectors, with Human Research Ethics Committees approvals obtained at each site including the SA Aboriginal Human Research Ethics Committee approval (see Appendix for Human Research Ethics committee approval forms).

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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CHAPTER ONE:

A LITERATURE REVIEW OF GBS

&

OVERVIEW OF GBS SCREENING IN AUSTRALIA

CHAPTER 1

LITERATURE REVIEW: OVERVIEW OF GROUP B STREPTOCOCCUS SCREENING AND NEONATAL GBS DISEASE MANAGEMENT IN AUSTRALIA

1.1 Group B Streptococcus: Pathogenicity & Epidemiology

Group B streptococcus (GBS) *Streptococcus agalactiae* is responsible for the majority of serious neonatal infections. [1, 2] Neonatal group B streptococcus infections are categorised as early-onset GBS (EOGBS) disease, occurring in the first week of life, or late-onset GBS (LOGBS) disease, occurring after the first week until 90 days of life. [2] EOGBS infection is the result of transfer of GBS bacterium from the mother's colonised genital tract to the fetus. [3] During delivery vertical transmission of GBS from mother to infants can occur in 30–70% of cases. [4] The pathogenesis of late-onset infections is less clearly defined and likely multifactorial. [5] GBS pathogens can be acquired during delivery via the birth canal, but nosocomial and other maternal factors, such as GBS being passed to the infant via breast milk, are likely to be involved. [5]

In the 1970s GBS emerged as the principal pathogen responsible for neonatal sepsis. [6-8] Isolates of GBS can be divided into 10 capsular polysaccharide (CPS) serotypes (Ia, Ib, II - VIII, IX) which are each antigenically individual with serotype III being a major cause of neonatal disease, in particular GBS meningitis [9]. Further studies have also shown that on a molecular level, using GBS multi-locus sequence typing, the GBS capsular serotype clonal complex 17 (ST-17), also appears to be a key serotype causing neonatal disease. [10]

1.2 Group B Streptococcus Infections: Risk factors & Clinical Disease

Identified maternal and neonatal risk factors for GBS disease include: "prematurity, maternal group B streptococcus carriage, prolonged rupture of membranes (greater than 18 hours), and signs of maternal chorioamnionitis such as maternal intrapartum fever". [11] Neonates with EOGBS and LOGBS present with a wide range of clinical symptoms ranging from "respiratory distress, oxygen requirement, hypothermia, hyperthermia, lethargy, poor perfusion, hypotension and seizures". [12] The effectiveness of intrapartum antibiotic prophylaxis (IAP) to mothers in labour to prevent neonatal GBS disease was first described in the 1980s [7, 8, 11] and confirmed in a meta-analysis of five randomized trials. [8, 13] Administration of IAP during labour has proven to significantly reduce neonatal GBS disease. [11] Prior to screening protocols and IAP, the incidence of EOGBS disease in Australia was reportedly 2-3 per 1000 live births. [12, 14] The subsequent introduction of IAP into many countries' neonatal GBS screening protocols has led to a reduction in the incidence neonatal GBS disease by 50% - 80%. [8, 15, 16] Prior to the implementation of maternal IAP, the incidence of EOGBS was considerably higher than LOGBS, responsible for 'approximately 80% of neonatal GBS infections.' [17] Since the introduction of IAP into GBS prevention strategies, both syndromes are approaching similar rates in Australia. [17, 18]

1.3 Group B Streptococcus Infections: Risk-based vs Universal Screening Approaches

Two major screening approaches have been adopted internationally. The first is based on stratification of risk for pregnant women at the time of delivery with IAP administered to women in labour with clinical risk factors for the disease. [2] The second is based on the universal screening of pregnant women by vaginal and rectal swabs for GBS with IAP then offered to carriers.[2] Internationally it is recommended that screening for GBS is conducted via a rectal and vaginal swab for GBS detection at 34–37 weeks' gestation, [12] with the 'positive predictive value of GBS culture within this period of 87% and negative predictive value of 96%'. [12, 19] IAP is also offered to women if there are risk factors for GBS disease,

such as “a mother having a previous infant with invasive GBS disease, GBS bacteriuria in the current pregnancy, a positive GBS screening culture during the current pregnancy, prematurity, any suggestion of chorioamnionitis such as an intrapartum temperature (regardless of GBS status), and prolonged ruptured membrane of > 18 h where GBS status is unknown”. [12] While a screening-based approach has not been reported to change IAP use when compared to a risk-based approach, [12, 20] screening for GBS by culture rather than by assessing risk factors may significantly reduce antibiotic usage. [12, 21] The United Kingdom and the Netherlands have adopted a risk-based approach alone, [22-24] which is likely related to the concern of widespread maternal IAP usage. The major concerns regarding the use of maternal IAP for GBS screening protocols is that it ‘will lead to greater chance of selecting for non-GBS and more resistant organisms creating antibiotic resistance in particular organisms’ causing EOGBS and other serious neonatal infections. [12, 16]

1.4 Group B Streptococcus Infections: Impact on Screening Approaches

The data on the impact of screening on the incidence of GBS disease is similarly conflicting. An Australian study reported a fall in the incidence of EOGBS from 0.84 per 1000 live births during the pre-screening period to a significant 0.00 per 1000 live births after the institution of GBS screening. [12] As a result, the authors calculated that ‘in order to prevent one case of EOGBS, 1191 colonised women would be required to be given IAP’. [12] Furthermore, they concluded that ‘since maternal colonisation incidences of GBS are 24% and the positive predictive accuracy of antenatal culture-based screening is 87% [19] 5704 women would need to be screened *to prevent one case of EOGBS*’. [12] Similarly, after GBS screening guideline introduction in the United States of America (USA), which comprised a universal screening approach to GBS using rectovaginal swabs, there was a decrease of early onset GBS sepsis and meningitis from 1.7 per 1000 livebirths to 0.6 per 1000 livebirths in (between 1990 to

1998); [16, 25] and after widespread introduction of universal screening in 2002 in the USA, the incidence of early-onset disease fell further, from 0.47 per 1000 livebirth to 0.34 per 1000 livebirths. [25]

However, a study conducted in the Netherlands showed that the introduction of GBS screening (using the risk-factor based approach) and treatment guidelines for invasive group B streptococcus disease in 1999 'did not reduce the incidence of disease in neonates in the following 25 years'. [2]. In fact, there was an increase in the incidence of invasive GBS infection from 0.20 per 1000 livebirths to 0.32 per 1000 livebirths in 2011 (p<0·0001), and increased incidence of EOGBS from 0.11 per 1000 livebirths to 0.19 per 1000 livebirths (p<0·0001) between 1987 and 2011. [2] This was attributed to a rise in the number of cases caused by GBS belonging to a specific GBS serotype III (clonal complex 17) and a decrease in a specific GBS serotype III (clonal complex 19), resulting in largely the same distribution of GBS serotype III before and after the introduction of IAP. [2]. The authors postulated that the rise in incidence may be due to "changes in the host, medical practice, increased submission of isolates to the National Laboratory, or the pathogen itself". [2].

Similarly, an epidemiological study from England and Wales spanning 20 years between 1991 and 2010, showed a steady increase for GBS from 0.42 per 1000 live births to 0.70 per 1000 live births, largely accounted for by marked increases in late-onset disease, from 0.11 per 1000 live births to 0.29 per 1000 live births, [26] following introduction of guidelines in 2003 using the risk factor approach. This steady increase was thought to be related increased numbers of premature infants, [26] but the authors determined that they may not have captured the true levels of EOGBS treated by IAP, as only culture proven GBS was included in this study. [26]

In Australia, the approaches used include both the universal screening with swabs and risk-based approach, and may explain why we have seen a decrease in EOGBS in Australia, like the USA which adopted the universal screening approach. Unlike the USA and many European countries, the Netherlands and the UK have only adopted the risk-based screening approach [22-24] which may explain the steady incline of EOGBS in these countries. Worldwide there appears to be ongoing contradictory data regarding GBS incidence and burden, and only by knowing the true incidence of EOGBS, LOGBS and disease burden in Australia will we be able to make informed public health choices regarding a future GBS immunisation program, which has the potential to ameliorate the disease.

1.5 Group B Streptococcus Infections: Current knowledge gaps

This study will provide important data on the true incidence of the disease, as well the exploration of potential risk factors for disease and incidence, for example ethnicity and whether it is an additional risk factors for disease or disease mortality. This data will help inform whether a future GBS vaccination program for pregnant women would be beneficial. For instance, studies conducted in the USA have shown black ethnicity groups have a higher incidence of GBS, [27] however in Australia we do not have conclusive evidence to say whether individuals of Aboriginal or Torres Strait Islander (ATSI) ethnicity is an independent risk factor for maternal GBS colonisation or neonatal GBS disease. One study conducted in 1995 showed that Aboriginal Australian infants have a rate three times higher of GBS than non-Aboriginal infants (5.2 per 1000 births vs 1.7 per 1000 infants), [14] however more recent data did not find that Aboriginal newborns were more at risk of neonatal sepsis. [28] The discrepancies between these two studies is further evidence that the true disease burden and risk factors for EOGBS and LOGBS in Australia remains unknown, and further evidence is required to ascertain the true disease incidence and burden. Only then will we be able to develop and implement a vaccination program to target certain population groups if they are shown to be at greater risk for disease.

1.6 Evaluation of South Australian Perinatal Practice Guidelines GBS Screening Practices & Why Further Studies Are Required

South Australia (SA) has had formal guidelines for the management of GBS colonisation in pregnant mothers at 36 weeks with a low vaginal swab and treatment of neonatal GBS disease since 2004, [29] following a publication by the Centre for Disease Control (CDC) for a consensus approach to GBS screening and maternal IAP in 2002. [30] It is recommended that IAP for GBS should be "given as soon as possible in labour" with adequate GBS prophylaxis considered to have been achieved if at least "1 dose of antibiotics is given 4 hours before birth". [29] There has been ongoing debate as to whether antibiotics given less than 4 hours before birth will confer some benefit to the neonate. While some studies suggest that administration as little as 1-2 hours before delivery may offer some protection, this is not as effective in preventing EOGBS as maternal antibiotic administration 4 or more hours prior to birth. [31] In reality, these guidelines are followed to the treating clinician's discretion, and there is currently no available data from any auditing process in SA regarding the true incidence of GBS neonatal disease or if mothers received antibiotics and how soon before delivery this occurred.

The SA perinatal guidelines suggest that infants are deemed to be at risk for early onset neonatal GBS sepsis if there are any of the following: 'evidence of maternal chorioamnionitis (maternal temperature above 38° C, maternal pulse > 100/min, fetal heart rate > 160 bpm, uterine tenderness, rising CRP or white blood cell count, unless there is another obvious cause), preterm labour at less than 37 weeks gestation, preterm or pre-labour rupture of membranes, and prolonged rupture of membranes greater than 18 hours at term (greater than 36 weeks gestation) with or without labour.' [29] An infant is also considered high risk if the mother is GBS positive, defined as: 'maternal GBS vaginal colonisation during this pregnancy based on a swab taken less than 5 weeks before labour, maternal GBS bacteriuria in the current pregnancy, and early-onset neonatal GBS sepsis in a previous pregnancy'. [29]

There is no current data on which of the presenting clinical features are the most accurate predictors for the risk of vertical transmission of GBS from mother to infant. Further data collection is required to determine the true risk factors for GBS disease in our Australian population and any new risk factors for EOGBS and LOGBS disease.

Over time there has been variation in the clinical guidelines with respect to the type of investigations ordered on the mother and infant. With regards to maternal investigations, compared to earlier iterations of the clinical guideline, the updated version published in 2009 placed greater emphasis on not solely relying on a negative maternal GBS swab as a reliable indicator as reduced risk. [32] This was based on data from a retrospective cohort study of 61% of term infants with EOGBS where the antenatal maternal screening GBS swab was used as a guide to GBS status at birth was falsely negative. [33] In addition, maternal GBS bacteriuria, demonstrated in the current pregnancy, and the mother having a previous infant infected with GBS was also recognised as increasing the risk of neonatal GBS infection. [32] Interestingly the 2009 guidelines reiterated the importance of recto-vaginal swab sampling, as opposed to low vaginal alone, which resulted in an increase in the detection of maternal GBS carriage from 22% to 27%. [32] A 22% detection rate of maternal GBS colonisation seems low when considering it is the basis for screening all women during pregnancy. Therefore, the determination of the true percentage of maternal GBS colonisation, how it was detected (rectovaginal vs vaginal only) and what percentage of these women then have an infant with proven neonatal GBS disease are all critical in refining the clinical management of this patient group.

Since 2007 the guidelines have recommended that neonates displaying signs of sepsis or with whom had mothers with maternal chorioamnionitis, should have a blood culture, complete blood picture and a band (immature neutrophils)/total neutrophil ratio. [34] In addition, the neonate should receive antibiotics

and a lumbar puncture, an endotracheal aspirate, gastric aspirate and surface swabs to determine colonisation of flora soon after a birth (however the 2004 guidelines did note that this had a poor correlation with invasive sepsis). [29] Previously utilised neonatal urine latex tests are a poor screening test for assessing suspected sepsis in newborns, [34] and as a result are no longer routinely conducted in the workup of infants.

The 2012 guidelines stipulated that normal ranges for neonatal complete blood pictures 'vary with population, gestation and postnatal age,' [35, 36] and that the band (immature neutrophils): total neutrophil ratio was the most sensitive indicator of sepsis [37] with a band neutrophil ratio (or [I/T] ratio) of > 0.2 a suggested cut-off for treatment for the neonate with antibiotics. [38] However, the blood picture may be normal if taken too early after birth in a colonised baby and sensitivity increases at 4-6 hours after birth. [39] There has been no data since the implementation of these guidelines in SA to corroborate how many infants with EOGBS and LOGBS are demonstrating a total [I/T] of > 0.2 and whether this is the sole factor in the treating clinicians' decision to administer antibiotics. Owing to the 'high false positive rate of the blood picture' in asymptomatic term babies at risk of sepsis, [39] antibiotics are often given until blood cultures are negative at 24 hours, and the complete blood picture has normalised. [39] Therefore, this study will collect data on what percentage of asymptomatic infants with risk factors are receiving these antibiotics, compared to 'population, gestation and postnatal age' of infants with true disease. This data will help inform if these infants are truly at a risk for EOGBS and LOGBS and may result in rationalisation of antibiotic usage. In turn, this may potentially decrease the economic burden of unnecessary antibiotic usage and associated prolonged hospital stay.

Currently, term asymptomatic infants whose mothers are GBS positive, or GBS unknown with ROM > 18 hours with incomplete IAP, are investigated with a complete blood picture (see appendix for

treatment algorithm). However, if an asymptomatic term baby has a *negative* maternal GBS swab (or is GBS unknown with ROM < 18 hours), the guidelines suggest they do not require a full blood count but have 'four hourly respiratory rate and temperature observations for 24 hours.' [29] Preterm babies that are asymptomatic and whose mothers received inadequate IAP should be investigated and treated with antibiotics. [29] If these mothers received adequate IAP, these newborns are investigated but 'antibiotics are given selectively based on results of preterm cultures or degree of prematurity.' [29] This study will collect data on neonatal investigations on premature or asymptomatic term infants with positive maternal GBS swabs, or prolonged rupture of membranes, and relate this data to subsequent development of EOGBS or LOGBS. In addition to determining the compliance to current guideline recommendations, this data may support rationalisation of maternal IAP use.

There is no doubt that one consequence of following these clinical guidelines may be a prolongation of hospital stay for some infants. Previous SA guidelines (2009 – 2011) stated that infants with risk factors for sepsis should be observed in hospital for at least 24 hours (in the discussion of early discharge home < 48 hours after birth of the term asymptomatic infant with risk factors), with a caveat that some individual circumstances may indicate a longer period of observation. [32, 40, 41] In 2012 the recommendation was made that "term asymptomatic babies at risk for sepsis but with adequate intrapartum antibiotic prophylaxis, and those where mother is GBS unknown but with no other risk factors, may be discharged after a minimum observation period of 4-6 hours. If discharged, parents should be advised to seek immediate medical attention is their baby develops breathing difficulty or poor feeding over the following 24 hours". [39]

1.7 Routine GBS screening and treatment with IAP vs future vaccination programs

Both the universal screening approach and the assessment of maternal risk factors approaches have advantages and disadvantages, for example, the former being more expensive [12]. The latter approach is 'easier to implement, but difficult to monitor because there is no specimen collection, processing and reporting of results.' [8, 12] It has been demonstrated that the screening-based approach was almost '50% more effective in preventing early-onset GBS disease (0.33 per 1000 vs 0.59 per 1000 live births)'. [20] The study stated that 'risk factors were present in 24% of women and the use of antibiotics was similar in both groups including the screened group and unscreened group (31% and 29% respectively), demonstrating that the screening-based approach did not result in significant increase in antibiotics usage'. [12, 20] Australia currently employs both the risk based and screening-based approach.

A Cochrane review on the topic evaluated three trials (capturing 500 women) assessing the effects of maternal antibiotic prophylaxis versus no treatment. The review showed that IAP did 'not significantly reduce the incidence of all-cause mortality, mortality from GBS infection or from infections caused by bacteria other than GBS'. [40] The incidence of early GBS infection was reduced with IAP compared to no treatment [risk ratio (RR) 0.17, 95% confidence interval (CI) (0.04 to 0.74)] with a calculated number needed to treat to of 25.[40] However, the 'incidence of LOGBS was not significantly different between groups', [40] with the authors proposing that 'giving antibiotics was not supported by conclusive evidence'. [40] Importantly, the authors concluded that even though IAP appeared to reduce EOGBS, this result was at high risk of bias due to the included studies' methodology and execution which did not include preset sample sizes, the lack of a placebo in the control groups, and the exclusion of women who developed signs of infection in labour. [40]

This systematic review also reiterated that little data has been collected in North America following the implementation of GBS screening guidelines and IAP, and that there were only three randomised controlled trials conducted more than 20 years ago in three different countries that have been published, encompassing a total of 500 women. [40] Similarly in Australia, there is also a sparsity of data on GBS, highlighting the importance of further data collection to elucidate the true disease incidence and burden, in order to address EOGBS and LOGBS effectively in our local and global community.

1.8 Future GBS vaccination programs

With the lack of conclusive evidence supporting IAP and cost of universal screening, it appears that the future management of this disease lies in prevention with a maternal vaccine in pregnancy as opposed to treatment with maternal IAP and neonatal antibiotics. Given the significant morbidity and mortality that GBS causes in our infant population worldwide, such a vaccination program may finally be the answer to decrease the stable incidence of LOGBS, which IAP has not been able to do, and potentially eradicate the disease altogether. There are several advantages to such an immunisation program. Maternal immunisation would be more cost effective than IAP, does not need to be administered during each pregnancy, it would eliminate the concern regarding 'development of antimicrobial resistance in GBS with maternal IAP, and most importantly, it has the potential to prevent LOGBS'. [41] Immunisation would offer several advantages over maternal IAP as maternal IAP is not without its own risk and would be an acceptable approach to disease prevention in Australia, where maternal vaccination programs for pertussis and influenza to confer immunity to the fetus already exist. IAP given to pregnant women is not without risk as they can cause allergic reactions in the mother, which can be severe and potentially life-threatening. Maternal IAP can also increase the possibility of resistant strains of GBS, and concerningly it is reported that '20% of GBS isolates are already resistant to clindamycin and 30–40% to erythromycin'. [42, 43]

Developing an appropriate vaccine requires an understanding of the main virulence factors associated with GBS. GBS is a gram-positive encapsulated coccus which occurs in pairs or short chains which shares a common Lancefield group B polysaccharide antigen. It is further distinguished on the basis of type-specific CPS into ten antigenically unique serotypes (Ia, Ib, II-IX).' [4, 44] In past decades it has been proposed that '95% of infant and maternal GBS disease is caused by only five capsular polysaccharide serotypes: Ia, Ib, II, III and V', [45, 46] and for serotypes Ia, Ib, III and V, and several studies indicate that protective human immunity is associated with sufficient amounts of maternal antibodies to these capsular polysaccharides'. [47] GBS virulence factors include the use of capsular polysaccharide (CPS), adhesion factors that increase binding to host cells, inducing pore-forming toxins into host cells which cause damage, evasion factors which prevent complement binding and lead to a decrease in recruitment of neutrophils, and repelling and resisting antimicrobial peptides. [48] CPS is the 'most widely studied GBS virulence factor as it acts by facilitating evasion of the host's immune system on a molecular level', [49] and it has been suggested that there is a 'correlation between invasive neonatal GBS infection and low levels of maternal antibodies to CPS antigens'. [4, 50]

CPS has emerged as a popular vaccination target in the last decade as a result of its importance as a virulence factor. [51] A study by Baker et al demonstrated that high 'maternal antibodies correlate with protection against serious GBS infection in neonates and that vaccination of pregnant women against CPS might be an effective strategy to protect neonates against GBS infection'. [4, 50] This may be incredibly important for premature infants, as they only possess approximately 30-50% of maternal antibody compared to term infants. Mothers at risk of having premature labour would be good candidates for a GBS vaccine to provide 'higher antibody levels that can compensate for prematurity and potentially protect their infants from late-onset disease'. [52]

GBS vaccine development has only advanced to phase 1b/II trials by vaccine manufacturer Novartis/GSK [53], which is a trivalent (Ia, Ib, and III) GBS polysaccharide conjugate vaccine. [54] In 2017 the vaccine manufacturer Pfizer started phase 1 trials to assess a pentavalent GBS polysaccharide targeting GBS serotypes Ia, Ib, II, III, and V. [55] Vaccination to target GBS disease prevention would revolutionise the treatment and management of this disease, and not only would it finally lead to decreasing levels of late onset GBS disease (which the advent of IAP has not been able to achieve), but it would also decrease the rates of miscarriage and stillbirth related to overwhelming GBS infection. [44]

1.9 Summary of current concerns regarding neonatal GBS and the need for this study

There is currently no mandatory reporting for neonatal GBS infection or its complications in Australia, and previous reported incidences of early onset and late onset GBS disease has come from studies now over 10 years old and have relied on passively reported data from clinicians to the Australian Paediatric Surveillance Unit. As a result, we do not know the true incidence of early onset and late onset infection in SA or the NT. There is also concern regarding the use of intrapartum antibiotic usage in the management of mothers found to be at high risk for an infant with neonatal GBS disease. This study will ascertain if there are any new risk factors for neonatal GBS infection and identify the true incidence of the disease in SA and NT. Gathering this data will be imperative in deciding on a feasibility for a future perinatal GBS vaccination program in Australia in order to potentially eradicate this significant neonatal disease.

CHAPTER TWO:

GBS STUDY PROTOCOL

Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns

A CASE CONTROL STUDY

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Dr. Marianne Yanni		
Contribution to the Paper	Involved in protocol design and ethic submissions, involved in data collection at South Australian Sites, involved in data entry for all South Australian & Northern Territory Sites, involved in data interpretation, & report writing of all 3 chapters of thesis (principal author of both publications).		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	14/2/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. *the candidate's stated contribution to the publication is accurate (as detailed above);*

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Primary supervisor, involved in protocol design and ethic submissions, involved in checking data analysis & report writing		
Signature		Date	11 Feb 2019

Name of Co-Author	A/Prof Michael Stark		
Contribution to the Paper	Primary supervisor, involved in protocol design and ethic submissions, involved in checking data analysis & report writing		
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A case control study to assess risk factors for neonatal group B streptococcal infection in Australian infants

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ABSTRACT

Introduction

Group B streptococcus (GBS) is the most common cause of life-threatening infections in the neonatal period and the leading infectious cause of morbidity and mortality in newborns. The GBS bacterium colonises approximately 10% to 30% of pregnant women. Understanding the incidence, risk factors and outcomes of neonatal GBS will help inform hospital guidelines in the appropriate use of intrapartum antibiotic prophylaxis (IAP). It will also inform use and the potential for the introduction of a GBS vaccine program in Australia for pregnant women to prevent further neonatal morbidity and mortality.

Methods and analysis

Cases of neonatal GBS disease will be identified by laboratory database searches for positive GBS cultures and medical record clinical auditing using international statistical classifications of disease (ICD 10) code P 36.0 (sepsis of the newborn due to group B streptococcus). A 16-year period from 2000-2015 in South Australia (SA) and Northern Territory (NT) will be reviewed. Cases will be distinguished into early onset GBS disease (<7 days) and late onset GBS disease (≥7 days to 90 days).

Two control cases will be selected for each index GBS case. These will be the first baby born before and after the index GBS case, falling within in a similar weight category and matched for sex. The control infants will be excluded if they have evidence of sepsis during the first 90 days of life.

Risk factors for GBS neonatal infection in SA and NT will be collected using a data collection tool and determined via a case control design and multivariable logistic regression analysis.

Ethics and dissemination

This study was approved by all institutional Human Research Ethics Committees responsible for participating sites. Additional ethics approval was applied for and granted by the Aboriginal Health Research Ethics Committee in South Australia. Study findings will be published in peer review journals and presented at national and international conferences.

ARTICLE SUMMARY

Strengths and limitations of this study:

- This study will provide generalizable data on risk factors for early and late onset GBS for Australian mothers and infants with data collected from three hospitals in South Australia and two hospitals in the Northern Territory, Australia over a 16-year study period.

- This study will provide an accurate incidence of Group B streptococcal infection in Australian infants <90 days of age.

- Both clinician-diagnosed and laboratory-confirmed cases will be included and hospitalisation data and laboratory data cross-matched to ensure complete ascertainment of cases.

- A limitation of this study includes clinician bias when interpreting whether infants had clinical signs of GBS disease in the absence of laboratory confirmation, 'probable cases' of GBS disease were included in this study but were not included in the statistical analysis when determining risk factors for early and late onset GBS.

INTRODUCTION

Group B Streptococcus (GBS) is a bacterium that commonly colonises the gastrointestinal tract and vagina of adult women, the urethra of adult men, and the upper respiratory tract of young infants.[56] Approximately 10% to 30% of pregnant women are colonised with GBS.[57] When newborns are exposed to GBS it can cause sepsis and meningitis. Neonatal and infant GBS infections are categorised according to age at onset of infection. Early onset disease refers to disease occurring during the first week of life (0 to 6 days), frequently presents as sepsis or pneumonia and is usually due to exposure to GBS before or during the birth process. Late onset disease applies to infants with disease from 7 to 90 days post birth, often presenting as bacteraemia and/or meningitis and may reflect vertical transmission or transmission from community or nosocomial sources.[58]

Infants who develop neonatal sepsis may be at risk of neurodevelopmental impairment, although there is limited information regarding the long-term outcome for survivors of GBS bacteraemia or sepsis.[59] Those with neonatal sepsis who are born premature, or of low birth weight, are likely to be at even greater risk of adverse neurodevelopmental sequelae.[60-65]

Pro-inflammatory cytokines in amniotic fluid and in foetal or neonatal blood appear to increase the risk for neonatal brain injury and adverse long-term outcome, with experimental data indicating that inflammatory cytokines may be neurotoxic and can increase the permeability of the preterm blood brain barrier [63]. Neonates with infection are also at risk for circulatory and respiratory insufficiency with decreased systemic blood pressure, hypoxemia, and pathologic alterations in cerebral blood flow, which also contributes to adverse neurodevelopmental sequelae.[63]

Accurately characterising the outcomes of serious infections is a crucial component of disease surveillance. Much of the information on outcomes for survivors of neonatal GBS infection is based on children who survived GBS meningitis prior to 1980. Of those children 25% to 50% had permanent neurologic sequelae including profound intellectual disability, quadriplegia, cortical blindness, deafness, uncontrolled seizures, and hypothalamic dysfunction.[66-72] More recent studies conducted in the USA

and UK suggest that there has been little improvement in outcomes for children with neonatal GBS meningitis.[73-75] No similar studies have been conducted in Australia.

At present, neonatal GBS sepsis and meningitis is not a notifiable disease and there are sparse data on disease incidence in Australian infants. In addition, data on GBS affecting Aboriginal and Torres Strait Islander infants (ATSI) is similarly limited.[28, 76, 77] The identification of risk factors for neonatal GBS disease is critical for an understudied Australian population.

Currently there are two main strategies used in Australia and internationally to try and reduce the incidence and severity of neonatal sepsis and meningitis; routine GBS screening of all women (vaginal and rectal swab) as well as risk-based assessment versus risk based GBS assessment only. However, there is currently no consensus on which should be routinely applied, and critically, both approaches are supported by low quality evidence.[58, 78]

In SA and the NT, public hospital guidelines recommend all pregnant women between 35-37 weeks' gestation be screened using a recto-vaginal swab for GBS culture. If women are found to be colonised, they are offered IAP treatment. Women who return a negative swab for GBS but who have a complication during pregnancy/labour such as premature rupture of membrane are also offered IAP.

However, in many countries and other jurisdictions in Australia, routine screening with recto-vaginal swab for GBS culture is not performed and only a risk-based strategy is used. This approach is also preferred by 44% of Australian neonatologists.[17, 79] Infants at greatest risk of EOGBS sepsis are those born to women who experience preterm labour or delivery, have membrane rupture greater than 18 hours prior to delivery, intrapartum maternal fever or maternal chorioamnionitis, or a previous delivery of an infant with GBS disease.[17] The risk-based method has been shown to be less effective at reducing GBS infections in newborns compared to the universal screening method, but is more cost effective with significantly lower rates of antibiotic administration.[17] Importantly, it has been reported in settings using an antenatal screening approach that approximately 60% of EOGBS cases occur among women with negative GBS cultures at antenatal screening, highlighting an inherent limitation with screening and

IAP.[33] Further, maternal IAP does not reduce the incidence of late-onset disease.[51] Similarly, not all cases of EOGBS are identified using a risk based approach, a recent study in the UK showed that the majority of babies with EOGBS do not have risk factors evident at delivery so will be missed by such a strategy, with only 35% of EOGBS cases had 1 or more risk factors antenatally.[80]

Current Surveillance within Australia

In 2012 a systematic review only identified three studies investigating the incidence of neonatal GBS infection in Australia.[81] Each study confirmed that since the introduction of intrapartum antibiotics, the incidence of early onset neonatal GBS has fallen.[12, 82, 83] However, all reported data are now over a decade old. One of the studies conducted over a 10-year period in Australia and New Zealand reported that the incidence of early onset neonatal GBS sepsis had dropped from 143 per 100 000 in 1993 to 25 per 100 000 live births in 2001.[82] A slight decrease was reported in late onset GBS disease incidence with 94 per 100 000 prior to the introduction of IAP and 72 cases per 100 000 after its introduction.[12]

A more recent prospective surveillance study by the Australian Paediatric Surveillance Unit (APSU), published in 2015, identified GBS disease in infants aged 0–90 days between July 2005 and June 2008 at 12 major public hospitals across Australia (the NT was not included in this study).[84] Despite a reporting rate of one-third of that of known GBS cases to the APSU in this time, indicating the limitations of relying on passively reported data and not laboratory confirmed cases, the authors estimated rates of EOGBS to be 38 cases per 100,000, and LOGBS 19 cases per 100,000 live births.[84]

In comparison, a retrospective study conducted in Townsville, Queensland (QLD) estimated the incidence of EOGBS as 43 per 100,000 live births and 38 per 100,000 for LOGBS, [77] with LOGBS incidence being more than national figures estimated by the APSU.

Burden of GBS in Aboriginal and Torres Strait Islander population

Minimal research has been conducted in Australia to identify the burden and risk factors for GBS disease in the Aboriginal and Torres Strait Islander population. A 2011 study conducted in Townsville, QLD did not find that Aboriginal newborns were more at risk of neonatal sepsis, despite this being a finding in previous studies.[28] The study also identified risk factors not currently used as part of IAP strategies, such as previous foetal loss.[77] Indigenous status was not found to be a risk factor for GBS sepsis in the limited study conducted by the APSU.[84]

Impact of antibiotics in the perinatal period on health outcomes

The long-term impacts of intrapartum antibiotic administration on antibiotic resistance and on intestinal flora is currently not clear.[17] It is becoming evident that microbiota colonisation during the neonatal period influences adult health.[85] Medical interventions and antibiotics administered during this period that disturb microbial colonisation may therefore increase the risk of coeliac disease, atopy, type 1 diabetes, obesity and asthma.[85] Some authors have suggested that increased administration of antibiotics due to GBS screening may also increase the incidence of neonatal infections caused by pathogens other than GBS, including β- lactam-resistant strains.[86]

New GBS vaccines for pregnant women

The introduction of a GBS vaccine for pregnant women is a key development for the prevention of neonatal GBS infection. Advantages of a vaccine include potential eradication of early onset GBS sepsis, reduction in the use of antibiotics, prevention of late onset GBS, and a reduction in the costs of screening. There may also be an additional impact on endpoints for which the association with GBS is less clear, such as stillbirths and prematurity. 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.[87] A recent study in the UK has shown that such a maternal vaccination program would be cost effective against neonatal invasive GBS.[88] Several different GBS antigens have been considered for inclusion in potential vaccines.[89] A trivalent polysaccharide conjugate vaccine has been studied in pregnant women with efficient transplacental antibody transfer to the foetus and persistence of antibody until 2 months of age.[90] One concern with the development of a globally effective vaccine is the existence of up to 10 GBS serotypes capable of causing disease, with different geographical distributions around the world. Currently, phase I studies using hexavalent GBS vaccine have been started (evaluating serotypes Ia, Ib, II, III, IV, and V) in non-pregnant women, which will likely proceed into phase Ib/II studies in pregnant women by 2020.[91]

Rationale and objectives for proposed study

The objectives for this study are to determine the risk factors for neonatal GBS in an Australian population, and to determine the true incidence of early onset and late onset GBS in SA and the NT. Knowing the true incidence, and whether certain populations pose a higher risk for EOGBS and LOGBS, will provide critical information necessary to assess the feasibility of a GBS vaccine program in Australia. This study phase will consist of a descriptive study that identifies GBS infections in infants less than 90 days old between 2000 and 2015 in SA and NT.

METHODS AND ANALYSIS

Study Design

The SA and NT pathology databases will be searched for GBS positive sterile site specimens from infants aged less than 90 days at time of diagnosis as well as using the "ICD 10 CODE P36.0" (Sepsis of newborn due to streptococcus, group B). Once potential cases have been identified a case note audit will be conducted to confirm or exclude cases. Cases will be classified using an adapted case definition from the Ontario Public Health Standards Infectious Disease Protocol case definition in which a "confirmed GBS case" will be an infant less than 90 days of age in whom GBS has been cultured from a normally sterile site, together with clinically compatible signs and symptoms of invasive disease.[40] Clinical presentations of GBS disease are characterised by an infant having either: (1) Early onset disease (<7 days), usually characterised by sepsis, pneumonia, meningitis, osteomyelitis or septic arthritis OR (2) Late onset disease (≥7 days to 90 days), usually characterised by sepsis and meningitis.

A "probable GBS case", i.e. a clinically suspected case, will be that of an infant with clinically compatible signs and symptoms with a diagnosis of neonatal 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. Probable GBS cases will be included in the study to determine the incidence of GBS disease and to ensure completeness of reporting in cases where an infant is treated early with antibiotics before all the appropriate specimens have been taken, however these cases will not be included in the statistical analysis of this study when determining risk factors for neonatal GBS disease.

Both cases and controls will be identified at 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, NT.

Two controls per case will be selected using the hospital birth register, one control will be an infant born as soon as possible before the case and the other control as soon as possible after the case, where both

infants are the same sex and fall in the same birth weight category as the case (categories: <749 g, 750–999 g, 1000–1499 g, 1500– 1999 g, 2000–2499 g, 2500–2999 g, 3000–3499 g, >3500 g). The control infants must have no evidence of clinical infection requiring IV antibiotics during the first 90 days of life, which was ascertained during medical case note and pathology database audit.

To determine risk factors, a standardised data collection tool will be used to obtain clinical information from GBS cases and control mothers and neonates including (but not limited to): age, sex, indigenous status and geographical distribution; disease type (i.e. meningitis, pneumonia or septicaemia); disease symptoms & date of onset; date of admission & date of discharge; level of admission, and length of time at each level i.e. ICU/HDU/general medical ward; results of investigations performed; outcomes and identified sequelae; clinical interventions; screening (maternal risk assessment, type of swab or culture, and antibiotic administration); and clinical information (parity, gestation, membrane rupture greater than 18 hours prior to delivery, intrapartum maternal fever, suspicion of chorioamnionitis, GBS colonisation, birth weight, mode of delivery, APGAR scores, whether resuscitation was performed, history of previous fetal death (in this study defined as death during any gestation during pregnancy), or previous delivery of an infant with GBS disease).

Study sample

In SA and NT, all the major teaching hospitals will participate to ensure a large proportion of births in each region are captured in the search. All infants born between 2000 and 2015 who are identified as being GBS positive through hospital coding or laboratory results will be included in the study. Control infants born immediately before and after the case in the same sex and weight category will be selected.

Sample Size and analysis plan

The number of live births identified from the Australian Bureau of Statistics in SA over the study period was 303,453 births of which 25,387 births were of Aboriginal or Torres Strait origin (ATSI). The number of births in NT over the study period: 61, 628 live births of which 5146 births were of ATSI origin. Using a conservative estimate of cases obtained from rates published by the APSU, which was a rate of 0.11 per 1,000 births for early onset disease and a rate of 0.08 per 1,000 births for late onset disease,[92] approximately 40 early-onset neonatal GBS sepsis cases and 29 late onset GBS cases could be expected over the 16-year study selecting this time period.

In 2012 the Women's and Children's Hospital, Flinders Medical Centre and Lyell McEwin Hospital made up approximately 53% of the births in the state, representing 28%, 19%, and 14% of Aboriginal infant births in SA.[93] In the NT the Royal Darwin Hospital and Alice Springs Hospital represent approximately 67% of the births in NT, with 35% and 55% Aboriginal infant births in NT respectively.[94]

A sample size of approximately 70 cases and 140 controls (1:2 matched design) would provide 100% power to detect an odds ratio of 6.88 for maternal GBS carriage,[27] assuming 20% maternal GBS carriage.[57] It will provide 98% power to detect an odds ratio of 4.17 for chorioamnionitis,[27] assuming 10% maternal infection,[95] and 34% power to detect an odds ratio of 1.82 for prolonged rupture of membranes[27] assuming this will occur in an average of 12.5% of pregnancies.[95]

Potential risk factors will be descriptively summarized among the neonatal GBS disease and GBS cases. The association between risk factors and infection will be assessed by logistic regression, controlling for matching covariates (weight and sex) and hospital, and expressed as odds ratios with 95% confidence

intervals. All potential risk factors will be entered into a multivariable logistic regression, and backward selection will be used to determine the final model.

Risk factors and clinical details of GBS early onset and late onset neonatal infection cases will be descriptively summarized. To determine risk factors for GBS early onset and late onset neonatal infection, potential risk factors will be considered in a multivariable logistic model, controlling for hospital.

If required, missing data will be addressed using multiple imputation under a missing at random assumption.

ETHICS AND DISSEMINATION

In SA, ethics approval was granted by the South Australian Aboriginal Health Research Ethics (Reference Number 04-16-663) Committee and by the Women's and Children's Health Network Human Research Ethics Committee (HREC/16/WCHN/025). For the NT, ethics approval was granted by the Central Australian Human Research Ethics Committee (HREC-16-388), the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC Reference Number 2016-2584).

This study will be conducted according to the Good Clinical Practice Guidelines, and thus consent to access medical history will be waived as it is not thought to be appropriate or feasible to obtain participant consent as the review extended back to the past 16 years of GBS cases. A waiver of consent is also applicable because the involvement in the research carries no more than low risk to participants, the benefits from the research justifies any risks of harm associated with not seeking participant consent,

there will be sufficient protection of their privacy and an adequate plan to protect the confidentiality of data.

There are no safety concerns identified with this study. Data generated by collection of information from medical records and pathology results will be identifiable until the completion of data extraction, for data quality assurance (e.g. review and validate the existence of participants in the study, verify their eligibility, and ensure the data recorded is accurate and complete). Information collected during the study will be entered in an electronic database in a re-identifiable manner. The database will not contain any identifying data apart from demographic details. The re-identifiable data is potentially identifiable only at the site where a master participant code list will be retained by the investigator. The investigators will analyse the collected data in direct relation to the study aims/objectives to determine the outcome of the study. Only non-identifiable results will be presented in the final study report or any publications.

The principal investigator will have access to the data and will keep a record of the data held in the department. The study documents will be kept as required of any study approved from the participating site's ethics committee and information published from this study will not identify any participants involved in this study.

DISCUSSION

Maternal gastrointestinal and genital tract colonisation with GBS is a significant determinant of GBS colonisation and infection in the neonate,[47] with up to 36% of pregnant women known to be colonised.[96] Once there is a failure of epithelial barrier function and immunological clearance of GBS, bacteraemia can lead to neonatal sepsis or septic shock.[47] In the years before GBS screening and widespread use of penicillin, fatal maternal puerperal sepsis due to GBS infection and neonates cultured with GBS at autopsy was a relatively common event.[97] Although in many countries IAP has had a significant impact

in decreasing the incidence of early-onset GBS disease, it has not reduced the incidence or burden of late onset GBS disease.[97]

In some jurisdictions in Australia, routine GBS screening of all pregnant women between 35 and 37 weeks gestation includes a vaginal/rectal swab, with the mother offered IAP if the swab is positive. In many countries routine swab-based screening is not performed and a risk-based strategy is employed, however this method is less effective at reducing GBS infections in newborns.[17]

The most recent Australian study conducted by the APSU in 2015 relied on clinician's to passively identify GBS disease in infants aged 0–90 days between July 2005 and June 2008 at 12 major public hospitals across Australia and after comparison with laboratory findings, identified that clinician's identified less than one third of true GBS cases.[84] Knowing the true incidence of early onset and late onset GBS disease in Australia, as well as which groups are at higher risk, will be important to help inform a local and national GBS maternal vaccination policy.

Currently Australia has successful pertussis and influenza vaccine programs for pregnant mothers whereby vaccination is primarily to protect the infant. [98] Whilst GBS infections rarely cause infection that leads to maternal death, it is reported that as high as 60% of infections can result in miscarriage or stillbirth of the infant.[49] Neonatal GBS meningitis can cause long term neurological deficits, greater than 20% of these patients suffer moderate to severe deficits such as learning issues, deafness, global developmental delay and cerebral palsy.[49]

There have been many virulence factors that have been identified with GBS infections for a potential vaccine antigen, however the most promising to date is vaccine targeting GBS capsular polysaccharides (CPS).[49] Studies have demonstrated that maternal IgG antibodies to CPS correlate with protection against invasive neonatal GBS infections.[49] A CPS antigen vaccine would be especially beneficial to mothers at high risk for premature deliveries, as premature infants only have 29-51% as much maternal antibody as full term neonates.[52]

This study will provide much needed data to identify the true incidence and disease burden of early-onset and late-onset neonatal GBS infection in SA and NT, as well as help to identify any risk factors predisposing newborns to these infections.

CONCLUSION

Measuring the incidence, and risk factors of neonatal GBS disease is essential to inform decisions about developing interventions to prevent infection or reduce infection rates. It will also help guide local and national policy in the appropriate use of intrapartum antibiotics. With the development of a GBS vaccine for use during pregnancy, we need to understand the incidence, disease burden, and risk factors and outcomes of GBS in infants. Cost-effectiveness estimates for a funded immunisation program will be dependent on robust Australian data.

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DATA STATEMENT

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CHAPTER THREE:

GBS STUDY:

Assessing risk factors and incidence for neonatal group B streptococcal infection

A Case Control Study

(Pending submission to “Pediatrics”)

Statement of Authorship

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Contribution to the Paper	Involved in protocol design and ethic submissions, involved in data collection at South Australian Sites, involved in data entry for all South Australian & Northern Territory Sites, involved in data interpretation, & report writing of all 3 chapters of thesis (principal author of both publications).		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	14/2/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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GBS STUDY: Assessing risk factors and incidence for neonatal group B streptococcal infection

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Conflict of Interest: This work will contribute towards a Master of Philosophy (Clinical Sciences) through the University of Adelaide, South Australia for Dr. M Yanni. All authors have indicated they have no potential conflicts of interest to disclose.

LIST OF ABBREVIATIONS

ATSI	Aboriginal & Torres Strait Islander
APGAR	A score measuring clinical condition of a Newborn infant
APSU	Australian Paediatric Surveillance Unit
BNR	Band neutrophil Ratio
CDC	Centre for Disease Control & Prevention
CPS	Capsular Polysaccharides
GBS	Group B Streptococcus/Streptococcal
EOGBS	Early Onset Group B Streptococcal
HDU	High Dependency Unit
HREC	Human Research Ethics Committee
IAP	Intrapartum Antibiotic Prophylaxis
ICD 10	International Statistical Classifications of Disease -10
ICU	Intensive Care Unit
I/T ratio	Immature Neutrophils (band neutrophils) / Total Neutrophil Ratio
LOGBS	Late Onset Group B Streptococcal
NICU	Neonatal Intensive Care Unit
NT	Northern Territory
PROM	Prolonged Rupture of Membranes
RANZCOG	Royal Australian & NZ College of Obstetrics & Gynaecology
ROM	Rupture of Membranes
SA	South Australia

Table of Contents Summary: Measuring the true incidence of neonatal GBS infection in SA and NT will help advice on feasibility of a future maternal GBS vaccination program.

What is known on this subject: Group B Streptococcus infection is a leading cause of morbidity and mortality in the neonate. Estimated national incidence is based on old data and there is limited data on incidence Aboriginal and Torres Strait Islander infants.

What this study adds: This study identifies a new risk factor for GBS, previous fetal death, which should be considered in future GBS screening programs. It also reports on the incidence of early onset and late onset GBS in South Australia and Northern Territory.

CONTRIBUTORS STATEMENT PAGE

Author contributions: MY, HSM, MS, PH, MM, EK, AG, JR, AW, RL, KC, OPQ, LF and JF were all involved in this work with regards to protocol design, data collection and authorship. HM acknowledges support from the NHMRC CDF APP1084951**.** MY is the primary author of this work.

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GBS STUDY

A case control study to assess risk factors for neonatal group B streptococcal infection in Australian infants

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ABSTRACT

Objective: To determine maternal and neonatal risk factors and the incidence of neonatal early onset (EOGBS) and late onset Group B Streptococcal (LOGBS) infection in South Australia (SA) and Northern Territory (NT).

Methods: A case control study design with 2:1 control to cases was used with retrospective data collected from a 16-year epoch (2000-2015). Univariate and multivariate analysis was used to determine risk factors for neonatal EOGBS and LOGBS.

Results: The SA incidence of probable and confirmed cases of EOGBS was 32 per 100,000 live births and of LOGBS was 17.8 per 100,000 live births; and NT incidence of EOGBS was 90 per 100,000 live births and 17.8 per 100,000 live births for LOGBS. When probable cases were removed the adjusted SA incidence for EOGBS was 18.1 per 100,000 live births and for LOGBS was 17.5 per 100,000 live births, and NT incidence for EOGBS was 35.7 per 100,000 live births and for LOGBS was 14.6 per 100,000 live births.

Univariate analysis identified the risk factors: maternal GBS carriage, previous baby with GBS, previous fetal death, maternal fever in labour/chorioamnionitis, prolonged rupture of

membranes > 18 hrs, and mode of delivery. Multivariate analysis identified maternal GBS carriage, previous fetal death, and maternal fever in labour/chorioamnionitis as risk factors. The strongest risk factors discriminating the likelihood of having LOGBS compared to EOGBS was female sex, non-Indigenous status, and low birthweight.

Conclusion:

The incidence and disease burden of GBS is still significant despite screening programmes and maternal intra-partum antibiotics. The implementation of a GBS vaccination program to pregnant women warrants urgent investigation.

INTRODUCTION

Group B Streptococcus (GBS) colonises approximately 10% to 30% of pregnant women.[17, 57] While GBS infections do not lead to maternal death, up to 60% of infections can result in miscarriage or stillbirth of the infant.[49] Further, GBS is the most common cause of neonatal infections worldwide.[1] Neonatal GBS infection is defined as EOGBS, occurring up to 7 days of life, and LOGBS occurring from 7 days to 90 days of life. EOGBS likely develops after aspiration of amniotic fluid infected with GBS from the colonised maternal genital tract. [3] The pathogenesis of LOGBS is less certain, with nosocomial sources implicated in addition to acquisition of the pathogen from the maternal genital tract.[5]

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 to 300 per 100,000 live births.[14] In SA and the NT, current public hospital guidelines recommend all pregnant women between 35-37 weeks' gestation be screened using a recto-vaginal swab for GBS culture (see appendix for treatment algorithm). If found to be colonised, they are offered IAP. However,

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 still remains a leading infectious cause of neonatal morbidity and mortality.[17]

There is little 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 only identified three studies investigating the incidence of neonatal group B streptococcal infection in Australia.[81] Each of the identified Australian studies confirmed that since the introduction of IAP, the incidence of early onset neonatal GBS fell.[12, 82, 83] The largest, multi-centre study reported a reduction in EOGBS incidence from 143 per 100,000 live births in 1993 to 25 per 100,000 live births in 2001.[82] However, little change was reported in LOGBS disease since the introduction of IAP with 94 per 100,000 prior to the introduction of IAP and 72 cases per 100,000 after its introduction. [12]

A more recent prospective study by the Australian Paediatric Surveillance Unit (APSU) in 2015 passively identified GBS disease in infants aged 0–90 days at 12 major public hospitals across Australia, notably the NT was not included in this study.[84] Despite clinicians reporting only one-third of actual GBS cases to the APSU in this time, indicating the limitations of relying on passively reported data and not laboratory confirmed cases, [84] the authors estimated rates of EOGBS to be 38 cases per 100,000, and LOGBS 19 cases per 100,000 live births. In comparison, a study conducted in Townsville estimated the incidence of early onset GBS as 43 per 100,000 and 38 per 100,000 for late onset GBS, [77] which was markedly more than national figures estimated by the APSU.

Recently, attention has focused on the potential role for maternal GBS vaccination. Internationally, GBS vaccine development has only advanced to phase Ib/II trials,[53] using a

trivalent GBS polysaccharide conjugate vaccine, composed of capsular epitopes from serotypes Ia, Ib, and III.[54] Accurate data on the incidence, risk factors, disease burden and outcomes of GBS in infants is critical to guide local and national policy focusing on a new immunisation program targeting this disease. Therefore, the aim of the current study was to identify the true incidence and disease burden of EOGBS and LOGBS infection in SA and NT, as well as help to identify any risk factors predisposing newborns to these infections. Such data are critical for the calculation of cost-effectiveness estimates for a funded immunisation program in Australia.

PATIENT AND METHODS

The study objectives are:

(1) To determine the risk factors for neonatal GBS in an Australian population, and

(2) To determine the true incidence of early onset and late onset GBS in SA and NT

This case control study was conducted at 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, NT. Retrospective data was collected for the period 2000-2015.

Clinical cases were identified by searching pathology databases for GBS positive sterile site specimens from children aged less than 90 days at diagnosis as well as identifying cases using the "ICD 10 CODE P36.0: Sepsis of newborn due to streptococcus, group B" and then a case note audit was performed.

Cases were classified using an adapted case definition from the Ontario Public Health Standards Infectious Disease Protocol case definition [99] with a "confirmed GBS case" defined

as an infant whom has GBS cultured from a normally sterile site, with clinically compatible signs and symptoms of invasive disease up to 90 days after birth. Clinically compatible signs and symptoms were characterised as having either: (1) early onset disease (<7 days), characterised by sepsis, pneumonia, meningitis, osteomyelitis or septic arthritis OR (2) late onset disease (≥7 days to 90 days), characterised by sepsis and meningitis. Clinical details during admission and up to 1 year of life were collected on all GBS cases via medical case note and pathology database audit.

A "probable GBS case" was defined as an infant with clinically compatible signs and symptoms and a diagnosis of neonatal 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. Probable, or 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 from the hospital birth register, with one control born as soon as possible before the case and a second control as soon as possible after the case, with both infants the same gender and in the same birth weight category as the case. Potential control infants were excluded if they had clinical evidence of sepsis during the first 90 days of life, ascertained during medical case note and pathology database audit.

Multivariable logistic regression analyses were performed based on risk factors that have previously been shown to be associated with neonatal GBS infection. In addition, the true incidence of GBS in SA and NT was determined comparing the incidence ascertained during the audit and comparing to the total number of live births in SA and NT obtained from the

Australian Bureau of Statistics. To assess any association between the risk factors and neonatal GBS disease, logistical regression models were applied to report odds ratios with 95% confidence intervals. A sample size of approximately 70 cases and 140 controls (1:2 matched design) was calculated to provide 100% power to detect an odds ratio of 6.88 for maternal GBS carriage[27] assuming 20% maternal GBS carriage [57] and 98% power to detect an odds ratio of 4.17 for maternal infection [27] assuming 10% maternal infection [95] .

A total of 353,081 (30,533 of Aboriginal and Torres Strait Islander (ATSI) origin) live births occurred in SA and NT over the study period. [100] Based on 2012 data, the Women's and Children's Hospital, Flinders Medical Centre, and Lyell McEwin Hospital sites account for approximately 53% of births in SA, representing 28%, 19%, and 14% of Aboriginal infant births in SA. [100] In the NT, the Royal Darwin Hospital and Alice Spring Hospital sites made up approximately 67% of all births, with 35% and 55% Aboriginal infant births in NT respectively. With a conservative estimate of 11 per 100,000 live births for early onset disease and 8 per 100,000 live births for late onset disease based on APSU data,[92] we expected approximately 40 early-onset neonatal GBS sepsis cases and 29 late onset GBS cases over the 16-year study period.

Ethical approval for the study was obtained from the South Australian Aboriginal Health Research Ethics (Reference Number 04-16-663) Committee, the Women's and Children's Health Network Human Research Ethics Committee (HREC/16/WCHN/025), the Central Australian Human Research Ethics Committee (HREC-16-388), and the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC Reference Number 2016-2584).

RESULTS

INCIDENCE OF GBS

During the 16-year study period, 219 cases of proven and probable GBS disease were identified. Of this total 79 cases (36.1%) had proven culture-positive EOGBS disease, and 60 cases (27.4%) had proven culture-positive LOGBS disease. There were 12 cases (5.5%) that had probable GBS disease with a negative maternal swab for GBS, and 49 cases (22.4%) had probable GBS disease with a positive maternal swab for GBS. There were 19 cases (8.7%) of probable GBS disease where a maternal swab was unknown. When these clinically suspected cases were stratified into early-onset and late-onset GBS disease, the total number of cases of early-onset disease was 154 cases (70.3%) and late-onset disease was 65 cases (29.7%) in SA and NT.

Using the number of live births identified from the Australian Bureau of Statistics in SA over the study period as 303,453 live births, the SA incidence (of probable and confirmed cases) was 32 cases per 100,000 for early onset GBS disease and 17.8 cases per 100,000 live births for late onset disease. The number of live births identified from the Australian Bureau of Statistics in NT over the study period as 61,628 live births. Therefore, the incidence (of probable and confirmed cases) in the NT was 92.5 cases per 100,000 live births for early onset GBS disease and 17.8 cases per 100,000 live births for late onset disease.

When probable cases were removed the adjusted SA incidence for EOGBS was 18.1 per 100,000 live births and for LOGBS was 17.5 per 100,000 live births, and NT incidence for EOGBS was 35.7 per 100,000 live births and for LOGBS was 14.6 per 100,000 live births.

RISK FACTORS

Univariate conditional analysis of maternal and labour risk factors (Table 2) identified the strongest independent risk factors associated with GBS disease. These included: known maternal GBS carriage, previous baby with GBS, previous fetal death (death at any gestation during pregnancy), maternal chorioamnionitis, prolong rupture of membranes > 18 hrs, and mode of delivery (vaginal delivery and Caesarean section with labour). Similarly, multivariable analysis (Table 3) demonstrated that the strongest independent risk factors associated with GBS disease were also known maternal GBS carriage, previous fetal death (death at any gestation during pregnancy), maternal chorioamnionitis or intrapartum fever, with the use of maternal antibiotics found to be a protective factor.

Multivariable analysis was performed to see whether risk factors exerted a different magnitude of effect according to the age at onset of GBS disease (Table 4). The strongest independent risk factors discriminating the likelihood of having late onset disease compared to early-onset disease were being a female infant, non-Indigenous status, and low birthweight.

A description of the respective clinical features for early onset disease and late onset disease infants can be seen in Tables 5 to 7. Infants with LOGBS were more likely to require intubation, have a longer stay in hospital, have a co-infection and less likely to be discharged breastfeeding compared to infants with EOGBS. During this study, 11 out of our 24 neonatal deaths were attributed to GBS infection, and during data collection of GBS isolates there were 7 stillbirths whose autopsy confirmed overwhelming GBS sepsis as cause of stillbirth.

DISCUSSION

Incidence of GBS

Despite the introduction of GBS screening program and maternal IAP use, it is clear the incidence and disease burden of GBS in South Australia and the Northern Territory is still significant. Furthermore, we identified a high incidence of EOGBS in the NT compared to APSU rates, which did not include NT data in their original study.[84] This highlights potential geographical differences in Australia with implications for future refinements in the clinical management of this significant disease, 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 actually increasing, and that the burden of disease was not declining despite national screening and prevention guidelines, [80] previous Australian studies have reported falls in the incidence of EOGBS in particular. This difference may be due to the fact that in SA and NT the approach employs both universal screening vaginal swabs and the risk-based approach, whereas the UK have only adopted the risk-based screening approach. [22-24] In the Netherlands, where a risk based approach is applied, the rising incidence of GBS disease was attributed to a rise in the number of cases caused by GBS belonging to a specific GBS serotype III (clonal complex 17) and a decrease in a specific GBS serotype III (clonal complex 19), resulting in largely the same distribution of GBS serotype III before and after the introduction of IAP. [2]

The incidence of probable and proven EOGBS cases in the NT was higher in this study compared to previous Australian data. Previous Australian studies have reported a fall in the

incidence of EOGBS. [82, 84] While the APSU study was conducted between 2005-2008 at 12 major public hospitals across Australia, [84] it did not include the NT. Further, the authors concluded that clinicians only reported about one-third of known GBS cases in this time, indicating the importance of having multiple sources of surveillance in national studies. [84]

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 there are likely geographical and potentially socioeconomic factors that may predispose this area to higher areas of disease. Antenatal attendance did not differ between our GBS cases and control groups so remoteness and access to antenatal clinics in the NT was not likely to be a factor. When evaluating use of IAP in SA, 38% of pregnant mothers of infants with GBS disease who had prolonged rupture of membranes received antibiotics in labour compared to 47% of mothers in the NT, thus antibiotic usage does not seem to be an explanation for increased EOGBS, and in fact IAP was shown to be a protective factor in this study, as supported by previous findings. [101] In fact, there appeared to be more judicious use of antibiotics in the NT with only 15% of mothers in the control group receiving antibiotics compared to 34% of control mothers in SA. As our study did not collect data on GBS strain, more virulent strains in NT resistant to penicillin may explain the higher incidence in this region.

Risk factors

In general, the risk factors identified for EOGBS and LOGBS in this study where identical to those already known which included: maternal GBS carriage, intrapartum fever/ chorioamnionitis, prolonged rupture of membranes, prematurity, previous baby with GBS and low birth weight.[27] Previously known risk factors such as young maternal age and black

ethnicity groups were not identified during this study.[27] However, the current data did identify additional factors not currently recognised in current screening protocols, such as previous fetal death. Previous fetal death has been shown in a study conducted in 2013 to be a risk factor for GBS [102] and in a systematic review conducted in 2013 GBS was responsible for causing stillbirth worldwide, with up to '12.1% proportion of stillbirth attributable to GBS in at least one low-income country'. [103]

During multivariable analysis, maternal IAP was found to be a protective factor against neonatal GBS disease, which can be expected as antibiotics are used to prevent the onset of neonatal GBS disease with this finding seen in other studies where the use of maternal IAP was 'linearly associated with decreasing EOGBS'. [101] Despite the use of maternal antibiotics appearing to have a protective effect on the infant developing neonatal GBS in our study, the long term implications of widespread IAP include disruption of neonatal microbiota which may increase their risk of 'coeliac disease, atopy, type 1 diabetes, obesity and asthma' [85] and thus should be administered thoughtfully and according to current guidelines only.

Studies conducted in the United States of America (USA) have shown black ethnicity groups have a higher incidence of neonatal GBS, [27] however in Australia there is no conclusive evidence to say whether being an Aboriginal or Torres Strait Islander (ATSI) individual, is an additional risk factor for maternal GBS colonisation or neonatal GBS disease. A study conducted in Western Australia over the years 1980-1998 showed that 'Indigenous infants were more likely to die in-utero or postnatally' than their non-Indigenous counterparts, with the 'highest relative risks seen in the potentially preventable category of infections'.[104] A study conducted in 1995 showed that Aboriginal Australians have a three times higher rate of GBS than non-Aboriginal infants (5.2 per 1000 births vs 1.7 per 1000 infants) and found that

Aboriginal infants had the highest rates of GBS disease in the world, the authors concluding that these findings were determined not to be related to prematurity but conceded that they did not collect data on GBS colonisation in Aboriginal women. [14]

ATSI status was not identified as a risk factor for GBS in this study unlike previous studies, [14] but it was shown that ATSI infants were more likely to have EOGBS compared to LOGBS. Our study did not find that ATSI mothers were more likely to be colonised with GBS than non-ATSI mothers and further evaluation into colonisation and GBS virulence strains is warranted amongst this cohort. Similarly, studies conducted in Townsville did not find that Aboriginal newborns were more at risk of neonatal sepsis [28] and a NZ study showed that Maori and Pacific Island infants were not at greater risk of GBS infection. [105] While the data for this specific population group appears conflicting, if ATSI status was proven to be a risk factor for GBS in the future, this cohort would be an ideal group for an antenatal GBS vaccination programme.

One potential new direction for the management of this important perinatal complication is maternal GBS vaccination. A GBS vaccination program would likely be generally acceptable to pregnant Australian women, as there are already successful pertussis and influenza vaccine programs for this cohort whereby vaccination is primarily to protect the infant.[98] It is becoming increasingly apparent that a future vaccination program is be the most effective approach to lowering the incidence and disease burden of LOGBS. Maternal IAP has made a significant impact in decreasing neonatal morbidity and mortality due to EOGBS but it has not reduced the incidence or burden of LOGBS. [106] 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.[87] A vaccination program could also contribute to the avoidance of bacterial antibiotic resistance [29] and unwanted future health risks in infants caused by microbiota disturbance.[85] Other potential vaccination benefits include the prevention of preterm labour caused by GBS as well as reduced stillbirth rates caused by GBS infection.[29]

A number of factors make GBS a suitable target for an immunisation program. GBS is a gram-positive encapsulated coccus which occurs in pairs or short chains which shares a common 'Lancefield group B polysaccharide antigen. It is further distinguished on the basis of type-specific CPS into ten antigenically unique types (Ia, Ib, II-IX)'.[4, 44] 95% of infant and maternal GBS disease is caused by only five capsular polysaccharide serotypes: Ia, Ib, II, III and V' [45, 46], and several studies indicate that protective human immunity is associated with sufficient amounts of maternal antibodies to CPS serotypes Ia, Ib, III and V.[47] CPS serotype III is a major cause of neonatal disease, and is particularly associated with neonatal GBS meningitis.[9] As a result this serotype has become a popular vaccination target. However, the current vaccine preparations are based on serotypes and multi-locus sequencing types that are especially prevalent in the USA and Europe but not necessarily elsewhere in the world.[89]

Currently, GBS vaccine development has only advanced to phase 1b/II trials by vaccine manufacturer Novartis/GSK [55] with a trivalent (Ia, Ib, and III) GBS polysaccharide conjugate vaccine. [56] In 2017 the vaccine manufacturer Pfizer started phase 1 trials to assess a pentavalent GBS polysaccharide targeting GBS serotypes Ia, Ib, II, III, and V. [57] CPS-based vaccines alternatives based on antigenic proteins have been explored, but these are restricted to particular serotypes and offer no complete cross-serotype protection. [107] Multi-genomic

approaches have already identified new GBS proteins and may be the answer to future GBS vaccine development. [89]

Currently the obstacles to vaccine production include collating the most prevalent GBS serotypes and sequence types in all the regions of the world, and developing a vaccine that will have global benefit, offering the most cross-serotype protection. [89] Further Australian data on GBS serotypes is required in order to contribute towards vaccine and policy development. In terms of economic viability of such a programme, further Australian studies are necessary to ascertain whether it is economically viable to implement a GBS vaccination programme to pregnant women. However, a 2018 UK study clearly established cost-effectiveness of such a vaccination programme when considering the cost and the burden of invasive GBS disease. [88]

This study has a number of limitations. The study was retrospective study design and 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. Another study limitation was that the small numbers 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 birthweight infants as these were often transferred interstate to major tertiary centres for ongoing care). Finally, we did not evaluate which specific GBS strains were responsible for GBS disease burden, and in future this serological information would be very relevant to determine what strains are more prevalent in NT vs SA and better inform future vaccine development.

It is also important to highlight that whilst probable cases were included in the data collection stage of the study to calculate incidence of GBS, they were excluded in data analysis of risk factors to ensure the validity of the data. Exclusion of probable 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 labour. [108] However, by excluding probable cases from data analysis, this may have influenced the identification of risk factors associated with early onset disease.

CONCLUSION

At present neonatal GBS disease is not a notifiable disease and there are sparse data on incidence and disease burden in Australian infants. In addition, data on GBS affecting Aboriginal and Torres Strait Islander infants is similarly limited. [75-77] This study identified that in addition to prior known risk factors, 'previous fetal death' should be considered a risk factor neonatal GBS infection, and maternal antibiotics a protective factor against neonatal GBS disease. The incidence of EOGBS in the NT appears much higher than the national average and would potentially benefit from a future maternal GBS vaccination programme, which may lower both the incidence of EOGBS and LOGBS and potentially lead to disease eradication.

TABLES

Table 1: Description of proven GBS cases and control cases in SA and NT

	Confirmed GBS n/N (%)	**Controls n/N (%)**
	N=139 **	**N=264****
SA Hospitals	108/139 (77.7)	210/264(79.5)
Flinders Medical Centre	31/139 (22.3)	59/264 (22.3)
Lyell McEwin Hospital	8/139 (5.8)	16/264 (6.1)
Women's & Children's Hospital	69/139 (49.6)	135/264 (51.1)
NT Hospitals	31/139 (22.3)	54/264 (20.5)
Alice Springs Hospital	9/139 (6.5)	18/264 (6.82)
Royal Darwin Hospital	22/139 (15.8)	36/264 (13.6)
EOGBS* (Confirmed in SA)	55/139 (55.4)	
EOGBS* (Confirmed in NT)	22/139 (15.8)	
LOGBS* (Confirmed in SA)	53/139 (38.1)	
LOGBS* (Confirmed in NT)	9/139 (6.5)	
Mother's mean age at delivery (SD)	28.5 years (6.0)	28.8 years (6.0)
Gestational age		
Prematurity (< 37 weeks)	63/138 (45.7)	111/264 (42.0%)
Term infants	75/138 (54.3)	153/264 (58.0%)
Birth weight, mean (SD)	2486g (1184g)	2565g (1138g)
< 1500g	41/135 (30.4)	71/264 (26.9)
1500 – 2499 g	19/135 (14.1)	37/264 (14.0)
≥ 2500g	75/135 (55.6)	156/264 (59.1)
Sex		
Female	62/139 (44.6%)	124/264 (47%)
Male	77/139 (55.4%)	140/264 (53%)

*EOGBS = Early-onset Group B Streptococcus; LOGB = Late-onset Group B Streptococcus, † Clinically suspected and probable cases were not included in the statistical analysis, they were included in the description of clinical features and disease burden. **A difference in denominator indicates missing data

Table 2: Maternal and perinatal risk factors using conditional univariate analysis of proven GBS cases

	Cases n (%)	Controls n (%)	Odds ratio (95% CI)	P value
	(N=139) **	**(N=264)** **		
Age, median (SD)	28 (6.0)	28.8 (6.0)	0.99 (0.95 to 1.02)	0.52
Aboriginal or Torres Strait Islander	24/136 (17.6)	32/258 (12.4)	1.54 (0.85 to 2.75)	0.15
Maternal smoking				
Non-smoker	15/49 (30.6)	25/93 (26.9)		0.89*
Current smoker	26/49 (53.1)	52/93 (55.9)	0.82 (0.37 to 1.85)	
Past smoker	8/49 (16.3)	16/93 (17.2)	0.85 (0.28 to 2.44)	
First-time pregnancies	40/125 (32.0)	91/259 (35.1)	0.86 (0.54 to 1.35)	0.51
Multiparous mothers	73/128 (57.0)	137/259 (52.9)	1.20 (0.78 to 1.84)	0.41
Prematurity (< 37 weeks)	63/138 (45.7)	111/264 (42.0)	1.25 (0.57 to 2.73)	0.58
GBS bacteriuria†	0/139 (0)	3/264 (1.1)		
GBS carrier	40/91 (44.0)	28/170 (16.5)	4.16 (2.32 to 7.58)	<0.001
Previous baby with GBS infection	4/129 (3.1)	1/263 (0.4)	8.58 (1.25 to 168.98)	0.028
Previous fetal death	12/128 (9.4)	8/263 (3.0)	3.26 (1.31 to 8.56)	0.012
Maternal fever/ chorioamnionitis	39/94 (41.5)	19/224 (8.5)	8.75 (4.65 to 17.10)	<0.001
Rupture of membranes ≥ 18 hours	30/125 (34.3)	32/258 (13.6)	2.21 (1.27 to 3.86)	<0.001
Maternal antibiotics in labour	41/115 (35.7)	78/261 (29.9)	1.27 (0.79 to 2.04)	0.33
Antibiotics 4 hrs prior to delivery	23/122 (18.9)	56/261 (21.5)	0.78 (0.44 to 1.34)	0.37
Method of delivery				
Caesarean section without labour	16/133 (12.0)	75/260 (28.8)		<0.001*
Vaginal delivery	87/133 (65.4)	134/260 (51.5)	3.58 (1.93 to 6.97)	
Caesarean section with labour	30/133 (22.6)	51/260 (19.6)	2.95 (1.46 to 6.11)	

* Global p-value, † Unable to calculate due to small numbers and wide range of error (Too few positive GBS bacteriuria results to fit a logistic regression model and obtain a reliable estimate of the odds ratio.) **A difference in denominator indicates missing data

Table 3: Multivariable conditional logistic regression analysis of risk factors

	Odds ratio (95% CI)	P value
Sex		
Male		0.86
Female	0.92 (0.39 to 2.16)	
Maternal Group B streptococcus carriage		
No		<0.001
Yes	6.53 (2.46 to 18.4)	
Previous fetal death		
No		0.01
Yes	8.11 (1.63 to 43.3)	
Suspected maternal chorioamnionitis		
No		<0.001
Yes	28.1 (9.87 to 93.8)	
Maternal antibiotics in labour		
No		0.04
Yes	0.36 (0.11 to 0.95)	

Table 4: Multivariable conditional logistic regression analysis: discrimination between late onset disease versus early onset disease

	Odds ratio (95% CI)	P value
Maternal GBS carriage		
No		0.002
Yes	0.03 (0.0007 to 0.31)	
Suspected maternal chorioamnionitis		
No		0.80
Yes	0.81 (0.14 to 4.35)	
Duration of rupture of membranes		
< 18 hours		0.56
≥ 18 hours	0.50 (0.039 to 4.98)	
Sex		
Male		0.03
Female	7.02 (1.18 to 61.13)	
Aboriginal or Torres Strait Islander		
No		0.01
Yes	0.06 (0.003 to 0.5)	
Birthweight	0.998 (0.996 to 0.999)	<0.001

Table 5. Clinical Features between EOGBS & LOGBS cohort* (Proven and Probable cases)

Presenting signs and symptoms	**EOGBS n/N (%)**	**LOGBS n/N (%)**
	(n = 154)	**(n =65)**
Temperature instability T < 36.5	32/154 (21)	19/65 (29)
Pyrexia ≥ 37.5	55/154 (36)	25/65 (39)
Vomiting	5/154 (3)	10/65 (15)
Poor feeding	23/154 (15)	21/65 (32)
Irritable/unsettled infant	23/154 (15)	24/65 (37)
Abdominal Distension	4/154 (5)	6/65 (11)
Cyanosis	30/154 (20)	6/65 (11)
Respiratory distress	100/154 (65)	42/65 (65)
Apnoea	30/154 (20)	24/65 (37)
Bradycardia	26/154 (17)	18/65 (28)
Poor peripheral perfusion	59/154 (38)	22/65 (34)
Hypotension	25/154 (16)	7/65 (11)
Unexpected need for resuscitation	44/154 (29)	3/65 (5)
Hypoglycaemia	38/154 (25)	9/65 (14)
Lethargy	26/154 (17)	21/65 (32)
Seizures	7/154 (5)	10/65 (15)
Capillary refill time > 2 seconds	20/154 (13)	7/65 (11)
Metabolic and/or respiratory acidosis	49/154 (32)	10/65 (15)
Tachycardia	16/154 (10)	19/65 (29)
Shock	13/154 (8)	1/65 (2)
Persistent fetal circulation	7/154 (5)	0/65 (0)
Disseminated intravascular coagulation	2/154 (1)	1/65 (2)
Overall Clinical Presentation(s)		
Sepsis	109/154 (71)	58/65 (89)
Meningitis	11/154 (7)	15/65 (23)
Pneumonia	60/154 (39)	10/65 (15)
Other invasive disease	12/154 (8)	6/65 (9)
Mean White Cell Count (x10^9/L)		
EOGBS n = 140; LOGBS n=63	13.3 (95% CI, 11.1 to 15.4)	10.2 (95% CI, 8.6 to 11.7)
Mean Total Neutrophil Count (x10^9/L)		
EOGBS n = 125; LOGBS n=55	5.3 (95% CI, 4.5 to 6.2)	5.1 (95% CI, 4.0 to 6.2)
Mean Total Band Count (x10^9/L)		
EOGBS n = 125; LOGBS n=56	1.7 (95% CI, 1.2 to 2.1)	2.1 (95% CI, 0.04 – 4.1)
Mean Band neutrophil ratio [I/T ratio] (%)		
EOGBS n = 125; LOGBS n=55	26.5 (95% CI, 22.2 to 30.8)	19.1 (95% CI, 15.2 to 23.1)
Gastric aspirate microscopy positive		
Yes	17/154 (11.0)	1/65 (1.5)
No	1/154 (0.6)	0/65 (0)
Unknown/Not done	136/154 (88.3)	64/65 (98.4)
Urine latex GBS agglutinins positive		
Yes	38/154 (24.7)	3/65 (4.6)
No	19/154 (12.3)	10/65 (15.4)
Unknown/Not done	97/154 (63.0)	52/65 (80.0)

* EOGBS = Early-onset Group B Streptococcus; LOGB = Late-onset Group B Streptococcus; **A difference in denominator indicates missing data

Table 6: Clinical details of cases EOGBS vs LOGBS*

	Odds ratio (95% CI)	P value
Respiratory distress		
EOGBS		0.44
LOGBS	0.76 (0.38 to 1.53)	
Required intubation or ventilation		
EOGBS		<0.001
LOGBS	3.2 (1.60 to 6.70)	
Baby required intensive care or high dependency		
EOGBS		0.06
LOGBS	1.94 (0.98 to 3.92)	
**Number of days in hospital ** **		
EOGBS, mean 14.8 days (SD 19.3)		<0.001
LOGBS, mean 67.3 days (SD 107)	RR 4.54 (3.29 to 6.29)	
**Age at disease (days) ** **		
EOGBS, mean 0.62 days (SD 1.2)		<0.001
LOGBS, mean 41.7 days (SD 26)	RR 66.84 (46.31 to 98.35)	
Neonatal death due to GBS infection		
EOGBS		0.32
LOGBS	1.99 (0.53 to 9.57)	
Sterile site blood culture or PCR positive		
EOGBS		0.86
LOGBS	0.78 (0.03 to 19.91)	
Sterile site CSF culture or PCR positive		
EOGBS		0.009
LOGBS	4.43 (1.43 to 16.73)	
Co-infections		
EOGBS		<0.001
LOGBS	3.42 (1.65 to 7.25)	
Discharged exclusive breast feeding		
EOGBS		0.003
LOGBS	0.31 (0.14 to 0.67)	

* EOGBS = Early-onset Group B Streptococcus; LOGB = Late-onset Group B Streptococcus ** 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 7. Burden of disease between EOGBS & LOGBS cohorts during admission and at 1 year of life* (Proven and Probable Cases)

	EOGBS n/N (%) (n = 154) **	LOGBS n/N (%) (n =65) **
Complications within acute infection		
Pneumonia	16/154 (10)	9/65 (14)
Focal skin or soft tissue infection	8/154 (5)	5/65 (8)
Focal infection of urinary tract	2/154 (1)	1/65 (2)
Meningitis	3/154 (2)	2/65 (3)
Developmental delay	0/154 (0)	3/65 (5)
Spastic quadriplegia	3/154 (2)	1/65 (2)
Seizures	6/154 (4)	5/65 (15)
Cortical blindness	1/154 (1)	1/65 (2)
Deafness	0/154 (0)	1/65 (2)
Periventricular Leukomalacia	2/154 (1)	3/65 (5)
Complications present in first year of life		
Pneumonia	2/154 (1)	1/65 (2)
Focal bone infection/osteomyelitis	1/154 (<1)	2/65 (3)
Focal skin or soft tissue infection	3/154 (2)	0/65 (0)
Focal infection of urinary tract	3/154 (2)	0/65 (0)
Meningitis	2/154 (1)	0/65 (0)
Developmental delay	7/154 (5)	6/65 (9)
Spastic quadriplegia	0/154 (0)	1/65 (2)
Microcephaly	0/154 (0)	1/65 (2)
Seizures	1/154 (1)	2/65 (3)
Cortical blindness	1/154 (1)	1/65 (2)
Deafness	1/154 (1)	2/65 (3)
Periventricular Leukomalacia	3/154 (2)	2/65 (3)

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

**A difference in denominator indicates missing data

THESIS DISCUSSION & SUMMARY

The main objective of this study was to measure the true incidence of neonatal GBS disease in South Australia and the Northern Territory, and to identify any risk factors for GBS disease. Additionally, the study sought to provide a description of the clinical features of EOGBS and LOGBS and GBS disease burden in Australia. Unfortunately, neonatal GBS sepsis and meningitis is not a notifiable disease, with notification to the APSU conducted on individual discretion of the treating clinician. As a result, there is limited data on disease incidence in Australian infants, and data on GBS affecting Aboriginal and Torres Strait Islander infants is similarly limited [75-77]. Although IAP has made a significant impact in decreasing EOGBS neonatal morbidity and mortality, it has not reduced the incidence or burden of late onset GBS disease [31], which theoretically may only be decreased with the institution of a maternal immunization programme in pregnancy. Mandatory notification of this disease would enable us to collect accurate data of disease incidence and burden of disease across Australia, which would help immensely with categorisation of GBS strain and virulence factors and help inform future vaccine development with up to date and cohesive Australian data.

Whilst there is worldwide data available on the incidence of maternal GBS colonisation and neonatal EOGBS and LOGBS disease, there has been a lack of Australian data in the last decade. There is also a shortage of data specifically in relation to the Aboriginal & Torres Strait Islander population, with conflicting information in the past regarding whether Aboriginality is an additional risk factor for neonatal GBS infection or not. A study conducted in 1995 postulated that Aboriginality may be a potential risk factor, showing that Aboriginal Australians have higher rate of GBS than non-aboriginal infants (5.2 per 1000 vs 1.7 per 1000 infants) [106] .

On evaluation of both probable and proven cases, this study found a surprisingly high incidence of EOGBS in the Northern Territory, 98 per 100,000 live births which is much higher than the national average provided by the APSU of 38 per 100,000 live births with LOGBS. Probable GBS cases were

included in the study to determine the incidence of GBS disease and to ensure completeness of reporting in cases where an infant is treated early with antibiotics before all the appropriate specimens have been taken, which can often occur in the era of universal neonatal GBS screening programmes and the administration of IAP. Australia currently has successful pertussis and influenza vaccine programs for pregnant mothers, where vaccination is given to mothers primarily to protect the unborn infant, and thus it can be assumed a similar antenatal GBS vaccination program will be acceptable to the Australian population.

Future Australian studies are required to ascertain whether this higher incidence of EOGBS in the NT is valid, and if so, what changes in policy and practice could provide could reduce this incidence. From our retrospective study it did not appear that the NT used IAP less than the SA cohort, and in fact the opposite was identified as 25% of NT mothers whose infants had neonatal GBS disease received antibiotics at least 4 hours prior to baby delivery from onset of ROM, compared to 15.9% of SA mothers whose infants had neonatal GBS disease. However, if looking at overall rate of antibiotics given to mothers in labour (including those that received them less than 4 hours prior to their infant was born) this was only given to 37.7% SA mothers with GBS infants and 47% of NT mothers respectively, and thus the increased usage of IAP in the NT compared to SA.

Traditionally, benzyl penicillin is used as IAP and is administered at least 4 hours before delivery. Despite the fact that 4 hours has been found to be highly effective at preventing EOGBS in clinical trials, it has been proposed in some studies that even 1-2 hours may confer some benefit to the neonate as well but may not be as affective at preventing EOGBS. [31] The use of maternal IAP in the NT was higher than use of maternal IAP in SA, and thus IAP does not account for the higher incidence of probable and confirmed cases of EOGBS in the NT. One might conclude there may be a geographical factors to GBS disease such as antibiotic resistance, or strains of GBS that are more

virulent dependent on local geography, or a higher force of infection, carriage density or prolonged carriage. Further studies would be required to evaluate this in the future as to whether there are more virulent strains in the NT compared to SA, less sensitive to maternal IAP.

A future antenatal vaccination program is likely to be the feasible option in the future for lowering the incidence and disease burden of LOGBS. Worldwide universal screening and maternal IAP has made a significant impact in decreasing neonatal morbidity and mortality due to EOGBS, but it has unfortunately has not reduced the incidence or burden of LOGBS [106] . A vaccination program would help prevent avoid the development of antibiotic resistant bacteria [29] and unwanted future health risks in infants caused by microbiota disturbance [85]. Other vaccination benefits include preventing preterm labour caused by GBS as well as stillbirths caused by GBS infection, and the prevention of allergic reactions caused by antibiotics [29].

Whilst there may be clinician bias when interpreting whether infants had clinical signs of GBS disease in the absence of laboratory confirmation, these infants on medical notes review had several indicators of sepsis clinically and thus 'probable cases' of GBS disease were included in the study for incidence calculation. However, these probable cases were not included in the statistical analysis when determining risk factors for early and late onset in order to ensure that the data analysis remained robust based on laboratory confirmation. When probable cases were removed the adjusted SA incidence for EOGBS was 18.1 per 100,000 live births and for LOGBS was 17.5 per 100,000 live births, and NT incidence for EOGBS was 35.7 per 100,000 live births and for LOGBS was 14.6 per 100,000 live births, in this instance both EOGBS and LOGBS are both lower than the proposed APSU national average of 32 per 100,000 live births for early-onset and 17.8 per 100,000 live births. [84] Further studies are required to investigate whether this lower incidence represents clinicians' adherence to GBS screening and IAP treatment guidelines, or whether it is due to geographical or maternal factors.

Prior to this study, known risk factors for EOGBS disease included: maternal GBS carriage, intrapartum fever and maternal chorioamnionitis, prolonged rupture of membranes, prematurity, low birth weight, young maternal age, black ethnicity groups (based on studies conducted in the USA), previous baby with GBS, and low levels of GBS anticapsular antibody. [27] Risk factors for LOGBS are less well-defined in literature, however nosocomial and maternal sources have been implicated [27]. From this study maternal age, ethnicity, maternal smoking status, poor antenatal attendance, maternal drug use, and number of prior pregnancies did not appear to be risk factors for neonatal GBS disease. We were unable to ascertain if GBS bacteriuria was a risk factor for GBS (likely due to lack of data), although it is acknowledged that women with GBS bacteriuria are presumed to be colonised with GBS and managed accordingly during pregnancy. [109]

From previously published literature maternal age and prematurity are known risk factors for GBS disease [27] which was not identified in this study, perhaps due to small numbers of cases. This study was similarly not able to elucidate if sex, ATSI status or premature labour were risk factors for GBS disease compared to the control group, however it did identify that male and female infants both had a 50% chance of having EOGBS, with males slightly higher chance of LOGBS (55.4% vs 44.6%). ATSI infants had a higher chance of EOGBS than LOGBS (25.3% vs 12.3%) when both groups were compared. Although this study was not able to determine if being Aboriginal or Torres Strait Islander predisposes to GBS neonatal infection our data suggests a trend with a higher odds ratio for disease in Aboriginal infants.

Interestingly, infants below 1.5 kg tended to have LOGBS rather than EOGBS (55.4% vs 18.1%) and those above 3.5 kg tended to have EOGBS rather than LOGBS (33.1% vs 11.1%); whilst infants of low birth weight are often premature, we cannot assume this of the entire cohort as some term infants may

be affected by intrauterine growth restriction and thus be small for gestational age. Prematurity may not have been found to be a risk factor in this study for GBS due to the sample size restrictions from several hospital sites, especially of that in the NT, where very premature infants are often transferred in utero to tertiary centres interstate for pending delivery. The results in the study regarding the risk factor of prematurity may have arisen due to the small numbers of patients identified in the NT which made it impossible to match every case for gender and weight category (particularly in the case of very premature or low birthweight infants as these were often transferred interstate to major tertiary centres for ongoing care).

From this study risk factors for GBS disease included: maternal GBS carriage, previous fetal death (in this study defined as death at any gestation during pregnancy), maternal chorioamnionitis, and as one would assume, with maternal antibiotics in labour appearing to be a protective risk factor against neonatal GBS disease. Previous fetal death appears to be a new risk factor for GBS disease which should be highly recommended in guideline development of risk factors in future antenatal screening protocols.

This study was only able to comment on burden of disease if patients re-presented to any of the 5 hospitals involved in data collection the first year of life. As a result, there is a possibility that this data is incomplete and GBS is responsible for higher rates of complications than was ascertained during this study. It was found that infants with LOGBS were more likely than EOGBS to have focal bone infection or osteomyelitis (3.1% vs 0.6%), developmental delay (9.2% vs 4.5%), spastic quadriplegia (1.5% vs 0%), seizures (3.1% vs 0.6%), cortical blindness (1.5% vs 0.6%), and deafness (3.1% vs 0.6%). Paradoxically in our study, infants with EOGBS were more likely to present in the first year of life after discharge with meningitis than LOGBS (1.3% vs 0%).

Whilst maternal IAP continues to be a protective factor against neonatal GBS disease, the widespread use of IAP is already concerning for the development of resistant strains of GBS and non-GBS pathogens and should not be the default approach to management of GBS in the future. It is apparent from this study that the burden of early and late onset GBS disease in our Australian population is still prevalent despite the introduction of GBS screening programmes and maternal IAP use. A prospective surveillance study conducted in the UK showed the incidence of GBS disease was increasing, and that the burden of disease was not declining despite national screening and prevention guidelines. [80] A recent study conducted in the UK in 2018 has established cost-effectiveness of such a vaccination programme when considering the cost and the burden of invasive GBS disease, [88] but further Australian studies are required to ascertain whether it is cost-effective based on these results for implementation of a GBS vaccination programme to pregnant women. Other rare but debilitating diseases are being considered for immunisation programs in young infants such as meningococcal disease. Further research is required to determine the specific strains of GBS causing disease in infants in different Australian regions to help determine an effective maternal GBS vaccine to prevent potentially devastating neonatal GBS infections.

SUMMARY & RECOMMENDATIONS

In summary, the results of this study provide three recommendations:

1. A recommendation that all Australian states and territories move towards a mandatory reporting system for neonatal GBS early onset and late onset disease, and to formally collect data on any associated neonatal morbidity and mortality in order to ascertain the true incidence of disease, disease burden, and any potential geographic variations in Australia of GBS isolate strains.

2. A recommendation for previous fetal death to be included as a risk factor to current GBS screening guidelines alongside previously known risk factors.

3. A recommendation to consider a national GBS vaccination program for pregnant women, once a safe and effective GBS vaccine becomes available, particularly for at risk pregnant women, based on risk factors such as prior foetal death. This would potentially improve pregnancy outcomes and is likely be acceptable to the Australian women given the successful introduction of similar vaccination programmes for influenza and pertussis where the primary aim is to confer neonatal immunity when given to mothers during pregnancy.

The benefits of a GBS vaccination program include but are not limited to: decreasing the incidence of late onset GBS, which has remained steady despite the introduction of GBS screening programs and reduced use of maternal intrapartum antibiotics, and potential eradication of early and late onset GBS including serious neurodevelopmental sequelae. An immunisation program for pregnant women would potentially prevent preterm labour as well as stillbirths caused by GBS infection, and prevent side effects caused by antibiotics such as allergic reactions and the development of antibiotic resistant bacteria and unwanted future health risks in infants caused by microbiota disturbance such as gastrointestinal conditions and atopic diseases such as asthma.

Implementation of these 3 recommendations has the potential to eliminate neonatal GBS disease but further Australian data will be required regarding GBS serotype and geographical distribution in order to evaluate potential coverage of potential GBS vaccines in Australia.

APPENDIX

CENTRAL AUSTRALIAN HUMAN RESEARCH ETHICS COMMITTEE
Centre for Remote Health
PO Box 4066 Alice Springs NT 0871
Ph: (08) 8951 4700 Fax: (08) 8951 4777
Email: cahrec@flinders.edu.au

Associate Professor Helen Marshall
Women's and Children's Health Network
Discipline of Paediatrics
72 King William Rd
North Adelaide SA 5006

29th June 2016

Our Ref: HREC-16-388

Dear Associate Professor Marshall

RE: Ethics Application – Approval

The Central Australian Human Research Ethics Committee (CAHREC) Chair has considered your response to the Committee's request for further information about and/or amendment(s) to your research project **'Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns'.**

The Chair agreed that this project now meets the requirements of the National Statement on Ethical Conduct in Human Research.

The Chair decided to **grant approval** for your project to proceed.

The period for which approval has been given is from the date of this letter until the **2nd January 2017**. If you do not complete the research within the projected time please request an extension from CAHREC.

Ethics approval is contingent upon the submission of an annual Progress report and a Final report upon completion of the project. It is the responsibility of researchers to make a note of the following dates and submit these reports in a timely manner, as reminders may not be sent out. Failure to submit reports will result in your ethics approval lapsing.

Your Final report is due on:

2nd January 2017

Copies of the report form can be downloaded from the CAHREC website.

Yours sincerely

Chris Schwarz
Secretariat Support
Central Australian Human Research Ethics Committee

CENTRAL AUSTRALIAN HUMAN RESEARCH ETHICS COMMITTEE
Centre for Remote Health
PO Box 4066 Alice Springs NT 0871
Ph: (08) 8951 4700 Fax: (08) 8951 4777
Email: cahrec@flinders.edu.au

Associate Professor Helen Marshall
Women's and Children's Health Network
Discipline of Paediatrics
72 King William Rd
North Adelaide SA 5006

28th July 2017

Our Ref: HREC-16-388

Dear Associate Professor Marshall

RE: Progress Report and Extension Approval

The Central Australian Human Research Ethics Committee (CAHREC) Chair has considered the annual report and the application for an extension to the completion date of your research project **'Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns'.**

The Chair is satisfied the research is being conducted within the guidelines set out by the Ethics Committee. He has ***granted approval*** for an extension until the **30th December 2017**.

Your Final report is due on the **30th December 2017.**

Yours sincerely

Chris Schwarz
Secretariat Support
Central Australian Human Research Ethics Committee

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school of health research

Postal: PO Box 41096, Casuarina NT 0811, Australia
Location: John Mathews Building (Bldg 58),
Royal Darwin Hospital Campus, Rocklands Drv, Casuarina NT 0810
Ph: (08) 8946 8600 Fax: (08) 8946 8464
Website: menzies.edu.au
ABN: 70 413 542 847

Ethics Administration Office
File Reference Number: HREC-2016-2584
Phone: (08) 8946 8687 or (08) 8946 8692
Email: ethics@menzies.edu.au

31 March 2016

Associate Professor Helen Marshall
Paediatric Trials Unit,
Women's and Children's Hospital,
Level 2, Clarence Reiger Building,
72 King William Road,
North Adelaide, SA, 5006.

Dear A/Prof Marshall,

HREC Reference Number: 2016-2584
Project Title: ***Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns.***

Thank you for submitting the above Quality Assurance Activity /case study for ethical review. This project was considered by the Chair of the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC), in accordance with guidelines for review of negligible/low risk research. The study activity has been found to meet the criteria and requirements for a quality assurance/audit activity as outlined in the NHMRC National Statement on Ethical Conduct in Human Research (2007).

I am pleased to advise that the Chair has granted **ethical approval** of this research project. Please note that approval applies only to research conducted after the date of this letter.

This approval will be ratified at the next meeting of the Human Research Ethics Committee.

Approved Project Timeline: ***31/03/2016 – 31/03/2017***

Dr Joshua Francis, A/Prof Rob Baird, Dr Michael Stark and A/Prof Helen Marshall will participate in the **retrospective** data collection and data analysis.

The nominated participating site/s in this project is/are:

- **Royal Darwin Hospital**
- **Alice Springs Hospital (Subject to local CA HREC approval)**

Approval is granted for a maximum period of twelve months. An annual progress report or final report is required on or before the ***31/03/2017***.

You are reminded that a final report must to be lodged with this Office by ***31/03/2017***. The final report must also outline the feedback mechanism used for reporting back to the health care unit where the study was undertaken.

APPROVAL IS SUBJECT TO the following conditions being met:

1. The Coordinating Principal Investigator will **immediately report anything that might warrant review** of ethical approval of the project.

2. The Coordinating Principal Investigator will notify the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) of any event that requires a **modification or amendment to the protocol or other project documents** and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found on the Menzies' website.

3. The Coordinating Principal Investigator will submit any necessary reports related to the **safety of research participants (e.g. protocol deviations, protocol violations)** in accordance with the HREC's policy and procedures. These guidelines can be found on the Menzies' website.

4. The Coordinating Principal Investigator will **report** to the HREC **annually** and notify the HREC when the project is completed at all sites using the specified forms. Forms and instructions may be found on the Menzies' website.

5. The Coordinating Principal Investigator will notify the HREC if the project is **discontinued at a participating site before the expected completion date**, and provide the reason/s for discontinuance.

6. The Coordinating Principal Investigator will notify the HREC of any plan to **extend the duration of the project past the approval period listed above** and will submit any associated required documentation. The preferred time and method of requesting an extension of ethical approval is during the **annual progress report**. However, an extension may be requested at any time.

7. The Coordinating Principal Investigator will notify the HREC of his or her **inability to continue as Coordinating Principal Investigator**, including the name of and contact information for a replacement.

8. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).

9. Researchers should immediately report anything which might affect continuing ethical acceptance of the project, including:

    - Adverse effects of the project on particpants and the steps taken to deal with these;
    - Other unforeseen events;
    - New information that may invalidate the ethical integrity of the study; and
    - Proposed changes in the project.

10. Approval for a further twelve months, within the original proposed timeframe, will be granted upon receipt of an annual progress report if the HREC is satisfied that the conduct of the project has been consistent with the original protocol.

11. Confidentiality of research participants should be maintained at all times as required by law.

12. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details.

13. The Patient Information Sheet must provide a brief outline of the research activity including: risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Administrators can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.

14. You must forward a copy of this letter to all Investigators and to your institution (if

applicable).

This letter constitutes ethical approval only. This project cannot proceed at any site until separate research governance authorisation has been obtained from the CEO or Delegate of the institution under whose auspices the research will be conducted at that site.

Should you wish to discuss the above research project further, please contact the Ethics Administrators via email: ethics@menzies.edu.au or telephone: (08) 8946 8687 or (08) 8946 8692.

The Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research wishes you every continued success in your research.

Yours sincerely,

Dr Lewis CampbellChair
Chair
Human Research Ethics Committee
of Northern Territory Department of Health
and Menzies School of Health Research
NHMRC Registration No. EC00153
http://www.menzies.edu.au/page/Research/Ethics_approval/

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*. The processes used by this HREC to review multi-centre research proposals have been certified by the National Health and Medical Research Council.

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Website: menzies.edu.au
ABN: 70 413 542 847

5 December 2017

Ethics Administration Office
File Reference Number: HREC-2016-2584
Phone: (08) 8946 8687 or (08) 8946 8692
Email: ethics@menzies.edu.au

Professor Helen Marshall
Paediatric Trials Unit
Women's and Children's Hospital
Level 2 Clarence Reiger Building
72 King William Road
North Adelaide SA 5006

CC. Dr Marianne Yanni

Dear Professor Marshall,

HREC Reference Number: 2016-2584
Project Title: ***Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns***

The amendment to the above project submitted on **04/12/2017** was approved and will be ratified at the next meeting of the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC). Please note that this approval applies only to research conducted after the date of this letter.

The following amendments are approved:

1. **Extension of project timeline from 31/12/2017 to 30/03/2018**

Please note that all requirements of the original ethical approval for this project still apply.

Approved timeline: ***31/03/2016 – 30/03/2018***

Annual progress report due: ***30/03/2018***

APPROVAL IS SUBJECT TO the following conditions being met:

1. The Coordinating Principal Investigator will **immediately report anything that might warrant review** of ethical approval of the project.
2. The Coordinating Principal Investigator will notify the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) of any event that requires a **modification or amendment to the protocol or other project documents** and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found on the Menzies' website.
3. The Coordinating Principal Investigator will submit any necessary reports related to the **safety of research participants (e.g. protocol deviations, protocol violations)** in accordance with the HREC's policy and procedures. These guidelines can be found on the Menzies' website.
4. The Coordinating Principal Investigator will **report** to the HREC **annually** and notify the HREC when the project is completed at all sites using the specified forms. Forms and instructions may be found on the Menzies' website.
5. The Coordinating Principal Investigator will notify the HREC if the project is **discontinued at a participating site before the expected completion date**, and provide the reason/s for discontinuance.
6. The Coordinating Principal Investigator will notify the HREC of any plan to **extend the duration of the project past the approval period listed above** and will submit any associated required documentation. The preferred time and method of requesting an extension of ethical approval is during the **annual progress report**. However, an extension may be requested at any time.
7. The Coordinating Principal Investigator will notify the HREC of his or her **inability to continue as Coordinating Principal Investigator**, including the name of and contact information for a replacement.
8. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).

9. Researchers should immediately report anything which might affect continuing ethical acceptance of the project, including:
- Adverse effects of the project on participants and the steps taken to deal with these;
    - Other unforeseen events;
    - New information that may invalidate the ethical integrity of the study; and
    - Proposed changes in the project.
10. Approval for a further twelve months, within the original proposed timeframe, will be granted upon receipt of an annual progress report if the HREC is satisfied that the conduct of the project has been consistent with the original protocol.
11. Confidentiality of research participants should be maintained at all times as required by law.
12. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details.
13. The Patient Information Sheet must provide a brief outline of the research activity including: risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Administrators can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.
14. You must forward a copy of this letter to all Investigators and to your institution (if applicable).

Should you wish to discuss the above research project further, please contact the Ethics Administrators via email: ethics@menzies.edu.au or telephone: (08) 8946 8687 or (08) 8946 8692.
The Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research wishes you every continued success in your research.

Yours sincerely,

Dr. Lewis Campbell
Chair
Human Research Ethics Committee
of the Northern Territory Department of Health
and Menzies School of Health Research
http://www.menzies.edu.au/ethics

This HREC is registered with the Australian National Health and Medical Research Council (NHMRC) and operates in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research (2007)*. NHMRC Reg no. EC00153

menzies
school of health research

Postal: PO Box 41096, Casuarina NT 0811, Australia
Location: John Mathews Building (Bldg 58),
Royal Darwin Hospital Campus, Rocklands Drv, Casuarina NT 0810
Ph: (08) 8946 8600 Fax: (08) 8946 8464
Website: menzies.edu.au
ABN: 70 143 542 847

Ethics Administration Office
File Reference Number: HREC-2016-2584
Phone: (08) 8946 8687 or (08) 8946 8692
Email: ethics@menzies.edu.au

3 July 2018

A/Professor Helen Marshall
Paediatric Trials Unit
Women's and Children's Hospital
Level 2 Clarence Reiger Building
72 King William Road
North Adelaide SA 5006

Dear A/Professor Marshall,

HREC Reference Number: 2016-2584
Project Title: ***Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns***

The Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) thanks you for taking the time to complete and return your annual progress report for the above project.

The report has been reviewed and noted.

The following amendment has been approved:

- An extension to the project completion date from ***31/03/2018 to 31/12/2018***

Continued ethical approval is granted for the above research project.

Please note that this approval applies only to research conducted after the date of this letter.

Approved timeline: ***31/03/2016 – 31/12/2018***

Annual progress report due: ***31/12/2018***

APPROVAL IS SUBJECT TO the following conditions being met:

1. The Coordinating Principal Investigator will **immediately report anything that might warrant review** of ethical approval of the project.

2. The Coordinating Principal Investigator will notify the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) of any event that requires a **modification or amendment to the protocol or other project documents** and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found on the Menzies' website.

3. The Coordinating Principal Investigator will submit any necessary reports related to the **safety of research participants (e.g. protocol deviations, protocol violations)** in accordance with the HREC's policy and procedures. These guidelines can be found on the Menzies' website.

4. The Coordinating Principal Investigator will **report** to the HREC **annually** and notify the HREC when the project is completed at all sites using the specified forms. Forms and instructions may be found on the Menzies' website.

5. The Coordinating Principal Investigator will notify the HREC if the project is **discontinued at a participating site before the expected completion date**, and provide the reason/s for discontinuance.

6. The Coordinating Principal Investigator will notify the HREC of any plan to **extend the duration of the project past the approval period listed above** and will submit any associated required documentation. The preferred time and method of requesting an extension of ethical approval is during the **annual progress report**. However, an extension may be requested at any time.

7. The Coordinating Principal Investigator will notify the HREC of his or her **inability to continue as Coordinating Principal Investigator**, including the name of and contact information for a replacement.

8. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).

9. Researchers should immediately report anything which might affect continuing ethical acceptance of the project, including:

    - Adverse effects of the project on participants and the steps taken to deal with these;
    - Other unforeseen events;
    - New information that may invalidate the ethical integrity of the study; and
    - Proposed changes in the project.

10. Approval for a further twelve months, within the original proposed timeframe, will be granted upon receipt of an annual progress report if the HREC is satisfied that the conduct of the project has been consistent with the original protocol.

11. Confidentiality of research participants should be maintained at all times as required by law.

12. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details.

13. The Patient Information Sheet must provide a brief outline of the research activity including: risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Administrators can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.

14. You must forward a copy of this letter to all Investigators and to your institution (if applicable).

Should you wish to discuss the above research project further, please contact the Ethics Administrators via email: ethics@menzies.edu.au or telephone: (08) 8946 8687 or (08) 8946 8692.

The Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research wishes you every continued success in your research.

Yours sincerely,

Ms Jane Thomas
Report Review Representative
Human Research Ethics Committee
of the Northern Territory Department of Health
and Menzies School of Health Research
http://www.menzies.edu.au/ethics

This HREC is registered with the Australian National Health and Medical Research Council (NHMRC) and operates in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research (2007)*. NHMRC Reg no. EC00153

29th June 2016

Women's & Children's Hospital

Research Secretariat
Level 2, Samuel Way Building
72 King William Road
Tel 08 8161 6390
Tel 08 8161 6521
www.wch.sa.gov.au

A/Prof H Marshall
University Dept of Paediatrics
VIRTU
WCHN

Dear Helen

Re: Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns. HREC/16/WCHN/25. Ethics expiry date: 30/06/2019.

Lead HREC for the above study for the following institutions/sites:

Women's and Children's Health Network
Lyell McEwin Hospital
Flinders Medical Centre

I refer to your letter dated 24th June 2016 in which you responded to matters raised by the WCHN Human Research Ethics Committee at its 24th February 2016 meeting. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

Specifically, the following documents have been noted/approved:

Document	*Version*	*Date*
LNR Application: AU/15/F10427		09 February 2016
Response to Request for Further Information: Response letter		24 June 2016
Cover Letter		10 February 2016
Study Protocol	1	10 February 2016

This letter constitutes advice on ethical consideration only. You must not commence this research project at a site until you have obtained separate research governance approval from the site concerned. A copy of this letter should be forwarded to all site investigators for submission to the relevant Research Governance Officer.

At the WCHN, or any other SA Health site, separate authorisation from the Chief Executive or delegate of that site must be obtained through a Site Specific Assessment (SSA) request. For information on this process at the WCHN, please contact the WCHN Research Governance Officer, Ms Camilla Liddy (telephone 8161 6688, email camilla.liddy@health.sa.gov.au).

I remind you approval is given subject to:
- immediate notification of any serious or unexpected adverse events to participants;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of an annual report on the progress of the study, and a final report when it is completed to the WCHN Research Governance Officer. It is your responsibility to provide these reports, without reminder. The proforma for the report may be found on the WCHN Research Governance and Ethics website.

Government of South Australia
SA Health

Approval is given for three years only. If the study is more prolonged than this, an extension request should be submitted unless there are significant modifications, in which case a new submission may be required. Please note the expiry date in the title above and include it in any future communications.

Yours sincerely

TAMARA ZUTLEVICS (DR)
CHAIR
WCHN HUMAN RESEARCH ETHICS COMMITTEE

Women's & Children's Hospital

Research Secretariat
Level 2, Samuel Way Building
72 King William Road
North Adelaide SA 5006
Tel 08 8161 6390
Tel 08 8161 6521
www.wch.sa.gov.au

31st May 2018

Prof H Marshall
VIRTU
WCHN

Dear Helen

Re: Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns. HREC/16/WCHN/25. Ethics expiry date: 30/06/2021.

At its meeting on 30th May 2018, the WCHN Human Research Ethics Committee approved your request to extend ethical approval for a further two years. Please note the amended approval number above reflecting the extension, and use it in any future communications.

As the consideration of annual reports is now part of research governance monitoring, I have referred your annual report to the WCHN Research Governance Officer, Ms Camilla Liddy.

I remind you continued approval is given subject to:
- immediate notification of any serious or unexpected adverse events to participants;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of an annual report on the study's progress and a final report on completion to the WCHN Research Governance Officer. It is your responsibility to provide these reports, without reminder from the Committee.

I also remind you of the institution's research governance requirements. If the study involves non WCHN staff or students, a signed Confidentiality Agreement is to be provided to Ms C Liddy, Research Governance Officer, WCHN Research Secretariat. Additionally, if they visit any WCHN site or access identifiable patient information, a verified copy of their Department for Communities & Social Inclusion (DCSI) National Criminal History Record Check (Child related employment screening) is to be provided to Ms C Liddy and the Human Resources Department. The study may continue on this proviso.

Yours sincerely

TAMARA ZUTLEVICS (DR)
CHAIR
WCHN HUMAN RESEARCH ETHICS COMMITTEE

Government of South Australia
SA Health

ABORIGINAL HEALTH
RESEARCH ETHICS COMMITTEE

24 June 2016

Assoc. Prof. Helen Marshall
Women's and Children's Hospital
University Department of Paediatrics
72 King William Road
North Adelaide SA 5006
By Email: Helen.Marshall@adelaide.edu.au; Mark.Mcmillan@adelaide.edu.au

RE: 'GBS Study' - Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns
Ref. No: 04-16-663

Dear Helen,
Thank you for your submission requesting ethical review from the Aboriginal Health Research Ethics Committee (AHREC).

I am pleased to inform you that your study met with the Committee's support and was recommended for full approval. The Committee originally reviewed the study at its meeting held on 5 May 2016 and your response to the Committee's query regarding de-identification that was reviewed out-of-session on 23 June 2016. Please be advised of the following standard conditions::

1) The duration of approval is from 23 June 2016 until the completion date of the study indicated as 1 August 2017.

2) In accordance with the NHMRC guidelines, AHREC requires annual reports from principal researcher(s). Please find the reporting template at:
http://ahcsa.org.au/research-overview/ethical-review-ahrec/

We wish you well with the study and look forward to receiving your progress reports. If you require further information, please do not hesitate to contact the Executive Officer, Dr Gokhan Ayturk, by email at Gokhan.Ayturk@ahcsa.org.au .

Sincerely yours,
Dr Gokhan Ayturk on behalf of

Kim Morey
Chairperson, AHREC

A/Prof Helen Marshall
Women's and Children's Hospital
72 King William Road
NORTH ADELAIDE SA 5006

Women's & Children's Hospital

Research Secretariat
Level 2, Samuel Way Buil
72 King William Road
Tel 08 8161 6390
Tel 08 8161 6521
www.wch.sa.gov.au

06 July 2016

Dear Helen

SSA Reference: **SSA/16/WCHN/108**
HREC Reference: **HREC/16/WCHN/025**
Study title: **Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns**

Site Specific Assessment Review (LNR/SA Health MA)

Thank you for submitting an application for research governance authorisation of this project. We are pleased to inform you that authorisation has been granted for this study to commence at the Women's and Children's Hospital.

In authorising this project, the following documentation was considered:

1. Covering letter dated 24 June 2016 from Ms Susan Lee;
2. SSA Form AU/16/71A5219;
3. WCHN HREC approval letter dated 29 June 2016;
4. Neonatal GBS Study Protocol version 1 dated 10 February 2016;
5. CV for Helen Marshall (Principal Investigator); and
6. Documentation reviewed and approved by the WCHN HREC.

Terms and conditions of governance authorisation

Please read the terms and conditions of Women's and Children's Health Network (**WCHN**) governance authorisation as researchers have a responsibility to comply with reporting requirements and other conditions. Failure to comply may have significant implications for the ongoing authorisation of the Study at the Women's and Children's Hospital (**WCH**). For example, failure to provide an annual report within the specified timeframe or failure to ensure that all non-WCHN staff and students satisfy the WCHN Confidentiality Agreement and DCSI Child Related Screening check requirements may lead to the withdrawal of site authorisation and suspension of the Study, and may result in further serious consequences.

In the letter dated 23 June 2016, the Chair of the WCHN Human Research Ethics Committee stipulated certain conditions for ethical approval of this study at the all sites approved under the SA Health Mutual Acceptance scheme. This authorisation imposes the following additional conditions:

1. Authorisation of the Study is limited to the site or sites identified in this letter.
2. Authorisation of the Study is granted for the term of your project as provided in Section 5 of the LNR SSA or until the project is complete, whichever is earlier.
3. The Study must be conducted in accordance with the conditions of ethical approval provided by the lead Human Research Ethics Committee (**HREC**) reviewing the Study, SA Health policies and in conjunction with all applicable standards, including the *National Statement on Ethical Conduct in Human Research* (2007 and updates) and the *Australian Code for the Responsible Conduct of Research* (2007 and updates).

Government of South Australia
SA Health

4. Where non-WCHN staff or students are involved in the Study, that person or those persons must execute a WCHN Confidentiality Agreement. This requirement applies to all non-WCHN staff and students identified in the SSA submission and to any and all non-WCHN staff or students involved in the Study at any time in the future. Non-WCHN staff or students are not authorised to perform any acts in relation to the Study without the Research Governance Officer reviewing and approving a WCHN Confidentiality Agreement.
5. Any non-WCHN staff or students working on the Study, whether identified in the initial SSA submission or in future, who visit the WCHN site for any amount of time or who have access to any identifiable WCHN patient information (WCHN patients under the age of 18 years) must provide the Research Governance Officer with evidence of a current Department for Communities and Social Inclusion (**DCSI**) Child-Related Employment Screening check, in accordance with SA Health policy and WCHN Human Resources requirements. Non-WCHN staff or students are not authorised to be on the site or access any identifiable WCHN patient data (WCHN patients under the age of 18 years) without the Research Governance Officer reviewing and approving a current DCSI Child-Related Employment Screening check.
6. The Research Governance Officer must be included in all relevant correspondence regarding the Study, including correspondence between the WCHN site and the lead HREC for studies approved under National Mutual Acceptance. This includes, but is not limited to, all correspondence relating to:
    a. protocol amendment applications;
    b. protocol deviations or violations at WCHN sites;
    c. Serious Adverse Events at WCHN sites;
    d. notification of study close out, study withdrawal or study completion;
    e. extension of approval requests; and
    f. anything that may change the ethical or scientific integrity of the Study.
7. An Annual Report must be provided to the Research Governance Officer within 30 days of each anniversary of the initial lead HREC approval date for the duration of lead HREC approval. The Annual Report must be submitted on the current WCHN Annual Report form. Failure to provide an Annual Report within the required timeframe may result in authorisation for the Study being suspended or withdrawn at the discretion of the Executive Director, Corporate Services, WCHN, the Director, Research Secretariat, WCHN or delegate.
8. Where University personnel are involved in the Study, the Principal Investigator must notify the University that WCHN HREC has approved the Study and WCHN research governance has authorised the Study. Prior to commencing the Study, the Principal Investigator must ensure all University requirements are complied with, including any indemnity and insurance requirements.

Additional condition of WCHN research governance authorisation – Data access and information disclosure

WCHN provides no consent for the data it has provided for this study to be used for any purpose which can generate a financial return from a third party either by the use of the data as standalone data or as a collection of data, except or unless WCHN has provided express written consent for such purpose to occur.

SA Health insurance

I confirm that based on the information provided by you, the Department for Health and Ageing's insurance arrangements will indemnify SA Health staff involved in the study.

The provision of this insurance is based on you maintaining ethics approval and ensuring that persons performing treatment or testing are qualified to perform such treatment or testing, or in the case of students they are appropriately supervised by persons that are qualified.

SA Health insurance does not include cover for deliberate breaches of confidentiality, wilful misconduct, or the misuse of information, fraud or similar risks.

Please contact me if you have any queries about the consideration of your Site Specific Assessment.

Please quote the SSA reference number in any correspondence about the Study.

We wish you every success in your research.

Yours sincerely

CAMILLA LIDDY
Research Governance Officer
Women's and Children's Health Network
Research Secretariat
P: (08) 8161 6688
E: camilla.liddy@sa.gov.au

CC: Ms Susan Lee, VIRTU

Key dates:

Annual Report due (every year):	June
WCHN research governance expiry date:	04 April 2018

Government of South Australia
SA Health

Northern Adelaide Local Health Network

Research Governance Office
Level 2, Clinical Trials Unit
Lyell McEwin Hospital
Haydown Road
ELIZABETH VALE SA 5112
Tel: 08 8182 9346
Email: healthnalhnrgo@sa.gov.au

21 March 2017

A/Prof Helen Marshall
Director, VIRTU
Women's and Children's Hospital
72 King William Road
NORTH ADELAIDE SA 5006

Dear A/Prof Marshall

HREC reference number: HREC/16/WCHN/25
SSA reference number: SSA/17/NALHN/22
Project title: Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns

I am pleased to advise that the above project is approved to be conducted at Lyell McEwin Hospital.

This approval is subject to compliance with the conditions set out below in addition to the conditions specified by the reviewing HREC.

1. Record keeping is maintained in accordance with GCP, NHMRC, State and National guidelines.
2. Notify the NALHN Research Governance Office of:

- Any HREC approved amendments to the project
- The annual progress of the project (annual report)
- Extensions to the ethical approval of the project
- Serious or unexpected adverse effects for NALHN participants
- Site based protocol deviations
- Any changes to the indemnity, insurance arrangements or CTRA for the project
- Your inability to continue as Principal Investigator or any other change in research personnel involved in this project
- Failure to commence the study within 12 months of site approval / or if a decision is taken to end the study at this site
- Any other unforeseen events
- Any other matters which may impact the conduct of the project in NALHN
- A comprehensive final report at study completion including any published material
- Site audits and final audit report

3. Maintain confidentiality of NALHN participants at all times, as required by law.
4. Dispose of research materials in accordance with the requirements outlined in the NHMRC Australian Code for the Responsible Conduct of Research.

If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.

The NALHN Research Governance Office may conduct an audit of the project at any time.

Please note: templates for the post approval submission of documents to the RGO can be accessed from: http://www.basilhetzelinstitute.com.au/research/information-for-researchers/nalhn/forms-and-templates/

SSA reference number: SSA/17/NALHN/22
Project title: Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns

Should you have any queries about the consideration of your Site Specific Assessment form, please contact me on 08 8182 9346 or healthnalhnrgo@sa.gov.au

The SSA reference number should be quoted in any correspondence about this matter.

Yours sincerely

Alison Barr
Research Governance Officer
Northern Adelaide Local Health Network (LMH/MH/PHC)

Key Dates:

Document	Due date
Annual Report	29 June 2018

SSA reference number: SSA/17/NALHN/22
Project title: Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns

Office for Research

Flinders Medical Centre
Ward 6C, Room 6A219
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

11 October 2016

A/Professor Helen Marshall
Discipline of Paediatrics
Women's and Children's Hospital
72 King William Road
NORTH ADELAIDE SA 5006

Dear A/Professor Marshall

HREC reference number:	HREC/16/WCHN/25 **324.16**
Project title:	Assessing disease burden and risk factors for neonatal group B streptococcal infection to inform the best strategies to prevent life threatening infections in newborns
Ethics approval:	29 June 2016 to 29 June 2019
Site:	Flinders Medical Centre
Subject:	Site Specific Assessment Review

Thank you for submitting an application for authorisation of this project.

On the basis of the information provided in your Site Specific Assessment submission, I am pleased to inform you that authorisation has been granted for this study to commence.

This authorisation is based on the following documents:

Site Specific Assessment AU/16/0AC5211 dated 1 May 2016

WCHN HREC approval letter dated 29 June 2016

Neonatal GBS Study Protocol v1.9 10 February 2016

A/Prof Helen Marshall, Principal Investigator CV 1 January 2016

HREC reviewed documents listed on the approval letter are accepted as part of the site authorisation.

The SSA reference number should be quoted in any correspondence about this matter.

If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.

Should you have any queries about the consideration of your Site Specific Assessment form, please contact Dawn Jennifer on 8204 6453.

Yours sincerely

Professor Villis Marshall
Director, Office for Research

Zoom out (Ctrl+Minus)

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. DK= Don' Know, UK= unknown, NA = Not applicable

DE-IDENTIFIED ID: _____

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. Country of Birth Australia ☐ Other ☐ **If other**, specify _____ ☐DK

7. Mother's Ethnicity _____ ☐DK

8. Father's Ethnicity _____ ☐DK

9. Is the child of ATSI descent? Aboriginal ☐ Torres Strait Islander ☐ Both ☐ No ☐ DK ☐

BIRTH HISTORY

10. Gestational age: Term ☐ Pre-term (<37 weeks) ☐ **If pre-term**, state gestational age _____(weeks) DK ☐

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 ☐)
- ☐ Induced delivery but due to complications, baby delivered by emergency Caesarian section
- ☐ Elective Caesarian section

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 ☐ DK ☐
If YES:
Nasopharyngeal suctioning ☐
Respiratory support – 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

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

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

If YES what gestation was swab taken at: ____ weeks

IF YES, What 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

IF YES to known previous GBS swab, what 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 ☐ U/K

Prematurity: ☐ Yes ☐ No ☐ U/K If yes, gestational age at birth _____ weeks (if known)

Asthma: ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Cardiovascular disease: ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Other respiratory disease: ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Co-infection (e.g. influenza, viral RTI): ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Details: .....

Diabetes mellitus: ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Obesity ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved; BMI _____

Other metabolic: ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Details: .....

Immunodeficiency conditions: ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Details: .....

Other: ..... ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Other: ..... ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

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 ☐

Enter the following

RECRUITMENT PROCESS

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

ADMISSION DETAILS

28. Date of Admission: ☐☐/☐☐/☐☐

29. Was the patient transferred from another hospital? Yes ☐ No ☐ DK ☐

If yes, name of referring hospital_____ 18b. Date of Admission at referring hospital ☐☐/☐☐/☐☐

NEONATAL CLINICAL DETAILS

Neonatal Initial Presentation:

30. 1st medical presentation or review by clinical staff:

Date: ☐☐/☐☐/☐☐ ☐ U/K
Time: ☐☐:☐☐ 24hrs ☐ U/K

31. Place of medical presentation:

Labour ward ☐ Postnatal ward ☐ Neonatal unit ☐ Emergency Department ☐ GP ☐ U/K ☐

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

Yes ☐ No ☐ DK ☐

If YES, was this because of:

Hospital protocol for maternal chorioamnionitis
Yes ☐ No ☐ DK ☐

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

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

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

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 Band count _____ (please include units)

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

33. 1st dose of parenteral antibiotics given:

Date: ☐☐/☐☐/☐☐ ☐ U/K
Time: ☐☐:☐☐ 24hrs ☐ U/K

Given by:

☐ U/K
☐ GP at GP clinic
☐ In ED
☐ Inpatient ward

Name and dose of antibiotics: ☐ U/K

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

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

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

/☐☐

☐ Benzathine penicillin Start Date: ☐☐/☐☐/☐☐ End Date: ☐☐/☐☐

/☐☐

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

/☐☐

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

/☐☐

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

/☐☐

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

/☐☐

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

/☐☐

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

/☐☐

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

/☐☐

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

/☐☐

Neonatal Clinical Presentation on Admission:

34. Date of presentation to NICU: ☐☐/☐☐/☐☐ ☐ U/K

35. Time of presentation to NICU: ☐☐:☐☐ 24hrs ☐ U/K

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

☐ Meningitis ☐ Septicaemia ☐ Pneumonia

☐ Other invasive disease: .....

37. Vital signs **on presentation**:

Heart rate: _____ Max _____ Min

Respiratory Rate: _____ Max _____ Min

Blood Pressure: _____/_____ Highest _____/_____ Lowest

Temperature: __ __.__ °C

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

Temperature instability ☐ Yes ☐ No ☐ DK

Vomiting	☐ Yes	☐ No	☐ DK
Poor feeding	☐ Yes	☐ No	☐ DK
Irritable/unsettled	☐ Yes	☐ No	☐ DK
Abdominal distension	☐ Yes	☐ No	☐ DK
Cyanosis	☐ Yes	☐ No	☐ DK
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	☐ DK
Hypotension	☐ Yes	☐ No	☐ DK
Unexpected need for resuscitation	☐ Yes	☐ No	☐ DK
Hypoglycaemia	☐ Yes	☐ No	☐ DK
Lethargy	☐ Yes	☐ No	☐ DK
Seizures	☐ Yes	☐ No	☐ DK
Capillary refill time more than 2 seconds	☐ Yes	☐ No	☐ DK
Metabolic and/or respiratory acidosis	☐ Yes	☐ No	☐ DK
Tachycardia	☐ Yes	☐ No	☐ DK
Shock	☐ Yes	☐ No	☐ DK
Persistent foetal circulation (Persistent Pulmonary Hypertension)	☐ Yes	☐ No	☐ DK
DIC	☐ Yes	☐ No	☐ DK

Clinical Information during Acute Hospitalisation

Neonatal Complications:

39. 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

40. Antibiotic treatment: ☐ Yes ☐ No ☐ UK

If yes:

Name: .....; Route: ☐ IV ☐ IM;

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

Name: .....; Route: ☐ IV ☐ IM ; Dosage: .....(e.g. 50mg tid);

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

Name: .....; Route: ☐ IV ☐ IM; Dosage: .....(e.g. 50mg tid);

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

41. 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: __ %

42. 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: ☐☐/☐☐/☐☐

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

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

44. **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: .....

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

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

General Follow-up

46. **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

47. **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

48. **Discharge weight:** _____ grams

TREATMENT/OUTCOME DETAILS

49. Was patient admitted to ICU/HDU? ☐ Yes ☐ No ☐ UK If yes, total length of ICU admission (incl. multiple ICU admissions):

☐☐ Days ☐☐ hours

50. Was patient transferred to another hospital?: ☐ Yes ☐ No ☐ UK

If yes, name of hospital: .....

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

Outcome at discharge

☐ Recovered and discharged without any complications or sequelae

☐ Transferred to another hospital with unknown outcome

☐ 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. DK= Don't Know, UK= unknown, NA = Not applicable*

DE-IDENTIFIED ID: _____

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 hospita 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. Country of Birth Australia ☐ Other ☐ **If other**, specify _____ ☐DK

7. Mother's Ethnicity _____ ☐DK

8. Father's Ethnicity _____ ☐DK

9. Is the child of ATSI descent? Aboriginal ☐ Torres Strait Islander ☐ Both ☐ No ☐ DK ☐

BIRTH HISTORY

10. Gestational age: Term ☐ Pre-term (<37 weeks) ☐ **If pre-term**, state gestational age _____(weeks) DK ☐

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 ☐)
- ☐ Induced delivery but due to complications, baby delivered by emergency Caesarian section
- ☐ Elective Caesarian section

GBS STUDY Page 1 of 7

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 ☐ DK ☐
If YES:
Nasopharyngeal suctioning ☐
Respiratory support – 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

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

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

If YES what gestation was swab taken at: ____ weeks

IF YES, What 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

IF YES to known previous GBS swab, what 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 ☐ U/K

Prematurity: ☐ Yes ☐ No ☐ U/K If yes, gestational age at birth _____ weeks (if known)

Asthma: ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Cardiovascular disease: ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Other respiratory disease: ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Co-infection (e.g. influenza, viral RTI): ☐ Yes ☐ No ☐ U/K If yes, ☐ PMH ☐ ongoing

Details: .....

Diabetes mellitus: ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Obesity ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved; BMI _____

Other metabolic: ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Details: .....

Immunodeficiency conditions: ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Details: .....

Other: ..... ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

Other: ..... ☐ Yes ☐ No ☐ U/K If yes, ☐ ongoing ☐ resolved

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 ☐

Enter the following

ADMISSION DETAILS

27. If required admission, Date of Admission: ☐☐/☐☐/☐☐

28. Was the patient transferred from another hospital? Yes ☐ No ☐ DK ☐

If yes, name of referring hospital_____ 18b. Date of Admission at referring hospital ☐☐/☐☐/☐☐

29. Did the neonatal experience any of these issues during admission? (*please tick all that may apply*):

Temperature instability	☐ Yes	☐ No	☐ DK
Vomiting	☐ Yes	☐ No	☐ DK
Poor feeding	☐ Yes	☐ No	☐ DK
Irritable/unsettled	☐ Yes	☐ No	☐ DK

Abdominal distension	☐ Yes	☐ No	☐ DK
Cyanosis	☐ Yes	☐ No	☐ DK
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	☐ DK
Hypotension	☐ Yes	☐ No	☐ DK
Unexpected need for resuscitation	☐ Yes	☐ No	☐ DK
Hypoglycaemia	☐ Yes	☐ No	☐ DK
Lethargy	☐ Yes	☐ No	☐ DK
Seizures	☐ Yes	☐ No	☐ DK
Capillary refill time more than 2 seconds	☐ Yes	☐ No	☐ DK
Metabolic and/or respiratory acidosis	☐ Yes	☐ No	☐ DK
Tachycardia	☐ Yes	☐ No	☐ DK
Shock	☐ Yes	☐ No	☐ DK
Persistent foetal circulation (Persistent Pulmonary Hypertension)	☐ Yes	☐ No	☐ DK
DIC	☐ Yes	☐ No	☐ DK

30. What diagnosis was the neonate given during this admission:

_____

Neonatal Complications:

31. 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 CLINICAL DETAILS

General Follow-up

32. **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

33. **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

34. **Discharge weight:** _____ grams

TREATMENT/OUTCOME DETAILS

35. Was patient admitted to ICU/HDU? ☐ Yes ☐ No ☐ UK If yes, total length of ICU admission (incl. multiple ICU admissions):

☐☐ Days ☐☐ hours

36. Was patient transferred to another hospital?: ☐ Yes ☐ No ☐ UK

If yes, name of hospital: .....

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

Outcome at discharge

☐ Recovered and discharged without any complications or sequelae

☐ Transferred to another hospital with unknown outcome

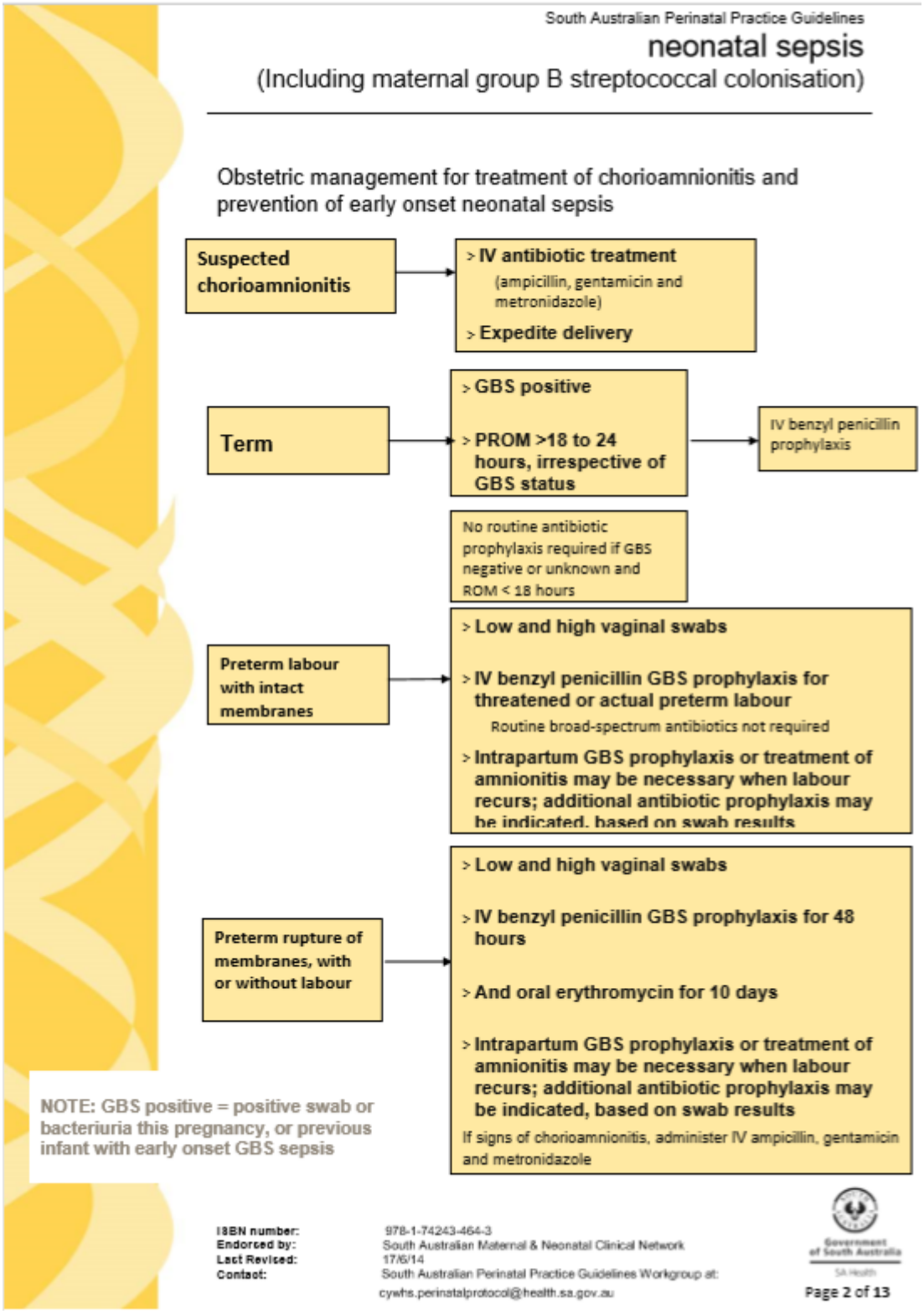
☐ Inpatient death; please specify cause of death .....

ICD-10 DIAGNOSIS CODES

49. Primary code: ☐☐☐☐

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

SOUTH ASUTRALIAN PERINATAL PRACTICE GUIDLELINES: GROUP B STEPTOCOCCAL OBSTETRIC AND NEONATAL MANAGEMENT GUIDELINES



neonatal sepsis

(Including maternal group B streptococcal colonisation)

Obstetric management for treatment of chorioamnionitis and prevention of early onset neonatal sepsis

Suspected chorioamnionitis →
- > **IV antibiotic treatment** (ampicillin, gentamicin and metronidazole)
- > **Expedite delivery**

Term →
- > **GBS positive** → > **PROM >18 to 24 hours, irrespective of GBS status** → IV benzyl penicillin prophylaxis
- No routine antibiotic prophylaxis required if GBS negative or unknown and ROM < 18 hours

Preterm labour with intact membranes →
- > **Low and high vaginal swabs**
- > **IV benzyl penicillin GBS prophylaxis for threatened or actual preterm labour**
  Routine broad-spectrum antibiotics not required
- > **Intrapartum GBS prophylaxis or treatment of amnionitis may be necessary when labour recurs; additional antibiotic prophylaxis may be indicated, based on swab results**

Preterm rupture of membranes, with or without labour →
- > **Low and high vaginal swabs**
- > **IV benzyl penicillin GBS prophylaxis for 48 hours**
- > **And oral erythromycin for 10 days**
- > **Intrapartum GBS prophylaxis or treatment of amnionitis may be necessary when labour recurs; additional antibiotic prophylaxis may be indicated, based on swab results**

If signs of chorioamnionitis, administer IV ampicillin, gentamicin and metronidazole

NOTE: GBS positive = positive swab or bacteriuria this pregnancy, or previous infant with early onset GBS sepsis

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