A study of the management of group B streptococcal colonisation in pregnant women: Benefits and risks of preventative modalities

A thesis presented in fulfilment of the requirements for the degree of

Doctor of Philosophy, Midwifery

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Centre for Midwifery, Child and Family Health

Faculty of Health

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Certificate of original authorship

I, Kathryn Tina Braye, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, Midwifery, in the Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution. This research is supported by the Australian Government Research Training Program.

Signature:

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Acknowledgements

It is unbelievable to me that I am sitting here, very close to my 60th birthday and just after my 36th wedding anniversary writing a dedication in a PhD thesis. My PhD thesis no less. I left school at 16, barely understanding the significance of a university (although knowing I wanted to continue my education). Well I've done that!

I am dedicating this PhD thesis to myself, as well as my parents. It has been a long haul and I have finally made it. I feel very proud. I would like to honour all mothers and babies whose birth journeys have been part of this work. I would like to honour my parents too, Joyce and Raymond Perry. My mother, Joyce died way too young, the same age as I am now. My babies were small, and she never knew I would still be studying when they were all grown. My dad, Raymond, died just before I started PhD studies, in the days before he died, I told him I was going to be a doctor and complete a PhD. I'm not sure he completely understood but actually it wouldn't matter if I had told him I was going to support a woman to birth her baby, walk 720km to Santiago de Compostela, or fly to the moon and back, he was always so proud of his little girl.

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One of my core values (thank you Carolyn and Ilze) is making a positive difference. Mothers want the best for their babies, no matter what their age. A long-standing vision throughout the period of my candidature was that the work in this thesis would add to the body of knowledge around the complex issue of Group B streptococcus (GBS) risk in pregnancy and enable and empower women to make (sometimes difficult) decisions and decide on the level of risk they are prepared to embrace.

Dedication

To my parents, Joyce and Raymond Perry

Scholarships and awards during candidature

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Presentations at conferences/meetings/reviews/activities associated with this thesis

- 2015: **Braye, K**., Catling, C., Ferguson, J., Foureur, M. Group B streptococcus: Are we doing more harm than good? *19th Biennial ACM Conference, Gold Coast, Queensland*. Poster presentation
- 2015: **Braye, K.,** Catling, C., Ferguson, J., Foureur, M. To douche or not to douche? Chlorhexidine for group B streptococcus (GBS) in otherwise well, healthy pregnant women. *Research Student Forum. University Technology Sydney.* Oral presentation
- 2015: **Braye, K.,** Group B streptococcus: Are we doing more harm than good? Multi- disciplinary meeting. Department of Maternity & Gynaecology John Hunter Hospital, Newcastle, New South Wales. Oral presentation
- 2015: **Braye, K**. Group B streptococcus: Are we doing more harm than good? *Research Students Forum. University of Technology Sydney.* Oral presentation
- 2015: **Braye, K**. Are current guidelines for group B streptococcus causing iatrogenic microbial and epigenetic harm for short term gain? *Australian College of Midwives*, *NSW Branch annual conference, Leura, New South Wales.* Oral presentation
- 2015: **Braye, K.** Group B streptococcus: Are we doing more harm than good? *Belmont Midwifery Group Practice midwives*. *Belmont. New South Wales* Oral presentation. Invited speaker
- 2016: **Braye, K**. Group B streptococcus: Are we doing more harm than good? *Hunter New England infectious diseases physicians and microbiologists. Newcastle. New South Wales* Oral presentation. Invited speaker
- 2016: **Braye, K**. Insights of a 3rd year PhD candidate. *Research Students Forum. University of Technology Sydney.* Oral presentation

- 2016: **Braye, K.** Group B streptococcus, are we doing more harm than good? Informing the narrative on intrapartum prophylaxis. *Australian College of Midwives. Webinar production.* Initial research findings**.** Invited speaker
- 2016: **Braye, K.**, Are current guidelines for Group B streptococcus causing iatrogenic microbial and epigenetic harm for short term gain? *11th International normal labour and birth conference, Sydney.* Oral presentation
- 2016: **Braye, K**. Stage one assessment and presentation in fulfilment of the requirements for the degree of Doctor of Philosophy, Midwifery. *University of Technology Sydney.* Written and oral presentation
- 2017: **Braye, K**. Why increase the dose of intrapartum antibiotic prophylaxis for maternal GBS colonisation: Are we doing more harm than good? *Virtual international day of the midwife conference, Sydney.* On-line presentation
- 2017: **Braye, K**. Group B streptococcus, are we doing more harm than good? Informing the narrative on intrapartum prophylaxis. Initial research findings. *31st ICM triennial congress, Toronto, Canada.* Oral presentation
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- 2017: **Braye, K**. The truth is out there! Informing the narrative on intrapartum prophylaxis for GBS management. *The 20th Australian college of midwives national conference. Adelaide, South Australia.* Oral presentation
- 2017: **Braye, K**. What are the maternal Group B streptococcal colonisation rates and GBS management experience of a cohort of pregnant women and their babies 2006- 2013? *Research Students Forum*, *University of Technology Sydney.* Oral presentation
- 2018: **Braye, K.** Review of *Microbirth online GBS course*. Invited reviewer
- 2018: **Braye, K**. Optimising maternal wellbeing. *Australian College of Midwives Victoria Branch. Annual update*. Oral presentation. Invited speaker
- 2018: **Braye, K.** Group B streptococcus (GBS) prophylaxis: Does it cause iatrogenic microbial harm for minimal short term gain? *Update for clinicians. Alice Springs.* On-line presentation. Invited speaker
- 2018: **Braye, K.** The Group B Strep dilemma: Are we doing more harm than good? 3 minute thesis (3MT) finalist. *Research Students Conference. University of Technology Sydney*
- 2018: **Braye, K.** Case study discussion New Zealand College of Midwives. Rotorua, New Zealand
- 2018: **Braye, K.** Stage two assessment and presentation in fulfilment of the requirements for the degree of Doctor of Philosophy, Midwifery. *University of Technology Sydney.* Written presentation and discussion
- 2018: **Braye, K.** Epidemiology of early-onset sepsis in a local health district 2006- 2016. *Annual update for Sydney Midwifery Educators*. *University of Technology Sydney*
- 2018: **Braye, K.** Epidemiology of early-onset sepsis in a local health district 2006- 2016. *University of Technology Sydney. Research Students Conference*

- 2019: **Braye, K.** Group B streptococcal screening, intrapartum antibiotic prophylaxis and neonatal early-onset infection rates in the Hunter New England local health district: 2006-2016. *The fourth Australian nurses and midwives conference, Newcastle, New South Wales*. Oral presentation
- 2019: **Braye, K.** Presented by Scarf, V. Antibiotic prophylaxis for women who are screened positive for GBS colonisation: compliance with guidelines. *The International Normal Labour and Birth Conference, Grange over Sands, Cumbria, UK*. Oral presentation

Publications in peer reviewed journals during candidature

This thesis contains four manuscripts outlined below, three published and one under peer review. The manuscripts have individual statements of authors' contributions to each manuscript. The CRediT Taxonomy as used by the journal, PLoS ONE, has been modified and used as a template to describe each author's individual contributions (PLoS ONE).

Area of contribution	Role Definition
Conceptualisation	Ideas; formulation or evolution of overarching research goals and aims
Data curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data
Funding acquisition	Acquisition of the financial support for the project leading to this publication
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection
Methodology	Development or design of methodology; creation of models
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs

Visualisation	Preparation, creation and/or presentation of the published work, specifically visualisation/data presentation
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages

Author's contributions to published manuscripts

Publication 1

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Area of contribution	Estimated percentage of contribution
Conceptualisation	KB 60%, MF 25%, CC 10%, DD 5%
Data Curation	KB 80%, EP 20%
Formal Analysis	KB 60% MF 40%
Methodology	KB 70%, MF 20%, AM 10%
Supervision	MF 70%, CC 20%, DD 10%, JF 10%, AM 10%
Validation	KB 50%, MF 40%, AM 5%, JF 5%
Visualisation	KB 50%, MF 30%, CC 10%, DD 5%, JF 5%
Writing – Original Draft Preparation	KB 100%
Writing – Review & Editing	KB 50%, MF 30%, CC 10%, JF 10%

Publication 2

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Area of contribution	Estimated percentage of contribution
Conceptualisation	KB 60%, JF 40%
Data Curation	KB 50%, EP 30%, MJ 10%, JF 10%
Formal Analysis	KB 60%, MJ 40%
Methodology	KB 40%, JF 30%, MF 15%, MJ 5%,
Supervision	JF 50%, MF 40%, KD 10%,
Validation	KB 30%, MF 30%, KD 5%, EP 5%, JF 30%
Visualisation	KB 60%, EP 20%, MF 20%
Writing – Original Draft Preparation	KB 100%
Writing – Review & Editing	KB, 40%, JF 30%, MF 20%, KD 5%, MJ 5%,

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Conceptualisation	KB 70%, MF 30%
Data Curation	KB 50%, MJ 10%, EP 30%, JF 10%
Formal Analysis	KB 60%, MJ 40%
Methodology	KB 50%, MF 30%, MJ 10%, JF10%
Supervision	JF 50%, KW, 10%, MF 40%
Validation	KB 50%, MF,10%, KD 5%, MJ 10%, EP 5%, JF 20%
Visualisation	KB 70%, MJ 30%, MF 10%
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Formal Analysis	KB 60%, JB 40%
Methodology	KB 50%, MF 20%, JB 30%
Supervision	MF 100%
Validation	MF 70%, JB 30%
Visualisation	KB 50%, MF 30%, JB 20%
Writing – Original Draft Preparation	KB 100%
Writing – Review & Editing	KB 50%, MF 30%, JB 20%

Table of contents

Abbreviations

Abbreviation	Term
3MT	Three minute thesis
ACM	Australian College of Midwives
ACOG	American College of Obstetricians and Gynaecologists
EOGBS	Early-onset group B streptococcal infection
EOS	Early-onset sepsis
g	Grams
GBS	Group B streptococcus
HMO	Human milk oligosaccharides
HNE	Hunter New England
HNELHD	Hunter New England Local Health District
HREC	Human Research Ethics Committee
IAP	Intrapartum Antibiotic Prophylaxis
IV	Intravenous
JHH	John Hunter Hospital
LHD	Local Health District
LMC	Lead Maternity Carer
LOGBS	Late-onset group B streptococcus
NICE	National Institute of Health Care and Excellence
NZCOM	New Zealand College of Midwives
PCR	Polymerase chain reaction
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists

RCOG	Royal College of Obstetricians and Gynaecologists
ROM	Release or rupture of membranes (the term release is preferred by the author of this work as it aligns with my preference for woman friendly terminology)
RSF	Research student forum
SROM	Spontaneous release or rupture of membranes
UK	United Kingdom
USA	United States of America
UTS	University of Technology Sydney

Definitions

Term	Definition
Adequate IAP	Common definition: ≥4 hours of IAP before birth of the baby
Bacteria	Microscopic living organisms, usually one-celled, that can be found everywhere. They can be beneficial or pathogenic
Blood culture	A blood test to detect and identify bacteria in the blood
Cerebrospinal fluid	A normally sterile body fluid found within and surrounding the brain and spinal cord
Colonisation	The presence of bacteria on a body surface, mucous membrane or body niche without causing disease in the person
Commensal	Living in a relationship in which one organism derives food or other benefits from another organism without hurting or helping it
Dysbiosis	An imbalance between the types of organism present in the microbiome
Early-onset	Within 72 hours of birth
Early-onset GBS sepsis	Sepsis arising within 72 hours caused by the GBS bacteria as shown by a positive blood or cerebrospinal fluid culture
Early-onset sepsis	Sepsis arising within 72 hours of birth. Generally microbiological culture-confirmed events are included
Eligible pregnancy	A woman's pregnancy that reaches ≥35 weeks gestation and therefore eligible for universal GBS screening. The term pregnancy rather than woman was used as many women had more than one pregnancy over the study period
Eligible preterm	A baby ≥35 weeks, but <37 weeks gestation, whose mother is therefore eligible for universal GBS screening
Eligible term baby	A baby ≥37 weeks, whose mother is therefore eligible for universal GBS screening

GBS management	The medical intervention for the prevention or reduction of the likelihood of having a baby with EOGBS. The management involves selecting women who are deemed most at risk and then offering IAP. After birth women may be asked to remain in hospital so the baby can be observed for signs of infection
Group B streptococcus (GBS)	Group B streptococcus GBS also known as *Streptococcus agalactiae* is a commensal bacterium forming part of the human microbiota or microbiome colonising the gastrointestinal and genitourinary tract
High-income country	The World Bank defines a high-income country as one that has a gross national income per capita exceeding $12,056 (2018 numbers)
IAP in accordance with Hunter New England (HNE) guidelines 2003-2018	IAP for at least 4 hours, repeated 4-hourly until birth
Iatrogenic	A state of ill health or adverse effect caused by medical treatment
Immunoglobulin IgG	Immunoglobulin G (IgG) is a type of antibody. It is the most common antibody found in blood circulation
Intrapartum	Occurring or provided during the process of labour and birth
Intrapartum Antibiotic Prophylaxis	Aims to reduce the likelihood of vertical transmission of maternal Group B Streptococcus and therefore prevent EOGBS in the neonate

Maternal GBS colonisation	GBS bacteria form part of the human microbiota or microbiome colonising the gastrointestinal and genitourinary tract of up to 30% of healthy human adults (asymptomatic carriers), including pregnant women
Microbiome	The genetic make-up of the whole of the microbiota: i.e. the genes from bacteria, eukaryotes, archaea and viruses
Microbiota	Microorganisms that are found within a specific environment
Neonatal	A newborn infant, or neonate under 28 days of age
Neonatal GBS colonisation	GBS bacteria may be passed from mother to her baby in utero prior to or during birth as part of a baby's founding microbiome, this leads to neonatal GBS colonisation which is usually asymptomatic and harmless
Pathogenic bacteria	Bacteria that cause disease
Prophylaxis	Measures designed to preserve health and prevent disease
Screening	The systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action
Screening for maternal GBS colonisation	Selection of women whose babies may benefit from IAP; screening can be universal or based on certain risk factors
Sepsis	A potentially life-threatening condition caused by the body's response to an infection. The body normally releases chemicals into the bloodstream to fight an infection. Sepsis occurs when the body's response to these chemicals is out of balance, triggering changes that can damage multiple organ systems
Symbiosis	Interaction between two different organisms living in close physical association, typically to the advantage of both

Therapeutic	Treats, prevents or alleviates symptoms of disease
Treatment	Medical care given to a patient for an illness or injury

List of tables

List of figures

Thesis Abstract

Background

In high-income countries ~ 30% of women and their babies are exposed to intrapartum antibiotic prophylaxis (IAP), for the prevention of neonatal early-onset group B streptococcal infection (EOGBS). This intervention aims to lower the risk of EOGBS but IAP is not without its own risks. Emerging evidence of the potential impact of antibiotics on the maternal/baby's microbiome is concerning. Evidence of the effectiveness of IAP and its application was needed to establish if current management was the optimum strategy for the reduction of EOGBS.

Purpose

To establish the impact of the normally commensal bacteria, group B streptococcus (GBS), on rates of neonatal early-onset sepsis (EOS) in one large health district; to describe local management of maternal GBS colonisation; and assess clinicians' adherence to GBS guidelines.

Methods

An integrative literature review was undertaken to examine the effectiveness and implications of IAP. Subsequently, two retrospective observational studies explored temporal trends in EOS, GBS management, and EOGBS, in one large health service over 11 years, using logistic regression and covariates for potential modifiers. A third study analysed a subset of women using ordered logistic regression. A 5% margin of error and a 95% confidence interval was used throughout.

Results

This research found management of GBS risk was sub-optimal. Clinical trials reported high effectiveness, but they had major methodological flaws. Observational studies showed poor adherence to GBS management. Whilst scant consideration was given to short-term risks; long-term consequences were not addressed.

In this work, group B streptococcus was the most common cause of EOS in term babies.

All cause EOS reduced significantly over time; EOGBS reduced but this did not reach statistical significance. Analysis of blood culture utilisation revealed intensity of surveillance did not change. Eighteen babies were diagnosed with EOGBS (0.19/1000 live births), ten of these were term. Seven were born to mothers screened negative for GBS. No evidence of difference in rates of EOGBS between screened and unscreened pregnancies was found. Prophylaxis in accord with local guidelines was received by one third of eligible women. Most missed opportunities for IAP were unavoidable, and mainly due to lack of time between admission for labour and birth. Despite this, rates of EOGBS were extremely low at 0.19/1000 live births.

Conclusion

Evidence for screening and IAP is poor. Current management has serious limitations, and risks may outweigh benefit. Overall, management of GBS risk warrants urgent reconsideration. Research is needed to understand factors, other than IAP, that may be contributing to protection from EOGBS.

Chapter 1

Background

"To study neonatal streptococcal B infection is to enter the realm of mysteries"

Michel Odent, 2015

Introduction

This work investigated intrapartum antibiotic prophylaxis (IAP) for pregnant women identified as colonised, or at risk of being colonised, with group with group B streptococcus (GBS). In particular the work considered whether contemporary GBS 'management' strategies provided the benefits intended, i.e. safe and evidenced based prevention of neonatal early-onset group B streptococcal infection (EOGBS), and whether the management of GBS colonisation in pregnant women should be reconsidered both in Australia, and internationally.

An integrative literature review followed by three, coherently linked epidemiological studies were conducted to investigate the research questions and are presented as peer-reviewed research constituting the body of this work. Ethical approval was granted from Hunter New England (HNE) Human Research Ethics Committee and ratified by University of Technology Sydney (UTS) Human Research Ethics Committee (Appendix 4&5). Permission has been obtained from relevant journals to include published manuscripts in this thesis, and data have been made available to other researchers via the UTS data repository (Foureur et al. 2019). Chapters 2-4 contain published manuscripts in their original form. Chapter 5 presents a manuscript under peer review. Each manuscript is presented in accordance with the publishing journals referencing requirement. Chapters 1 and 6, and the 'Thesis references' section are presented in UTS preferred referencing style (*Harvard_UTS*).

Rationale and scope of the project are outlined in this first chapter together with

background information of maternal GBS colonisation in pregnancy and descriptions of associated key concepts. The chapter highlights some controversies around maternal GBS screening and IAP, and examines claims made about the effectiveness of this intervention.

My aims, in this chapter, are to set the scene for the research data that follow, raising awareness that GBS management is not a straightforward undertaking and to present a reflective, but nevertheless disruptive contribution to knowledge on this subject.

The chapter consists of two sections. Section 1 describes the emergence of GBS in pregnancy, and its evolution to pathogen status. The chapter then considers management strategies employed in different countries and jurisdictions to reveal the sometimes confusing array of methods for selecting women whose babies may benefit from IAP and different approaches to antibiotic prophylaxis provision. Although research is sparse, Section 1 also explores women's perspectives on screening, and particularly, their experience of a GBS positive screening result in late pregnancy.

Section 2 presents emerging knowledge of the human microbiome and its impact in pregnancy and childbirth. This section also includes a brief exploration of the relationship between antibiotic exposure and microbial dysbiosis. It also explores the potential for iatrogenic harm by using current strategies for management of maternal GBS colonisation. The chapter concludes with an overview of the research methods employed in this work and a brief synopsis of what each chapter contains.

Section 1

Group B streptococcus in pregnant women and neonates

Group B streptococcus, in its native environment, is a commensal bacterium forming part of the flora of the human gastro-intestinal tract (GIT). As well as a commensal organism in the GIT, GBS is an asymptomatic coloniser of the human vagina. A systematic review of 78 studies, that included 73,791 pregnant women across 37 countries, estimated a mean prevalence of recto-vaginal group B streptococcus colonisation at 17.9% (95% CI, 16.2, 19.7%) (Kwartra et al. 2016). Rates were highest in Africa (22.4%, 95% CI, 18.1, 26.7%), followed by the Americas, (19.7%, 95% CI, 16.7, 22.7%), Europe (19.0%, 95% CI, 16.1, 22.0%). Studies from Southeast Asia had the lowest estimated mean prevalence (11.1%, 95% CI, 6.8, 15.3%) (Kwartra et al. 2016). A more recent systematic review found similar results and concluded that 18% (95% CI, 17, 19%) of pregnant women worldwide may be colonised by commensal GBS bacteria at any one time, with a regional variation of 11 to 35% (Russell et al. 2017). The authors noted prevalence and serotype distribution vary, even after adjusting for different laboratory methods.

The gastro-intestinal tract is the natural reservoir for GBS bacteria and is the likely source for maternal vaginal GBS colonisation. Women may carry the bacteria in their genito-urinary tract, in particular in the lower vagina, as well as in the lower GIT. It is not known how long humans have been colonised with GBS, or whether the bacteria provides any benefit. It is widely accepted that these common bacteria rarely cause harm, however, GBS bacteria can proliferate and may cause pathology in the host (Colbourn & Gilbert 2007).

Lancefield and Hare (1935) identified maternal GBS in vaginal swabs in 1935 at which time the bacterium was identified as a cause of puerperal sepsis. Reports of neonatal sepsis caused by GBS were sporadic until the early 1960s when GBS was recognised as a common cause of sepsis (Hood, Janney & Dameron 1961). By the 1970s GBS had become known as a dominant pathogen of the early neonatal.period (Baker 1997; Barton & Lins 1973). The logical link was made that maternal colonisation with GBS was a prerequisite to neonatal GBS infection (Baker & Edwards 1988). The reasons for vaginal conditions favouring GBS colonisation, and, albeit rarely, proliferation of the bacteria

causing pathology, are not completely understood (Collado et al. 2012; Le Doare et al. 2019). However the attention of researchers and clinicians turned towards identifying which pregnant women were colonised with GBS, or at risk of colonisation, and therefore could transfer the bacteria to their baby.

Maternal GBS colonisation

Maternal recto-vaginal GBS colonisation is typically intermittent and transient, but can be persistent (United Kingdom National Screening Committee (UK NSC) 2012). Reasons for such variation remain uncertain. Evidence from genetic and microbiological studies have demonstrated GBS carried in the GIT is identical to vaginally carried GBS strains, supporting the hypothesis of GIT to vagina transfer (Le Doare et al. 2019). A woman colonised with GBS in her lower bowel and/or vagina may pass the commensal bacteria to her baby prior to, or during birth, as a normal part of her baby's founding microbiome. This leads to neonatal GBS colonisation which typically has no adverse consequences (UK NSC 2012) .

Neonatal colonisation

A highly cited randomised controlled trial (RCT) reported neonatal GBS colonisation rates of ~50% in babies of women positive for GBS but not exposed to IAP (Boyer & Gotoff 1986). The conclusions of this trial were subsequently criticised in several iterations of the Cochrane Database of Systematic reviews (Ohlsson & Shah 2009; Ohlsson & Shah 2013; Ohlsson & Shah 2014). The authors found poor methodology, a high degree of selective reporting bias, and provision of incomplete outcome data. More recently, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), citing different references (Gilbert et al. 2002; Heath & Schuchat 2007; Jeffery & Lahra 1998), considered the neonatal GBS colonisation rate to be lower, at ~30% (RANZCOG 2016). Whilst the incidence of neonatal GBS colonisation may be uncertain, it is generally agreed that in the absence of intervention, neonatal GBS colonisation derived from the mother is common, with the vast majority of colonised babies remaining healthy and unaffected by this organism (UK National Screening Committee 2012).

A tiny minority of babies develop an infection caused by GBS bacteria. The Royal

College of Obstetricians and Gynaecologists suggest 1 in 2000 babies in the UK are affected by EOGBS (RCOG 2013). The infection may present during pregnancy or, more commonly, soon after birth (Tudela et al. 2012). This infection in the neonate is divided into early-onset (EOGBS) and late-onset (LOGBS) presentations, and these are considered to have different aetiologies. It is noted that EOS in neonates is caused by a range of organisms, of which GBS is but one. This work focuses on the early-onset condition based on GBS.

Early-onset sepsis

The terms 'sepsis' and 'infection' appear to be used interchangeably in the literature although 'sepsis' is more correctly defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al. 2016). Although experts disagree on time frames, the definition of EOS used by the National Institute for Health and Care Excellence (NICE) in the UK, and used here, is sepsis arising within 72 hours of birth (NICE 2014). Most babies with EOS present within the first 24 hours after birth (Tudela et al. 2012).

Early-onset sepsis, although uncommon in high-income countries, remains a significant cause of neonatal morbidity and mortality despite advances in maternity and neonatal intensive care (Le Doare & Heath 2013). Why a tiny minority of newborns develop EOS, and EOGBS in particular, is not completely clear. What is clear, is that EOS is more common in preterm babies, particularly those < 33 weeks gestation (Singh, Barnes & Isaacs 2019). This is partly due to the immaturity of the immune system in premature infants, which increases susceptibility to infection (Le Doare et al. 2019). Susceptibility of premature infants to EOGBS also occurs as these babies are not necessarily exposed to protective maternal antibodies. Maternal to fetal IgG transfer may not be evident until the beginning of the second trimester, linear transfer occurs as the pregnancy progresses, with the largest amount transferred in the third trimester (Palmeira et al. 2012).

Diagnosis of early-onset sepsis

Currently, a definitive diagnosis of EOS is made when a specimen, taken from a normally sterile site, such as blood or cerebral spinal fluid, grows pathogenic bacteria on a microbiologic culture medium. Newer molecular or genomic tests may reveal bacterial

nucleic acid material direct from specimens without using culture, but these modalities have not been used in the studies included in this thesis. To date, a newborn without culture-confirmed EOS, but with clinical symptoms, may be said to have a 'probable' or 'possible' diagnosis of EOS. This clinical (rather than culture-confirmed) diagnosis is commonly due to lack of laboratory support. As well as underestimation due to lack of culture-confirmed diagnosis, babies who are stillborn are not generally included in surveillance data. These limitations lead to a global underestimation of the burden of EOS (Seale et al. 2017). EOS caused by the GBS bacteria is reported worldwide on a voluntary basis, so true incidence is difficult to accurately record.

Incidence of early-onset group B streptococcal infection and the impact of antibiotic prophylaxis

In the 1970s and 1980s the reported incidence of EOGBS in high-income countries was up to 1.5-2/1000 live births and mortality was near 50% (Baker & Barrett 1974; Garland & Fliegner 1991). In the mid-1990s, maternal IAP was advocated to prevent EOGBS (Centers for Disease Control and Prevention 1996). However, there are, to date, no robust clinical trials that establish the effectiveness of IAP for the prevention of, or reduction in, the incidence of EOGBS. The terms 'reduction' and 'prevention' of EOS are used interchangeably in both the literature and guidelines for GBS management. The 2014 Cochrane systematic review and meta-analysis (Ohlsson & Shah 2014) agreed with previous reviews by the same authors and concluded IAP appeared to reduce EOGBS. This conclusion, however, was undermined by high risk of bias in the methodologies and conduct of the three studies analysed. Therefore, Cochrane authors have been unable to recommend IAP to reduce neonatal EOGBS.

A 2012 systematic review of contemporary rates of all culture-confirmed EOGBS, reported that rates had declined to a global mean of 0·43/1000 live births (95% CI, 0·37, 0·49%), with a case fatality of 12·1% (95% CI, 6·2, 18·3%) in babies of all gestations (Edmond et al. 2012). In the UK, without widespread use of universal screening, the incidence of term EOGBS is 0.2/1000 births (Royal College of Obstetricians and Gynaecologists (RCOG) 2013). Estimating the rates of morbidity and mortality is challenging as most estimates combine babies of all gestations and, in most jurisdictions, rates of EOGBS are reported on a voluntary basis. However, of all babies diagnosed with

EOGBS in the UK, RCOG (2013) estimates that 70% will recover fully, 20% will recover with some degree of disability and 10% of all babies with EOGBS will die. When estimating the likelihood of death from the bacteria for all babies born in the UK, modelling suggests that one in 17,000 babies would die as a result of EOS due to GBS with morbidity and mortality highest in the preterm cohort, particularly those < 33 weeks gestation (RCOG 2013).

Despite the lack of robust evidence there is almost universal acceptance of the dogma that the reduction of EOGBS is attributed to screening and IAP provision, and the intervention continues to be embraced in most high-income jurisdictions (Centers for Disease Control and Prevention 2010; Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2016; RCOG 2017). Benzylpenicillin, a narrow spectrum beta-lactam antibiotic, also known as penicillin G, is the antibiotic most commonly advocated for prophylaxis against GBS.

Intrapartum Antibiotic Prophylaxis

The aim of IAP is to reduce bacterial load although the pharmacodynamics of the process in pregnant women remains unclear as pharmacologic research into dosing regimens were obtained from non-pregnant individuals and only indirectly addressed tissue levels (Colombo et al. 2006). It is not clear exactly how IAP works to reduce the risk of EOGBS. The reduction could be caused by antibiotic loading of the fetus and amniotic fluid, by eradication of recto-vaginal colonisation, or by a combination of both (McNanley et al. 2007). Penicillins are known to enter both the fetus and amniotic fluid readily and also to decrease GBS recto-vaginal colony counts, which may partly explain the effectiveness of chemoprophylaxis. However, despite antibiotic loading of fetal and amniotic fluid compartments within minutes; the time taken to achieve optimal fetal prophylactic benefit is unclear (McNanley et al. 2007).

Although the duration of antibiotics needed to prevent vertical transmission of GBS has been debated, beta-lactam antibiotics for GBS prophylaxis administered for ≥4 hours before birth are reported to be effective at preventing vertical transmission of GBS from mother to infant (Centers for Disease Control and Prevention 2010; Fairlie, Zell & Schrag 2013; Lin et al. 2011). Observational studies agree on effectiveness of IAP given ≥ 4 hours, and some researchers have demonstrated shorter durations of appropriate

antibiotics may provide some protection (Fairlie, Zell & Schrag 2013; Lin et al. 2011). Despite unequivocal clinical guidelines recommending at least four hours of IAP, followed by IAP 4-hourly until birth, there are no well-designed clinical trials examining the optimal duration of this intervention for reduction or prevention of EOGBS.

Screening for GBS colonisation

In order for IAP to be offered, women whose babies are likely to benefit from IAP must be selected. Protocols have changed over time (Kurz & Davis 2015). Two standard strategies are currently recommended, either a universal culture-based screening or a selection approach based on risk factors (referred to as risk-based screening in this work). Some jurisdictions may use the two strategies in combination (Homer et al. 2014). Both methods are based on low quality evidence and opinion. Experts have been unable to agree on which of the two standard screening approaches is most effective and appropriate (Kurz & Davis 2015).

In order to further understand the complexities of the vexed issue of GBS management, the process of GBS guideline development from the influential Centers for Disease Control and Prevention (CDC) in the United States of America (USA) (CDC 1996, 2002, 2010)**,** and the development of guidelines in Australia were examined.

GBS guideline development

The first CDC EOGBS prevention guideline was published in 1996 in the USA. The guideline recommended selecting women whose babies may benefit from IAP using either a universal screening method or a risk-based approach. The recommended dose of IAP was stated in the guideline as 5 million units (3grams) (g) of intravenous (IV) penicillin initially, followed by 2.5 million units (1.5g) four hourly until birth (CDC 1996). These recommendations were partly based on a poor quality clinical trial by Tuppurainen & Hallman (1989) as discussed in chapter two. The trial was assessed as having a high risk of bias by Cochrane reviewers (Ohlsson & Shah 2014). Where evidence for the dose of IAP was lacking, recommendations were provided by 'experts from relevant disciplines' (CDC 1996, p. pg 1). The CDCs 1996 recommendations for GBS screening and IAP provision remained in place for six years. However, according to the CDC, the uptake of recommendations by clinicians in the United States of America

(USA), was disappointing (CDC 2002). Despite this EOGBS rates continued to decline in the USA. Data collected after the 1996 guidelines were published prompted re-evaluation of prevention strategies at a meeting of clinical and public health representatives in the USA in November 2001.

In 2002, the CDC revised their guidelines, primarily due to results of a large observational study from the USA (Schrag et al. 2002). The 2002 iteration of the CDC guidelines recommended universal screening to select women for IAP, with certain antenatally identified risk factors i.e. women with GBS bacteriuria during their current pregnancy or women who had had an infant with GBS infection in a previous pregnancy (CDC 2002). This screening recommendation remained in the 2010 iteration of the guidelines (CDC 2010) together with the CDC's initial dosing regimen (5 million units (3g) of penicillin). The CDC did, however, change the 4-hourly repeat dose(s), increasing from 2.5 million units to 3 million units (1.5 to 1.8g). This was due to the unavailability of a 2.5 million unit dose in the USA (CDC 2010). The dose of 1.8g was chosen to allow for administration 4-hourly and to remain within safe dosing parameters to prevent side effects such as maternal neurotoxicity (CDC 2010). In their 2019 update, the American College of Obstetricians and Gynaecologists (ACOG) recommend performing universal GBS screening between '36 0/7 and 37 6/7' weeks of gestation (ACOG 2019). This new timeframe for screening provides a five week window for valid culture results which may include births that occur up to a gestational age of 41 0/7 weeks but not beyond. The ACOG states that the update replaces the CDC 2010 GBS guidelines (ACOG 2019). The CDC GBS prevention guidelines remain influential internationally, including in Australia.

Australian GBS guidelines

Australian GBS guidelines were developed following the publication of a large retrospective cohort study undertaken in 1991 by Garland and Fliegner in Melbourne, Australia. This study revealed universal screening (at 28 weeks gestation), reduced the rate of EOGBS compared with an unscreened group. As a result of this early study, universal screening for GBS risk was recommended, predating the CDC recommendations of 1996. Although Australia has no national policy, and guidelines around the country vary, most jurisdictions use universal screening (at 35-37 weeks) to select women whose babies may benefit from IAP for GBS risk (Sheehy, Davis & Homer 2013).

In addition to the study by Garland and Fliegner in 1991, Australian GBS guidelines were subsequently influenced by the CDC (CDC 2010) and more recently by Australian Therapeutic Guidelines (Antibiotic expert groups 2014). In 2000, the Australian Therapeutic Guidelines proposed a regimen that differed from the CDC, by recommending benzylpenicillin 1.2g IV and then 600mg four hourly until birth, as prophylaxis for GBS risk (Antibiotic expert groups 2000). This recommendation remained until 2014 when the benzylpenicillin dose was increased to 3g followed by 1.8g, 4-hourly until birth (Antibiotic expert groups 2014) in order to align with the CDC (CDC 1996, 2002, 2010) and other international guidelines (RCOG 2012). Subsequently, most, but not all, states and territories in Australia changed their IAP dosing regimen to fall in line with the CDC and other international jurisdictions.

Hunter New England Local Health District's (HNELHD) GBS guideline, issued in 2003 and current until 2018 recommends universal screening for all pregnant women 35-37 weeks gestation. The guideline goes on to state "to achieve prophylaxis, IAP must be administered at least four hours prior to delivery. [The] antibiotic of choice [in the LHD] is IV benzylpenicillin 1.2g initially, then 600mg IV four hourly until delivery" (Johnson et al. 2001). In 2018 the guideline for the LHD was revised, and universal screening continues to be recommended. Unlike the majority of jurisdictions in Australia, the medication standing order HNELHD MSO 15_03 remains current, i.e. 1.2g benzylpenicillin followed by 600mg four hourly, when necessary (Hunter New England Local Health District 2018).

Universal screening

Universal screening implies that all pregnant women are offered either a low recto-vaginal or a low vaginal/perianal swab. Until recently universal screening has been offered at 35-37 weeks gestation. However, in a 2019 ACOG update, screening is now recommended for all women between reaching 36 to 37 6/7 weeks gestation (ACOG 2019). For the purposes of the work contained in this thesis, universal screening was recommended at 35-37 weeks gestation. Women who undergo universal screening and are found to be positive for GBS colonisation are offered IAP during labour, or at release of membranes (ROM) if this occurs first. Bacteriuria in the current pregnancy is thought to equate to heavy GBS colonisation (CDC 2010). These women, and women who have had a previous infant with EOGBS, are considered to be at higher risk of having a baby with EOGBS and are offered IAP without screening.

Risk-based approach

The risk-based approach requires women presenting with certain risk factors, typically ROM ≥18 hours maternal fever ≥ 38°celcius in labour, and/or premature labour, be identified and offered IAP. Like the universal screening approach, bacteriuria in the index pregnancy or a previous baby diagnosed with EOGBS are also considered risks when using this approach (UK National Screening Committee 2012). A combination of these risk factors will predict risk in more cases, according to a prospective cohort study from the UK (Oddie & Embleton 2002). However, generally only one risk factor is required to trigger eligibility for prophylaxis.

If a woman presents in labour at term with unknown GBS colonisation status and does not have risk factors but reports a known history of GBS colonisation in a previous pregnancy, the risk of EOGBS in the neonate is likely to be increased. Due to this increased risk, the ACOG state in their 2019 update that it is reasonable to offer IAP based on the woman's history of GBS colonisation (ACOG 2019).

Prior to this new recommendation, the CDC guidelines recommended women with unknown GBS status be offered IAP if other GBS risk factors arose. Women with a negative valid GBS screen did not require antibiotics for GBS risk even if risk factors developed (CDC 2002, 2010).

Limitations of the standard approaches to selecting women for IAP

In health care generally, screening tests are used to identify the presence of unsuspected pathology (Hoffmann & Del Mar 2017). Universal GBS screening is used to identify the presence of a commensal bacterium in the vagina. There is no disease present.

Screening in this setting is used to identify the potential risk of pathology. In general, a positive screening result is followed by a more specific diagnostic test to determine whether pathology is present. Currently there is no diagnostic test that can distinguish between women positive for GBS whose babies would be affected and those whose babies would not be affected by the bacteria. Hence a positive screening result has a very low predictive value for the infection (Seedat et al. 2019). Furthermore, when using a universal screening approach, the population screened, and in whom screening would direct management, are mainly pregnant women at term, with no risk factors. Most women with preterm birth would miss the opportunity for screening as their pregnancy may not reach 35 weeks gestation. However, in many jurisdictions, women presenting in preterm labour are offered antibiotics as prematurity is considered a risk factor for EOGBS (NICE 2015).

In 2017, the National Screening Committee estimated that the introduction of a universal screening program into the UK would offer a universal GBS screen to ~718,100 pregnant women annually. Assuming all eligible women accepted screening ~150,800 women would be positive for GBS and offered IAP. Of these, 0.2% (333/150,800) would have a baby with EOGBS. Therefore ~99.8% (150,500) of women screened positive for GBS and administered with IAP, and their babies, would be over- treated (Seedat et al. 2019).

All current approaches to screening for maternal GBS have limitations. Neither of the standard methods i.e. universal culture screening nor an approach based on risk factors, will predict all cases of EOGBS. Neither can reliably predict which women are at most risk of having a baby affected by EOGBS. The ability of antenatal testing to predict maternal intrapartum colonisation with GBS is moderate. The transient nature of maternal GBS colonisation may result in false positive and false negative results (Seedat et al. 2016). A 2010 systematic review found that on average ~70% of women who test positive for GBS on antenatal screening after 35 weeks' gestation also test positive during labour, and on average ~5% of women who test negative on antenatal screening will test positive

during labour (Valkenburg-van den Berg et al. 2010). The largest recent study looking at the performance of universal screening in the USA found less accuracy in practice; a positive predictive value in labour of 50.5%, and a negative predictive value of 91.7%. When considering only those women screened at the recommended time, the positive predictive value improved to 60.6%, while the negative predictive value remained similar (89.5%) (Lin et al. 2011). Universal screening for GBS risk is therefore imprecise.

The alternative approach, based on risk factors with no universal screen in pregnancy, requires correct identification of GBS risk. Having determined a risk factor, the clinician must then discuss this risk with the woman, prescribe and provide timely administration of IV medication. This two-step process can be challenging to complete and can therefore lead to an unacceptable rate of missed opportunities and non-compliance to GBS guidelines (Kurz & Davis 2015; Lin et al. 2011; Sheehy, Davis & Homer 2013).

Non-culture method for intrapartum specimen processing

An alternative to the two standard methods of identifying women whose babies may benefit from IAP, is the identification of maternal colonisation with GBS at presentation in labour or ROM (Di Renzo et al. 2014). A polymerase chain reaction (PCR), enables point-of-care, rapid GBS detection performed in the birthing unit without the logistics needed to transfer the specimen to a laboratory and await culture. This point-of-care process may enable a timely administration of an appropriate IAP. Strengths of a point-of-care test include the ability to identify women whose infants are at potential risk at the time of admission, thereby decreasing the number of false-positives and false- negatives incurred with either the culture-based or risk-based strategies. There are also limitations associated with this method of GBS detection; the method is still a screen for risk and cannot predict disease. Furthermore, there would be challenges around provision of a service equitable to all women, i.e. service provision to women in regional and rural areas as well as metropolitan centres and the cost and the logistics of maintaining equipment would require further evaluation (Di Renzo et al. 2014).

Currently a rapid point-of-care test is offered at a minority of facilities, most jurisdictions use either of the two standard approaches or a combination of the two (CDC 2010, RANZCOG 2016; RCOG 2017). However, limitations are associated with both risk factor determined IAP versus antenatal universal screening. Inadequate provision of IAP

(Berardi et al. 2017; Fairlie, Zell & Schrag 2013) leading to sub-therapeutic dosing is an important limitation. A consequence of inadequate provision of IAP is women and their babies are likely to be exposed to risks of antibiotic administration without having access to the reported benefits (Miller et al. 2018; Zimmermann & Curtis 2019).

Reduction in the prevalence of EOGBS

Although reductions in the rates of EOGBS have almost entirely been ascribed to the provision of widespread IAP, contemporary literature from both the UK (UK NSC 2012) and the USA (CDC 2002, 2010) reveal that EOGBS rates were already reducing before the first CDC screening and management guideline was introduced in 1996 (CDC) and the decrease continued until 2002 in many high- income countries. Globally, estimated EOGBS rates reduced dramatically between the 1970s and 2000s and have been relatively stable at below 0.5/1000 live births since 2002 (CDC 2010), albeit with minor fluctuations, both up (O'Sullivan et al. 2019) and down (Darlow et al. 2016) in some countries, reflecting the normal variations that may be expected with rare events such as EOGBS. At the same time, the proportion of women and babies exposed to IAP has increased in some high-income jurisdictions from ~12% to ~30% since the pre-prevention era (van Dyke et al. 2009).

As well as the increase of over 100% in the number of women and babies exposed to IAP, of considerable concern is that the recommended dosing regimen of IAP has also risen more than 100% from an initial 1.2g, followed by 600mg 4-hourly to 3g initially, followed by 1.5-1.8g 4-hourly (CDC 1996, 2002, 2010). The reasons for the sharp increase in the recommended dose of IAP despite a lack of evidence of decline in the level of GBS penicillin susceptibility, are unclear (Moroi et al. 2019). It is concerning that the 3g dose initially recommended by the CDC, and taken up by most high-income jurisdictions worldwide has been apparently based on evidence from a small RCT from 1989 conducted in Finland by Tuppurainen & Hallman (1989). The RCT was one of four clinical trials described by the latest Cochrane review on this topic as having arisen from research with poor methodology and high risk of bias (Ohlsson & Shah 2014).

There is no doubt that reported EOGBS rates have decreased overtime. How much of the decrease is associated with medical management of GBS risk using screening followed by IAP is debatable. While high-income countries continue to strive for a greater

reduction in the rates of infant GBS infection, and support groups lobby for improvement in the management of maternal GBS colonisation risk e.g. UK (Group B Strep support group) and USA (GBS/CIDP Foundation International 2019), it is important to consider the individual woman's perception of risk in maternity care, and how women feel about having their apparently healthy pregnancy 'managed' in this way.

Section 2

"Primum non nocere"

A woman's perception of risk

The literature describing women's views on GBS management in pregnancy is scarce. In a systematic review of 35 studies involving 27,323 women and men undergoing various screening tests, the majority of participants over-estimated the benefits of screening and under-estimated potential harms (Hoffmann & Del Mar 2015). Although this large systematic review was not specific to maternity care, it may be reasonable to equate these findings with the views of pregnant women involved in screening for GBS. The absence of data about women's views of GBS screening is a limitation when evaluating GBS screening and IAP programs.

Pregnant women are influenced by a number of competing discourses. 'Good' mothers should manage and avoid risks, thereby protecting their babies from harm. 'Good' mothers put their baby's needs before their own. For example, mothers should avoid ingesting or being exposed to potential toxins. On the other hand, 'good' mothers take, and act on, the advice of trusted clinicians (McDonald, Amir & Davey 2011). This situation presents an inherent conflict for women around GBS management (Blaser 2011; Blaser 2014; Bokulich et al. 2016; McDonald, Amir & Davey 2011).

Clinicians are encouraged to follow guidelines; this includes recommending women positive for recto-vaginal GBS colonisation accept prophylaxis to prevent a serious, but rare outcome for their baby. Until recently, guidelines have not seriously considered the risks of IAP so women are not well informed about these issues. A woman should have an opportunity to come to a decision that she considers is right for her and her baby (Healy, Humphreys & Kennedy 2016). However, shared decision making around this vexed issue is complex and not straightforward.

The issue of GBS is one example of the challenges inherent in translating evidence into discussion and recommendations (Sheehy, Davis & Homer 2013). There is a paucity of research around GBS management from a woman's perspective. More research is needed to gain insight into the opinions and feelings of women around this important topic.

Women's perspectives of medical GBS management

A small study in 2010 used discourse analysis to explore women's views relating to issues around GBS management. The authors concluded that when considering risk of EOGBS, the medical construct was to consider newborns as helpless and vulnerable, at risk from their mothers. Intrapartum antibiotics are therefore promoted as the solution to reduce the maternal threat to her infant and thereby prevent transmission of a pathogen from mother to her baby (MacDonald et al. 2010). While many women are likely to be unaware of the adverse effects of IAP, those who are aware may find it hard to resist the convention of current GBS management. One qualitative study has been conducted to determine how women feel about GBS screening and prophylaxis intervention (Darbyshire et al. 2003). The study occurred within the context of contemporary society in which pregnancy and childbirth are increasingly characterised as uncertain and dangerous events (Darbyshire et al. 2003). This environment influences a woman's understanding of her pregnancy as a state of embodied risk which has to be managed (Darbyshire et al. 2003). The researchers describe several factors which combine to make women's decisions to undergo GBS screening seem like no decision at all (Darbyshire et al. 2003). Although women may be asked whether they consent to a particular intervention, in an attempt to avoid making the 'wrong' or 'inappropriate' choice for the wellbeing of her baby, women often have little autonomy over their decisions (Darbyshire et al. 2003). Therefore, to choose not to take a recommended course of action is, for many women, not an option.

Since a woman may not be given the power to enable choice, it is the responsibility of clinicians to understand the complexities around GBS management and to ensure this medical intervention is used judiciously (Kurz & Davis 2015). An antenatal screen that is positive for GBS occurs at the end of a woman's pregnancy, or when using a risk- based method, risk may become apparent antenatally or in labour. A positive result may affect a woman's choice of birth place as well as initiate a process that will medicalise her birth (RCOG 2017). The woman will need to consider early admission to the birth unit when in labour or after ROM if this occurs first, since she will require an IV cannula to be placed and antibiotics provided for at least four hours prior to the birth of her baby and then every four hours until birth in order to comply with most guidelines (Zimmermann & Curtis 2019). In the immediate postnatal period, a positive GBS result may separate

mother and child effecting bonding and the establishment of breast feeding (Bergman 2019). Even if mother and baby, are able to remain together, a woman may be asked to stay in hospital so clinicians can regularly monitor her baby for signs of infection. Although guidelines disagree on length of stay, typical time frames range from 12-48 hours (New South Wales Ministry of Health (NSW MoH 2016; RCOG 2013). Since around a quarter of all women are positive for GBS, this extra postnatal stay affects a large portion of the birthing population, most of whom are well women with well babies. If these measures were effective and medically necessary to protect babies from EOGBS, they would be scientifically defensible. However, in the UK, it has been estimated, that introduction of GBS management with universal screening and IAP (as opposed to the risk-based approach currently recommended), would lead to ~99.8% of women screened and positive for GBS, and their babies, receiving unnecessary IAP (Bevan et al. 2019). Given these statistics, most babies at term could alternatively be considered healthy and robust with the necessary means to resist infection, except in an acknowledged minority of cases when perinatal vigilance and timely treatment of possible sepsis must occur.

Whilst we should not underplay the potential dangers of EOGBS, it is important to discuss GBS management logically with women from the standpoint that although antibiotics can be lifesaving, most women and babies are not affected by EOGBS, or any other infection at birth. A healthy woman has inherent and robust mechanisms to ensure her baby is born safely with processes to protect and sustain her/him (Faa et al. 2013). An example of one of these mechanisms is an abundance of maternal vaginal Lactobacillus.

Lactobacillus

Lactobacillus (a commensal vaginal bacterium) is a keystone vaginal genus in healthy pregnant women (Ravel et al. 2013; Romero et al. 2014). Lactobacilli are known to actively protect themselves and the vaginal environment from pathogens by the production of lactic acid. Lactic acid has a number of protective benefits for mother and child. For example, it acidifies the vaginal pH, making the environment unattractive to pathogenic bacteria, as well as reducing the adherence of pathogens to urogenital epithelial cells (Chu et al. 2017; Rosen et al. 2017).

Why and how GBS bacteria colonise the vagina remains unclear, but some research is revealing pathogenic vaginal colonisation may be associated with a depletion of healthy

vaginal microbes in some women. It may be that lack of certain Lactobacillus strains causes perturbation of the vaginal microbiome which in turn enables pathogenic proliferation of GBS in some individuals (Marziali et al. 2019; Spurbeck & Arvidson 2011).

The microbiome

Consideration of the connections between the human microbiome, childbirth and microbial dysbiosis form the final elements of the rationale for undertaking the research presented in this thesis. Whilst it is acknowledged that research is in the nascent stage, the importance of microbial health may have the potential to effect many areas of health and health care, including maternal and neonatal outcomes (Blaser & Dominguez-Bello 2016; Chu et al. 2017; Dominguez-Bello et al. 2019; NICE 2015; Tapiainen et al. 2019) .

The human microbiome encompasses an ecosystem of approximately 90 trillion microbes that impact on host physiology and are known to protect the host from pathogens (Blaser 2010). During vaginal birth, and possibly in-utero, the baby begins the process of seeding a founding microbiome (Aagaard et al. 2014; Stinson et al. 2019). Cohort study findings on the impact of early life on a healthy microbiome, are contributing to a more solid understanding of how the human microbiome develops (Collado et al. 2016; Penders et al. 2006; Zhong et al. 2019).

A woman's genito-urinary tract is traditionally investigated only when pathology is suspected, consequently the symbiotic attributes of the maternal microbiome are not well known. However, researchers have shown that a healthy woman's vagina and the bacterial communities that reside there represent a balanced symbiotic association (Faa et al. 2013). A healthy pregnant woman's vaginal microbiome is characterised by low microbial diversity which is highly stable through pregnancy (Faa et al. 2013). This stability is important to maintain a balance of low inflammation and protection for the growing fetus (Collado et al. 2012).

Emerging discoveries question beliefs that the fetus and his/her habitat i.e. the uterus, fetal membranes and placenta are sterile, unless infected (Aagaard et al. 2014). Recent studies have described the presence of a commensal microbiome that exists before labour

(Aagaard et al. 2014; Romero et al. 2014; Stinson et al. 2019). However, limitations to these assertions have been raised due to the scarcity of bacteria, and the difficulty of analysis leading to a high risk of contamination during the research process (Lauder et al. 2016).

Antibiotics and the microbiome

Antibiotics are commonly used as prophylaxis for specific infections, like GBS, but typically without consideration of their impact on gut microbiota (Blaser 2011). Antimicrobials are not exclusively selective for pathogens and may indiscriminately affect other members of the commensal microbial ecosystem (Blaser 2011). This imbalance causes microbial dysbiosis (Miller et al. 2018). Dysbiosis of the neonatal microbiome may also occur indirectly by the administration of IAP to a woman in labour (Azad et al. 2015). New technologies using high-throughput sequencing methods have enabled studies linking changes in the diversity of the human microbiota to disease (Neuman et al. 2018). Early exposure to antibiotics, including secondary exposure during labour, and the resultant perturbation in the establishment of the gut microbiota, have been associated with the development of a number of diseases such as asthma (Fujimura & Lynch 2015; Russell et al. 2013), inflammatory bowel disease (Neuman et al. 2018), obesity (Azad et al. 2014) and neurodevelopmental health (Cong et al. 2016; Yang et al. 2016) in both epidemiological and experimental studies (Chu et al. 2016).

Researchers have shown that the baby's founding microbes, transferred from mother to baby, together with exclusive breastfeeding are important in optimising newborn immune and epigenetic health (Dahlen et al. 2013; Dominguez-Bello et al. 2019). These shared interactions between a newborn and mother appear crucial for normal development of the child; but evidence of how host–microbe symbiosis evolves, is established and maintained, is still emerging.

A recent systematic review concluded that IAP for GBS has profound effects on the intestinal microbiota of infants by changing the balance of beneficial commensals (Zimmermann & Curtis 2019). While long-term research remains sparse, it is interesting to speculate whether changes during the early-life 'critical window' during which microbiota and the immune response develop concurrently, may have an important influence on the health of the child (Dahlen et al. 2013; Dominguez-Bello et al. 2019).

Potential long-term adverse consequences of this warrant further investigation.

It is becoming increasingly evident that exposing many thousands of women, and their babies, to large doses of antibiotics for a neonatal condition that is rare, is likely to cause short and long-term adverse health outcomes for the child, contravenes the principals of positive antimicrobial stewardship, increases the medicalisation of birth and may result in more harm than good (Bevan et al. 2019; RCOG 2017; Seedat et al. 2019). These findings contribute further important considerations for researchers, clinicians, and women when considering the benefits and risks of maternal GBS risk management to reduce the likelihood of EOGBS. As a midwife, these findings and my experiences with the management of GBS colonisation in healthy pregnant women, caused me to question clinical practice around this vexed issue.

Rationale and philosophical position

I subscribe to a constructionist theoretical framework and believe all women should have individualised information to enable informed and considered choice in maternity care. Health care and research is influenced by theories; social constructionism offers a framework to better address the individual needs of a broad range of women (Finfgeld 2001). Evidence based maternity care is the conscientious, explicit, and judicious use of current best evidence to enable shared decision making about the care of an individual woman and her baby (Sackett 1996). Whilst wanting the best outcomes for women and babies, it has been argued that clinicians may provide 'too much medicine' (Glasziou et al. 2013) and 'too much, too soon' (Miller et al. 2016). The alternative to this medical paradigm is a physiological or wellness paradigm (Schneider Jamner & Stokols 2000). Women and clinicians who espouse this way of thinking, consider that generally pregnancy and childbirth is a safe and normal part of a woman's life (Buckley 2015; Dahlen et al. 2014; Fahy, Foureur & Hastie 2008; Stenglin & Foureur 2013).

In this work, I argue that current 'management' of maternal GBS risk provides 'too much' medicine (Glasziou et al. 2013) i.e. large doses of antibiotics, 'too soon', as prophylaxis, and the implied assurance of a baby without EOGBS. There is no doubt that sometimes a woman and/or her baby need medical support and intervention in labour, but research is suggesting that some events and conditions that we identify as needing our intervention are iatrogenic, caused by the well-intentioned efforts of care givers (Dahlen et al. 2012;

Glasziou et al. 2013). The unexplained and incomplete evidence of IAP provision in a normal pregnancy should not be ignored or dismissed.

As a midwife, I have experienced the 'pre-prevention era' as well as the era of GBS medical management. Increasingly, I felt that we were imposing too much medicine and medical intervention on pregnant women; and, as clinicians, we are losing the ability to balance the potential benefits and risks of health decisions and interventions, and consequently women were not provided with optimal information. I felt compelled to understand the issues and undertake work that would identify gaps, add to the body of knowledge and provide women and clinical colleagues with a synthesis of available evidence.

Initially I planned to undertake a study using probiotics as an intervention aiming to reduce maternal GBS colonisation and ultimately EOGBS. As EOGBS is a rare condition, it would take a very large cohort to test a change in EOGBS rates that was significant. On reflection, and as I proceeded with initial research, it became clear that I could provide more insights about the current state of GBS management with a quantitative design methodology. Cohort studies are appropriate when researchers want to know the actual effects of variables under consideration in clinical practice, where RCTs are not feasible. The overarching research question was:

> *Are we using the optimal strategy to reduce the risk of neonatal early-onset group B streptococcal infection?*

More specifically the integrative review and the three studies that arose from the review explored the following questions:

> *What is the strength of evidence supporting current GBS management in pregnancy? What are the most common bacteria affecting newborns in one local health district in Australia, 2006-2016?*
>
> *In a health district that has used universal screening for over a decade, what are the maternal GBS colonisation, screening, EOGBS rates, and neonatal outcomes for this population?*
>
> *Are clinicians compliant with local GBS screening and management guidelines?*

Sources of Data

Information concerning babies and their mothers was obtained from the maternity ObstetriX database and the NSW Health Pathology database (Auslab). ObstetriX (now eMaternity) is a state wide surveillance system providing point-of-care data collection across antenatal, intrapartum and immediate postnatal periods. Clinicians contribute information soon after birth. The database is maintained by LHD data custodians. The medical records of babies affected by EOGBS, and their mothers, were also scrutinised. Provision of IAP was documented in the medical record with two clinicians signing for receipt and timing of the medication.

The second database used was the New South Wales (NSW) Health Pathology database which collects pathology data from throughout HNELHD. New South Wales Health Pathology is an operational grouping for diagnostic pathology services for public health facilities in NSW and services all major maternity units in the LHD with the exception of Moree, Gunnedah and Narrabri. These three rural units are serviced by private pathology facilities who either were unable to provide data or who could identify no EOS events. The NSW Health Pathology service conforms to the ISO15189 standards for international laboratory accreditation which includes maintenance of data (National association of testing authorities Australia). All data used in this body of work have been cleaned, de-identified and made available to other researchers, with ethical approval through the University of Technology Sydney Data repository (Foureur et al. 2019).

Accuracy of data

There is evidence to support the validity of midwife-entered responses into an electronic data base. An American study (Stapleton 2011) examined 3,966 variables and reviewed the consistency between the online data record with the woman's paper record as transcribed by midwives working in a combination of five free standing birth centres and hospitals. The results showed a high level of consistency (97.1%) between the two sets of records. Similarly in Australia, a validation study conducted in 2003 compared the paper medical record with the electronic version (The Victorian Perinatal Data form). This study demonstrated a similar level of consistency (96.3%) between the two records (Knight et al. 2009).

Overview of the thesis structure

An overview of all chapters, including the methodology used for each study is now provided. The thesis is presented in six chapters.

Chapter 1 has provided an insight into the complexities of current management of GBS risk and given an overview of the background of this complex topic. Four chapters, (Chapters 2 to 5) are presented in the form of peer reviewed journal manuscripts (three published and one submitted and currently undergoing peer review). References for Chapters 2 to 5 appear at the end of each manuscript and in the final list of references for the thesis. The introduction and background to each of the four manuscripts are similar as they cover the same topic. Therefore, the reader may choose to move past study introductions and backgrounds and on to the methods for each study.

Chapter 2 presents an integrative review of the literature. The review aimed to provide insight for discussion surrounding the effectiveness of IAP. To achieve this, the review utilised an integrative methodology framework (Whittemore & Knafl 2005). This framework includes problem identification, a comprehensive literature search and a findings and discussion section. The framework enables a robust review which may influence evidence-based practice initiatives and changes in maternity care. The review revealed the absence of high quality RCT evidence for the effectiveness of IAP to reduce risk of EOGBS. Observational studies were incorporated into this integrative review to provide insights into clinical experiences with maternal and neonatal GBS colonisation and EOGBS infection. Although the observational studies critiqued found IAP to be effective, importantly these studies showed screening and administration to be sub-optimal and consequently informed the direction and focus of this work.

Chapter 3 presents a cohort study describing the epidemiology of EOS, including EOGBS in one Australian LHD that has used universal GBS screening for over a decade. The cohort includes 62,281 mothers, who had 92,055 pregnancies, resulting in 93,584 live born babies over an 11-year period from 2006 to 2016. Logistic regression with linear temporal trend and covariates for potential effect modifiers were employed. Blood culture utilisation was determined by examining the rate of babies undergoing blood culture within 72 hours of birth. The study provides analysis of two data sources, a point-of-care maternity database (ObstetriX) and a pathology database from NSW Health Pathology.

The study found GBS and *E. coli* were equal in prevalence over the study period but GBS was more common in term infants and *E. coli* more common in preterm babies. All cause EOS and *E. coli* reduced over time whilst EOGBS remained constant.

Chapter 4. Having established GBS was the most common bacteria affecting term babies in our LDH, a study was designed to describe management of maternal GBS colonisation in our LHD and assess rates of EOGBS over the same time frame and using the same population as Study 1. In this retrospective cohort study, we explored the rates of maternal GBS colonisation, the uptake of universal screening for detection of maternal GBS management and assessment of EOGBS incidence over time. Linking routinely collected maternity and pathology data as in Study 2, this study explored temporal trends using logistic regression and covariates for potential effect modifiers. The study concluded that the rate of EOGBS was low, 18 babies had culture-confirmed EOGBS, ten were term and seven of these had mothers who were negative for GBS. There was no change detected in rates of EOGBS over time and no difference in EOGBS in babies of screened and unscreened women in the study population. Screening and prophylaxis rates were modest and limitations of universal screening strongly suggested alternatives be considered.

Chapter 5 presents the final of the three studies that constitute this body of work. This study examined details of GBS guideline compliance which included screening, reporting of results and IAP provision. The purpose of this study was to examine potential associations between receipt of IAP, time to birth, and maternal characteristics. We used an ordered logistic regression modelling to determine the effect of potential confounders; parity, onset of labour (spontaneous or induced), place and mode of birth on the provision of IAP. The study population was drawn from 4,098 women who had 4,100 babies in one birth unit and its associated birth centres within one LHD in 2016. A random sample of 223 women positive for GBS who birthed in 2016 was selected from a total of 523 women reported as positive for GBS in that year. This provided a sufficient power to produce a 5% margin of error and a 95% confidence interval. Data were extracted from the same database as the previous two studies and were entered into Microsoft Excel and SPSS v.25 for descriptive and correlational statistical analysis. The study found compliance with IAP guidelines was very low. Primiparous women and/or women experiencing an induction of labour were three times more likely to be provided with IAP in accord with guidelines.

Chapter 6 synthesises findings from the literature review and the three epidemiological studies which constitute this thesis. The significance of the work is addressed and findings are discussed in relation to the extant literature and the broader context of maternity care, ultimately providing insights for future research and implications for practice and policy.

How the included studies are interrelated

Figure 1.1 below illustrates the four major components of this work, being (1) the integrative literature review beginning the process by critiquing the evidence for the effectiveness of IAP, identifying the poor quality of the evidence on which guidelines for GBS prophylaxis were based and forming the framework for the three subsequent studies. The first of these studies, (2) the epidemiology of early-onset sepsis, investigated all-cause EOS with a particular focus on EOS caused by GBS and identifying its place as the most prevalent, documented cause of term EOS in our LHD. Having established GBS was the most common bacteria affecting term babies in the first 72 hours post birth, the second study (3) Maternal GBS colonisation, screening and IAP, analysed the rates of maternal colonisation, maternal screening and EOGBS events in the same LHD over the same period of time as Study 1. This study revealed EOGBS rates were low and relatively stable even though EOGBS was the most common bacteria affecting term babies in this population. A key finding from Study 2 was that universal screening and IAP provision appeared sub-optimal in our LHD. This led to the final study (4) that examined the ability of clinicians to adhere to local GBS guidelines. With focused analysis on a cohort of women positive for GBS, the study investigated in detail screening rates and provision of IAP. The study found current local guidelines were unable to be met and most 'missed opportunities' were unavoidable in this setting. The study concluded that urgent re-consideration of guidelines was warranted.

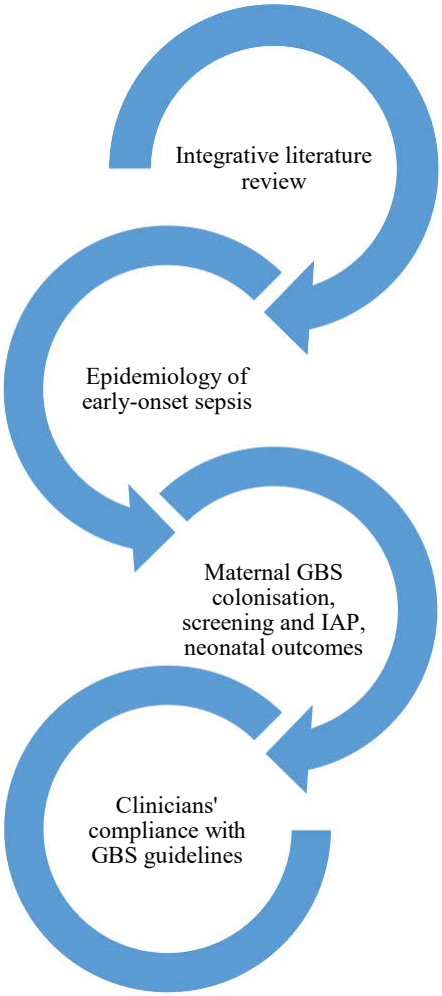


Figure 1.1 - The interrelation of the literature review and three resulting studies

Summary of Chapter 1

The rationale and scope of this project have been outlined in Chapter 1 together with background to the topic of GBS colonisation in pregnancy, descriptions of key concepts and the medical management of this common situation in maternity care. The chapter has examined some of the controversies around maternal GBS screening and provision of IAP, and claims made about the effectiveness of this intervention. Finally, the chapter has described the four major components of this work; an integrative review and three interrelated, epidemiological studies.

Chapter 1 has placed GBS management in context within Australia, and internationally. I have described how the bacteria GBS is a common, commensal bacteria, meaning it is naturally present, and does no harm in the majority of cases. I have discussed how healthy women, and their babies, have an inherent mechanism to protect themselves from serious infection. Whilst acknowledging that antibiotics have saved countless millions of lives in the last decade, I have presented the possibility that current GBS medical management using screening and IAP may be causing more harm than good, in particular the possibility of serious long-term health effects due to dysbiosis of the baby's founding microbiome.

Chapter 2

Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B streptococcal infection: An integrative review

Chapter preface

The award-winning manuscript (Caroline Homer Writing Prize 2018) incorporated into Chapter 2 was published in the peer reviewed journal *Women and Birth* in 2018. This journal was chosen because *Women and Birth* is the official journal of the Australian College of Midwives (ACM), publishes on matters that affect women and their birth experiences and has a wide national and international readership. The vexed issue of GBS and its medical management is high on the agenda of many midwives, therefore the top Australian midwifery journal was appropriate for maximum exposure. Chapter 2 presents the manuscript 'Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B streptococcal infection: An integrative review' in its original form using the *Lancet* output referencing style. The manuscript is provided in its published form (Appendix 1). References for this manuscript are also presented in the 'Thesis references' section using the university's recommended referencing style (*Harvard_UTS*).

Key words: Group B strep*; early-onset Group B strep*; *Streptococcus agalactiae*; GBS infection; GBS disease; intrapartum; labor; labour; obstetric; antibiotic prophyla*

Abstract

Background

In some countries, up to 30% of women are exposed to intrapartum antibiotic prophylaxis for the prevention of early-onset group B streptococcal infection. Intrapartum antibiotic prophylaxis aims to reduce the risk of neonatal morbidity and mortality from this infection. The intervention may adversely affect non-pathogenic bacteria which are passed to the newborn during birth and are considered important in optimising health.

Since many women are offered intrapartum antibiotic prophylaxis, effectiveness and implications of this intervention need to be established. This review considers clinical trials and observational studies analysing the effectiveness of intrapartum antibiotic prophylaxis.

Methods

An integrative literature review was conducted. One systematic review, three clinical trials and five observational studies were identified for appraisal.

Findings

Randomised controlled trials found intrapartum antibiotic prophylaxis effective but all retrieved randomised clinical trials had significant methodological flaws. High quality observational studies reported high rates of effectiveness but revealed less than optimal adherence to screening and administration of the prophylaxis. Scant consideration was given to short term risks, and long-term consequences were not addressed.

Discussion

Studies found intrapartum antibiotic prophylaxis to be effective. However, evidence was not robust and screening and prophylaxis have limitations. Emerging evidence links intrapartum antibiotic prophylaxis to adverse short and longer-term neonatal outcomes.

Conclusion

Our review found high quality evidence of the effectiveness of intrapartum antibiotic prophylaxis was limited. Lack of consideration of potential risks of the intervention was evident. Women should be enabled to make informed decisions about GBS management. More research needs to be done in this area.

Summary of relevance

Problem/issue	Early-onset group B streptococcal infection (EOGBSI) is uncommon. Although studies show intrapartum antibiotic prophylaxis (IAP) to be effective, up to a third of women in some jurisdictions are given IAP without high quality clinical evidence of its effectiveness. Although observational studies found IAP to be highly effective, these studies showed screening and administration to be sub-optimal. The consequences and longer-term health implications of prophylaxis for EOGBSI are unknown
What is already known	A correlation between a decreased incidence of EOGBSI and the widespread introduction of IAP has been reported. Maternal GBS colonisation is common but neonatal infection rare. Current screening methods to select women for IAP are imprecise and may result in false negative or false positive findings
What this paper adds	This paper considers literature regarding the effectiveness of IAP for EOGBSI. The paper reveals a gap in current knowledge. Longer-term health effects have not been factored into assessments of the benefits and risks of this intervention

Introduction

Group B streptococcus (GBS), found primarily in the gastrointestinal tract, usually causes no harm to the carrier. GBS commonly colonises the vagina in pregnant women but may be transient in nature. The bacteria can be passed to the baby in utero prior to or during birth leading to neonatal colonisation. If unexposed to prophylaxis, neonatal GBS colonisation is common during vaginal birth and in most cases, has no known adverse effects on the newborn. Rarely, neonatal colonisation leads EOGBSI. To avoid this, IAP for women with GBS carriage has been embraced in high income settings.

Background

Maternal colonisation

In the 1970s, GBS infection emerged as a leading cause of neonatal morbidity and mortality in many high-income countries. In Europe, a large study revealed maternal GBS colonisation, ranged from 6.5% to 36% in different jurisdictions with a third of the studies in this highly cited systematic review reporting rates of 20% or more. A more recent systematic review and meta-analysis has estimated the global mean prevalence of maternal GBS colonisation to be 17.9% range (11.1%-22.4%).[1]

Neonatal colonisation

Neonatal colonisation with GBS is thought to be common in babies whose mothers carry the bacteria. Some studies rate neonatal colonisation as around 50% in babies not exposed to IAP,[2] whilst more recently lower rates have been estimated.

Early-Onset Group B Streptococcal Infection

A 2012 systematic review reported the likelihood of culture-confirmed EOGBSI, as 0·43/1000 live births (CI 0·37 to 0·49) and case fatality of 12·1% (CI 6·2% to 18·3%).[3] Studies that reported use of any IAP found this was associated with a lower incidence of EOGBSI 0·23/1000 live births (CI 0·13 to 0·59) and studies in which women were not exposed to prophylaxis had a higher incidence at 0·75/1000 live births (CI 0·58 to 0·89).[3]

Diagnosis of Early-Onset Group B Streptococcal Infection

A diagnosis of EOGBSI is obtained from blood culture or less commonly, cerebrospinal fluid. The 2014 Cochrane review defines early onset infection as that which occurs "…during the first seven days of life, with the vast majority of cases (approximately 90%) presenting during the first 24 hours of life".[4 p.3] A retrospective study found 93 of 94 babies with EOGBSI were diagnosed within the first hour of life.5 Diagnosis of EOGBSI within the first 72 hours is consistent with acquisition of the infection during the intrapartum period.[5] GBS infection occurring beyond the first week of life is known as late-onset GBS infection. Late-onset infection has a different aetiology and is beyond the scope of this paper.[6]

A newborn without culture confirmed EOGBSI but with clinical symptoms may be said to have a "probable" or "possible" diagnosis but these babies are not generally included in surveillance data leading to potential underestimation of the burden of infection.[6] Variation in reported rates of EOGBSI may also be caused by sampling errors, incomplete surveillance data and IAP in the newborn circulation leading to a negative blood culture.[6] Sero-positivity from GBS antibodies which change GBS serotype prevalence and virulence may also cause variation in EOGBSI rates. Consequently, the true incidence of EOGBSI remains difficult to establish.

Screening

Maternal colonisation is a prerequisite for EOGBSI. To select women whose babies may benefit from IAP, two standard screening strategies are recommended.

Universal screening

A universal screening approach requires that all women are offered either a low vaginal/rectal or a low vaginal/perianal swab at 35-37 weeks gestation for GBS detection which is then cultured in laboratory conditions. It is recommended that women found to be colonised with GBS are offered IAP.

The Centers for Disease control and Prevention (CDC) recommends universal screening at 35-37 weeks of pregnancy with some risk-factor based exceptions. Women known to have GBS bacteriuria in the current pregnancy or who have had a previous infant with

invasive GBS are considered to be high risk and are offered IAP without the need for additional screening.[7] The CDC recommend that women with *unknown* GBS colonisation status at the time of birth be managed according to the presence of intrapartum risk factors. Women who are < 35 weeks gestation and labour prior to screening are offered IAP as they have an unknown GBS status and pre-term labour is considered a GBS risk.[7] The CDC state:

> "…women with *negative* vaginal and rectal GBS screening cultures within 5 weeks of delivery do not require intrapartum antimicrobial prophylaxis for GBS even if obstetric risk factors develop (i.e., delivery at <37 weeks' gestation, duration of membrane rupture >18 hours, or temperature >100.4ºF [>38.0ºC])" [8, p.2]

However, most clinicians agree that signs of chorioamnionitis, regardless of maternal GBS status should be treated with broad spectrum antibiotics, (which also target GBS) rather than administration of IAP for GBS prophylaxis alone.[7,9,10]

Risk-based approach

This method requires women presenting in labour with certain risk factors (release of membranes for >18 hours, maternal fever ≥ 38° in labour and prematurity) be identified and offered IAP. Women are not routinely offered a GBS screen in late pregnancy, however some women may acquire an incidental GBS diagnosis in pregnancy and are then offered intrapartum prophylaxis. Bacteriuria in the index pregnancy and a previous baby diagnosed with EOGBSI are also considered risks.[6]

Limitations of screening

Neither approach to screening for GBS will prevent all cases of EOGBSI. Antenatal methods of collection, processing and reporting, ultimately affects accuracy. A universal approach will miss most pre-term babies and screening at the recommended 35-37 weeks of pregnancy is imprecise, given the transient nature of maternal colonisation and may result in false positive and false negative results.[6] A risk-based approach requires accurate identification of risk and then timely administration of an appropriate antibiotic. This two-step process can be problematic and lead to sub-optimal administration of IAP.[11]

Protocols for optimal GBS screening have changed over time despite a lack of high quality evidence. Experts have been unable to decide which screening strategy is most effective.[12] For example, citing the same evidence for their protocols, the UK recommends a risk-factor approach [6] whereas the USA recommends universal screening. [7] Recent guidelines published by RANZCOG in Australia and New Zealand state "all maternity services should have an established plan for prevention of EOGBS, whether by a universal culture or a clinical risk-factor based approach." [9, p.3]

A large, multistate review of births in the USA where universal screening is recommended, found absence of an antenatal screen in women birthing at term accounted for 34 of the 254 cases (13.4%) of EOGBSI.[13] This finding suggests better adherence to the recommended protocol is necessary to reduce the incidence of EOGBSI. In the same study, 61% of term infants with EOGBSI were born to women who had tested *negative* for GBS before birth highlighting the imprecise nature of this screening tool and the need for vigilance in labour.[13]

Intravenous Antibiotic Prophylaxis

When first introduced in the 1980s, IAP was viewed as an interim EOGBSI reduction strategy, partly because of concerns for the potential emergence of resistance and partly because of fears by some that intrapartum antibiotic exposure may increase the risk of sepsis due to non-GBS pathogens, an issue that was not evident in a recently published epidemiological report from the USA.[14] However, the use of IAP has doubled in the last 30 years from 12% to 30% in some jurisdictions which use universal screening and IAP remains the mainstay of prophylaxis against EOGBSI in high-income settings.[14]

Women thought to be at risk of transmitting GBS to their baby may be required to change their planned place of birth late in pregnancy. The woman is then asked to attend the hospital or birth centre early in labour to have an intravenous cannula sited and antibiotic administered, ideally at least 4 hours before birth. Once the first dose has been given, most protocols require intravenous antibiotics, usually a beta lactam such as penicillin, to be administered every four hours during active labour or from release of membranes, if this comes first, until the birth of the baby. Following a diagnosis of maternal GBS carriage or other GBS risk, with or without the administration of IAP, many protocols

require women and babies to remain in hospital for neonatal observation for signs of sepsis.

The aim of IAP is to rapidly achieve adequate levels of antibiotic medication in the fetal circulation and amniotic fluid while avoiding potentially neurotoxic serum levels in the mother or fetus.[7] Using evidence from a 1989 trial[15] and expert opinion, the CDC have recommended a 3-gram dose of penicillin followed by 1.5 to 1.8 grams four hourly until birth.[7] However globally, doses vary.

None of the antibiotics recommended for women with penicillin allergy (cefazolin, clindamycin, erythromycin and vancomycin) have been evaluated in clinical trials. These medications were chosen based on available pharmacokinetic and pharmacodynamic data plus expert opinion regarding safe medications for pregnant women.[7]

Risks of IAP

The widespread use of antibiotics in the past 80 years has saved millions of lives. However, administration of intravenous antibiotics to women in labour is not without risk and the safety of this intervention has not been adequately evaluated. Risks include increases in drug resistant organisms, adverse maternal reactions ranging from mild allergic responses to life threatening anaphylaxis, and medicalisation of birth.[16] Longer-term adverse health consequences have not been assessed. Research indicates an association between maturation of a baby's immune system and perinatal transfer of maternal commensal bacteria.[17] As antibiotics do not only select pathogenic bacteria, the microbial balance of both mother and baby may be adversely affected by giving IAP. Although maternal and neonatal health are inextricably linked, this paper concentrates on the effects of IAP on neonatal health.

Effectiveness of IAP

Declines in EOGBSI in the USA coincided with increased prevention activities in the 1990s. The decline in neonatal infection since the 1990s has been attributed to widespread use of IAP. The reported incidence of culture-confirmed EOGBSI in the USA decreased from 1.8/1000 live births in the early 1990s to 0.26/1000 live births by 2010, an actual reduction of 1.54/1000 live births which equates to an 86% reduction.[7,18] Similar

reductions have been reported in the UK.[6] These data appear to support the effectiveness of IAP, however**,** association is not causation. The initial implementation of IAP was not a coordinated process and cannot be closely fixed in time. Surveillance data in many jurisdictions are reported voluntarily and therefore will not represent all cases of EOGBSI. Furthermore, surveillance data for EOGBSI is likely to be unreliable owing to differing culture utilisation standards and difficulty capturing data from pathology services across jurisdictions.

Since 2002, reported rates of EOGBSI have not substantially changed in the USA.[7] Data from the UK suggest there has been a small increase in EOGBSI cases between 2003-2010.[6] Whether changes in USA and UK data and others worldwide reflect variations in reporting of cases, natural fluctuation in infection events, a true change in EOGBSI rates or less than optimal implementation of IAP, is difficult to assess. Furthermore, reported rates of EOGBSI cases apply to live births only. Stillbirths and miscarriage where GBS may be present are not included in surveillance data.[6]

With the absence of reliable data and a dearth of studies investigating potential harm, effectiveness of this intervention and consideration of the benefits and risks, need to be further understood. We undertook an integrative literature review to study the wider evidence of the effectiveness of IAP.

Method

An integrative literature review provides a broad understanding of a research question as it allows inclusion of studies with diverse methodologies. Our integrative review aimed to provide insight for discussion of the literature surrounding the effectiveness of IAP. To achieve this, the review utilised an integrative methodology framework by Whittemore and Knafl.[19] This framework includes problem identification as outlined above, a comprehensive literature search and findings and discussion sections. The framework enables a high-quality review which may influence evidence-based practice initiatives and changes in maternity care.

Literature search

A high quality literature review should demonstrate how relevant studies have been located in the wider body of research. To achieve this, our search strategy, undertaken in 2015 incorporated electronic searches in Medline, Embase and Science Direct. This was followed by ancestry searching of relevant theoretical articles and included studies. An example of the search used in the Medline database is outlined in Table 2.1. Search terms were Group B strep*; early-onset Group B strep*; *Streptococcus agalactiae*; GBS infection; GBS disease; intrapartum; labor; labour; obstetric; antibiotic prophyla*.

Table 2.1 - Examples of search strategy (Medline Database)

Steps	**Keywords** and **MeSH** terms
(1)	Streptococcal infections.mp or Streptococcal infections/
(2)	Group b strep*.mp.
(3)	Early-onset group b strep*.mp.
(4)	Streptococcus agalactiae.mp. or Streptococcus agalactiae/
(5)	gbs infection.mp.
(6)	gbs disease.mp.
(7)	1 or 2 or 3 or 4 or 5 or 6
(8)	Intrapartum
(9)	Labor, Obstetric/or labor.mp.
(10)	Labour.mp.
(11)	Obstetrics/or obstetric.mp.
(12)	8 or 9 or 10 or 11
(13)	Antibiotic Prophylaxis/or antibiotic prophyla*.mp.
(14)	7 and 12 and 13
(15)	Limit 14 to English language
(16)	Limit to humans
(17)	Limit 16 to year = "1980–2015"

Inclusion criteria

Due to the long-term use of IAP, publications were considered from 1980 onwards. Articles focused on efficacy or effectiveness and outcomes of GBS screening and IAP. Primary research including systematic reviews, RCTs and non-randomised observational studies originating in Australasia, Western Europe and North America were considered. The search included articles that were peer reviewed and written in (or translated to)

English. Participants included pregnant women, term and pre-term neonates with and without a diagnosis of EOGBSI.

Exclusion Criteria

Exclusion criteria included papers with a non-human focus, papers published before 1980, language other than English, papers originating outside the geographic inclusion area, and non-peer reviewed studies.

The search located 333 potentially relevant articles. Figure 2.1 reveals the process of reducing the number of articles from 333 to 9 for critical appraisal.

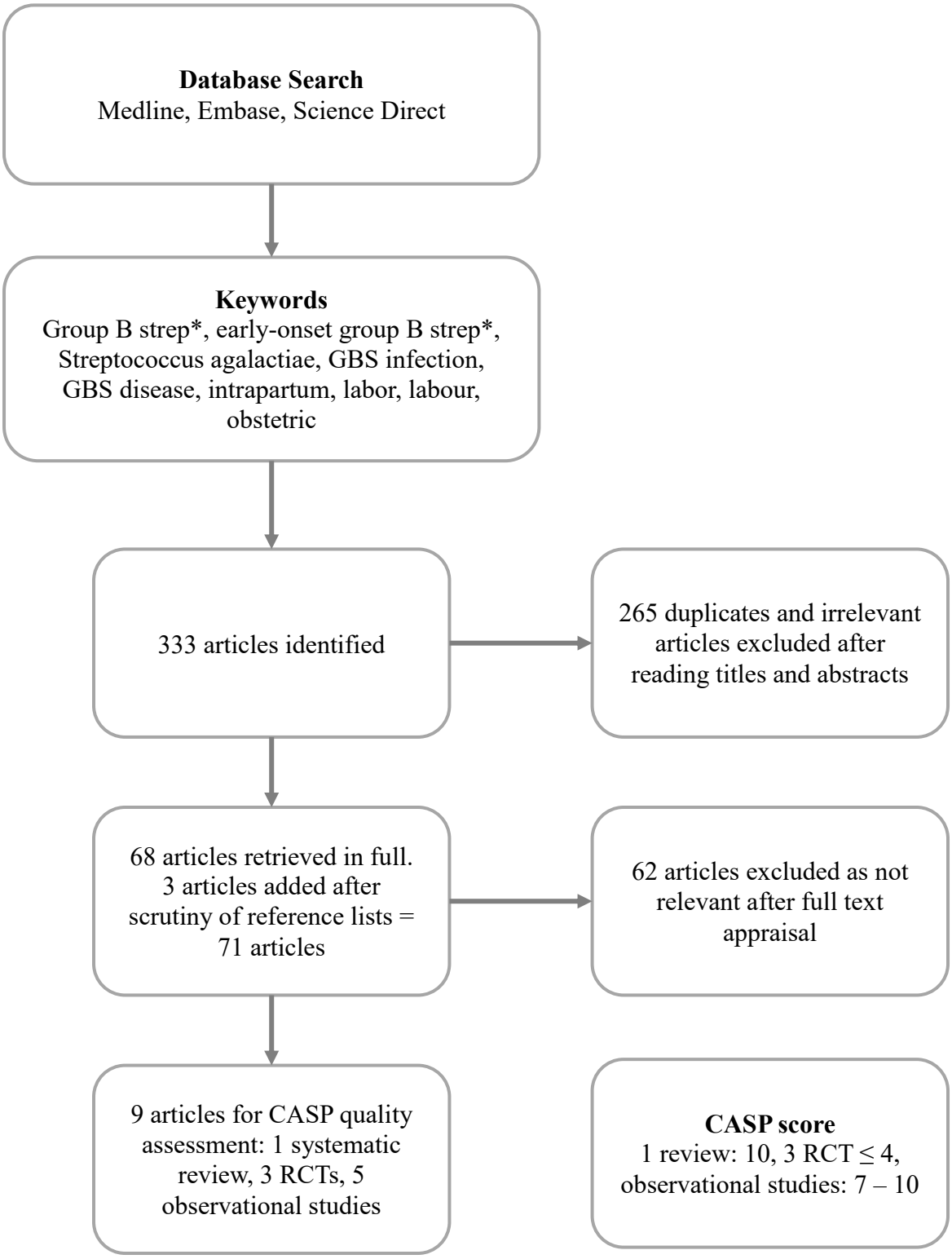


Figure 2.1 - Inclusion flowchart

Evaluation of study quality

Extraction of methodological features is recommended to assist in the evaluation of quality in included studies. This may be achieved by assigning quality scores to articles and is beneficial to reviews in which the sampling frame is narrow and studies are similar in age and design. Evaluation of studies becomes more complex when, as in our review, diverse methodologies are included.

Critical appraisal tools assist the reader to reach judgements about the quality of a study. The Critical Appraisal Skills Programme (CASP) tool was chosen to evaluate data for our review.[20] This tool allows for the assessment of methodological quality by using checklists that are intended specifically for various study designs.[20] The CASP tool approaches research by asking three main questions: Is the study valid? What are the results? Are the results useful? Articles are then further analysed and scored using a checklist relevant for the type of study evaluated. In our review, CASP scores ≥10 equated to high quality, 5-9 to medium quality and a score of ≤ 4 applied to low quality studies. Results of CASP scoring are available in Tables 2 and 3.

Analysis of the data

While 'effectiveness' in retrieved studies does not distinguish between efficacy and effectiveness, a distinction is made in this paper. Traditionally, efficacy of an intervention has been determined in clinical trials. In order to reduce bias clinical trials are highly regulated and have internal validity. Results are generalisable provided the characteristics of the population of interest is similar to the population in which the trial was done. Efficacy asks of an intervention: 'can it work under controlled conditions?' Effectiveness asks: 'does it work in the real world?'[21] Observational studies may therefore present a more realistic appreciation of effectiveness as these seek to explore the external validity of an intervention in day-to-day maternity care. We acknowledge that there is value in both study designs. In the studies retrieved in our search however, the term "effectiveness" was used in clinical trials as well as observational studies. We have therefore used the over-arching term "effectiveness" when describing both clinical trials

and observational studies. However, clinical trials and observational studies are assessed for effectiveness separately. A summary of each study-type appears in Tables 2.2 and 2.3.

Table 2.2 - Systematic review and meta-analysis plus randomised controlled trials of the effectiveness of intrapartum antibiotic prophylaxis (IAP) on early-onset group B streptococcal infection

Author/Year/Location	Olhsson et al. 2014	Boyer et al. 1986 USA	Tuppurainen et al. 1989 Finland	Matorras et al. 1991 Spain
Study design	Systematic review and meta-analysis	RCT	RCT	RCT
Question	What is the effect of IAP on maternal GBS colonisation, EOGBSI and neonatal mortality from organisms other than GBS?	Does IAP with Ampicillin prevent EOGBSI?	Does IAP for women heavily colonised with GBS prevent EOGBSI?	Does IAP reduce EOGBSI?
Participants	4 RCTs 852 women/meta-analysis 3 RCTs 488 women	164 women GBS pos., plus pre-term or pPROM > 12 h IAP = 85 control = 79	199 women heavily colonised with GBS IAP = 88 control = 111	121 women GBS pos. 69% had high risk pregnancy IAP = 57 control = 64
Term and pre-term	✓	✓	✓	✓
Method of screening	N/A	Antenatal culture and some risk factors	Latex agglutination test on admission for labour?	Antenatal culture and some risk factors
Time & dose of IAP	N/A	2 g stat and 1 g 4 hourly	3 g penicillin 6 hourly intrapartum	500 mg IV Ampicillin 6 hourly
Outcomes	Meta-analysis IAP reduced EOGBSI R.R. 0.17 (0.04–0.74)	EOGBSI 0% IAP vs 6% control (p = 0.024)	EOGBSI IAP 1.1% (CI 0%–3.4%) control 9.0% (CI 3.6%–14.4%) (P < 0.01)	EOGBSI IAP 0% vs 4.6% control (p = > 0.137) Clinically suspected EOGBSI 3.3% IAP v 13.8% control (p = 0.05)
Safety/Side effects		Urticaria one woman	Not reported	Not reported
Conclusion	Lack of evidence from robust trials to recommend IAP. High risk of bias for one or more key domains in the study methodologies and execution	In babies of high risk mothers EOGBSI was lower in the intervention group than control	EOGBSI was significantly lower in babies of mothers at high risk of GBS & exposed to IAP	IAP was not effective in reducing EOGBSI unless newborns with clinically suspected EOGBSI included
CASP Rating	10	3	4	4

EOGBSI = early onset group B Streptococcal infection, EONS = early onset neonatal sepsis, g = gram(s), hrly = hourly, IAP = intrapartum antibiotic prophylaxis, pSROM = pre-labour spontaneous release membranes, Pprom = pre-labour premature release membranes, RCT = randomised controlled trial, RR = risk ratio

Table 2.3 - Observational studies of the effectiveness of intrapartum antibiotic prophylaxis on early-onset group B streptococcal infection

Author/ Year/ Location	Lin et al. 2001 USA	Pinto et al. 2003 USA	Lin et al. 2011 USA	Berardi et al. Italy 2011	Fairlie et al. 2013 USA
Study design	Retrospective case-control study. 11 hospitals (53,702 births) 1992–1994 Cases and controls selected from infants born to women with ≥1 standard risk factor for GBS. Cases and controls matched by birth hospital and gestational age	Retrospective cohort study. Newborns from 23 institutions with confirmed EOGBSI 1996–2001.	Prospective cohort study. 3 hospitals 2008–2009 (307,148 births). Universal screening used with risk factor screen in labour. Further swab taken from women >32 weeks on admission in labour (rapid in-labour result)	Prospective population based study 2003–2010.	Secondary analysis of "Birthnet" 2003–2004 Effectiveness measured as 1-risk ratio: Risk ratio = rate of EOGBSI in babies of women receiving IAP/rate of EOGBSI in babies of women receiving no IAP)
Question	What is the effectiveness of a RFA for the prevention of EOGBSI?	What are the barriers and limitations to timely administration of IAP?	What is the accuracy of antenatal culture? What is the IAP use and rates of EOGBSI?	What factors affect IAP failure in prevention of EOGBSI?	Is standard IAP effective against EOGBSI in term and pre-term babies, with ≥4 h, <4 h of IAP and those using clindamycin
Participants	109 cases with EOGBSI and 207 controls without EOGBSI born to women with ≥1 GBS risk factors	92 babies with EOGBSI and their mothers	4696 women, 1172 were GBS pos. antenatally	79 cases of EOGBSI	7,691 births, 254 babies with EOGBSI
Term and pre-term	✓	✓	✓ ≥32w	✓	✓
Method of screening	RFA	RFA and some antenatal screening	US with some RF	US	US with some RF
IAP	≥ 2 h before birth or within 2 h of birth	24 women received IAP 9 ≥ 4 h before birth range = (4.5–31 h) and 15 ≤ 4 h before birth range = (0.1–3.8 h)	54.4% ≥ 4hrs before birth, 35.5% ≤ 2 h, 10.1% 2–3.9 h	1–10 h before birth	Active labour or after ROM
Outcomes	Overall effectiveness 86% (CI 66%–94%); ≥2 h before birth 89% (CI 70% TO 96%) ≤ 2 h of birth 71% (CI −8% to 92%). Effectiveness lowest in mothers with fever 72%(CI −9% to 93%). Highest in mothers with ROM> 18 h (90%).	68/92 mothers received no IAP. Of the 68, 34 mothers had risk factors (32 clinical and 2 GBS pos.). Of 34 with no risk factors, 22 had antenatal screening. Of 18 vaginal cultures that were neg., 15 were incorrectly taken or processed. 3 babies died, gestation not reported. No deaths occurred in babies who received≥ 4 h IAP	GBS maternal colonisation 24.5% US and 18.8% in labour IAP 83.7% (CI 77.6–88.1%) effective at preventing neonatal *colonisation*. 2 babies EOGBSI, both full term, one-woman GBS neg., one unknown	79 EOGBSI cases (0.26/ 1000). 15.2% were exposed to IAP; 85.8% were not. Most mothers of babies with EOGBSI had risk factors but GBS status not reported	IAP given ≥4 h before term birth is highly effective: IAP 91% (63%–98%) effective ≥4 h before birth; 2–4 h 47% (16% to 76%); <2 h 38% (21.7%–67%). Pre-term birth 86% (38–97%). Effectiveness of clindamycin 22% (−53 to 60%)
Safety/Side effects	Not reported	Not reported	0.2/1000 itchy throat, difficulty in breathing, swollen lips	Not reported	Not reported
Conclusion	IAP is highly effective. There was a reduced incidence of EOGBSI in babies whose mothers had risk factors and exposure to IAP. For maximum effect, 1st dose should be given at least 2 h before birth	Risk factors, including antenatal culture must be identified and acted upon. Strategies need to ensure timely administration of IAP; specimens should be obtained from correct sites using selective media within 6 weeks of birth. Nine babies with EOGBSI despite receiving a recommended IAP illustrate that infection may occur even when guidelines are correctly implemented	IAP effective in interrupting neonatal colonisation and therefore EOGBSI (0.36/ 1000). When US used correctly PPV 60.6% and NPV 89%. Need for rapid diagnostics in labour	Improved protocol adherence will reduce EOGBSI. CDC guidelines state women with suspected infection should be offered broad spectrum antibiotics	IAP given ≥4 h before birth is highly effective but reduces to under 50% if given <4 h. Effectiveness of clindamycin significantly lower than IAP with penicillin or ampicillin
CASP rating	10	10	10	7	10

IAP = intrapartum antibiotic prophylaxis, EOGBSI = early onset group B Streptococcal infection, NPV = negative predictive value, PPV = positive predictive value, RFA = risk factor approach, US = universal screening at 35–37 weeks

Findings

The 9 studies included in our integrative review consist of one systematic review and meta-analysis,4 three randomised controlled trials (RCTs) 2,15,22 located in Table 2.2 and five observational studies located in Table 2.3.[11,23-26] These tables provide a summary and CASP score for each study.

In the following section, we present our integrative review starting with an analysis of three RCTs. These RCTs are included in a 2014 Cochrane Systematic review and meta-analysis investigating IAP for known maternal GBS colonisation. Finally, we analyse the findings of five observational studies.

Effectiveness in a controlled context: Randomised Controlled Trials

Due to the widespread use of IAP since the 1980s and therefore lack of equipoise to conduct further clinical trials, we identified only three RCTs published between 1986-1991 (Table 2.2). The three clinical trials compared IAP with a placebo. The trials reported that IAP was an effective prophylaxis against EOGBSI. A fourth trial, which was considered by the Cochrane review did not meet our inclusion criteria as it compared the effect of two IAP medications, rather than using a placebo as a control.

When the three RCTs[2,15,22] were combined in the Cochrane meta-analysis, there was a statistically significant reduction in the risk of EOGBSI with a risk ratio of 0.17 (CI 0.04 to 0.74) demonstrating effectiveness of IAP in a controlled, clinical environment.[4] However, we assigned CASP scores of ≤4 for each of these studies since significant methodological flaws affected the internal validity of all studies, which undermined their rigour and therefore, confidence in their results.

Our assessment was aligned with the Cochrane review.[4] The Cochrane authors, Ohlsson and Shah, considered the quality of the three RCTs to be so low that even though a statistically significant reduction in EOGBSI was found in meta-analysis, the result could not provide robust evidence of the effectiveness of IAP.[4]

Biases in the three studies included inadequate reporting of sample size,[15] inappropriate allocation of randomisation[2,15,22] and selective reporting.[2,15] None of the RCTs complied with the Consolidated Standards of reporting Trials (CONSORT) as these guidelines were

not introduced until 1996.[27] Biases and limitations of the RCTs are discussed further in the following sections.

Selective reporting bias

Selective reporting bias can be defined as the selective revealing or suppression of information. Selective reporting bias was evident in two studies.[2,22] For example, the approach by Boyer and Gotoff (1986)[2] has been criticised by Ohlsson and Shah[4] as indicating a high degree of selective reporting bias and provision of incomplete outcome data. Boyer and Gotoff reported on results after different numbers of women had been enrolled in their study which was conducted over a five-year period, between 1979 and 1984. In their 1985 paper, these authors reported on outcomes for 79 women and in 1986, reporting on the same study, there were 160 women. Ohlsson and Shah[7] described these authors as waiting for an additional neonatal outcome in the control group to establish statistical significance before publishing in 1986.[4] Further, intention to treat did not guide their analysis as maternal and neonatal outcomes were not reported in 11% of women randomised. Curiously, women who developed a fever, and their babies, were excluded from analysis.

The RCT by Matorras et al.[22] took a novel approach to the definition of EOGBSI and included babies with possible EOGBSI based on symptoms as well as culture confirmed infection. These authors initially concluded that IAP was effective in reducing rates of neonatal GBS colonisation but this reduction did not translate into a significant decrease in culture-proven EOGBSI. Data were then re-analysed and included clinically infected newborns, defined as babies born to mothers with culture confirmed GBS, showing symptoms of EOGBSI, but without diagnosis confirmed by culture. The authors thought it appropriate to include babies with clinical symptoms, referred to as 'possible' or 'probable' EOGBSI, since they considered microbiological confirmation of EOGBSI in neonates was problematic in the 1990s.[22] It appears that, following a non-significant finding of the effectiveness of IAP on culture-proven cases of EOGBSI, the authors went on to include the group of babies with clinically suspected infection and found IAP had a significant impact on the reduction of clinically diagnosed EOGBSI. The inclusion of possible EOGBSI leaves the study open to bias as clinical judgement is subjective by nature. Therefore, the possible lack of objectivity in this trial may have undermined its

validity. Whether the inclusion of clinically infected babies was appropriate or not is debatable.

Measurement bias in un-blinded studies

Lack of objectivity is evidenced by the absence of double blinding in a clinical trial. The absence of double blinding was a criticism of all three studies.[2,15,22] Participating women and clinicians were aware of the mother's GBS status and receipt or not of IAP. Objectivity when assessing newborns for disease in a clinical trial cannot be achieved if women and clinicians are aware of group allocation. While the inclusion by Matorras and colleagues of clinically infected neonates reflects the difficulties of assessing the true incidence of EOGBSI, the lack of blinding in this trial may have exposed the study to assessment bias as diagnosing clinicians were aware of the mother's GBS status.[4]

Variation in screening techniques and timing

Presence of maternal GBS was ascertained by vaginal/rectal swab in only two of the included studies in our review.[2,22] Sub-optimal methods of collection and processing will decrease the accuracy of screening and these steps were poorly reported. Cultures were performed at various gestations, thus further limiting accuracy due to the transient nature of maternal GBS colonisation.[2,15,22]

Other risk factors for group B streptococcus

The RCTs[2,15,22] included women with mixed or unknown risk status but this was also poorly reported by the trial authors. It was not clear whether women with other risk factors, such as GBS colonisation plus pSROM or premature labour, were evenly distributed between intervention and control groups. Randomisation was not stratified by other risk factors in any of the studies.

Observational studies: an overview

Our integrative review also retrieved five observational studies published between 2001 and 2013 (Table 2.3). The studies assessed the practical effectiveness of screening and IAP in a variety of maternity settings. We found the methodologies of the studies to be sound. Unlike the RCTs which scored poorly in CASP assessment, the quality of

observational studies was assessed as medium (1 study) to high (4 studies). To capture meaningful data, all observational studies examined large cohorts of women and babies over significant periods of time and extending over wide geographical areas. This was important since EOGBSI is a difficult condition to study as the infection occurs rarely. Two of the five studies used matched controls to minimise bias inherent in observational studies.[23,25]

Centers for Disease Control and Prevention

To understand the different approaches to screening and IAP protocols undertaken by the observational studies retrieved, it is important to understand the timing and content of three iterations from the Centers for disease prevention and control (CDC) [7,8,28] recommending guidelines for screening and management for GBS risk.

Over the last two decades, the CDC has studied GBS risk. In 1996, they announced a two-armed protocol recommending clinicians choose either a universal screening or a risk-factor approach when selecting women for IAP.[28] Despite a dramatic fall in reported EOGBSI rates, "protocol failures" or "missed opportunities" were still occurring and a new guideline was published in 2002 aiming to address this issue.[8] The 2002 iteration recommended universal culture-based screening at 35–37 weeks gestation to optimise identification of women who should receive IAP. The CDC concluded universal screening with some risk factor exceptions (women with GBS bacteriuria at any time during their current pregnancy or women who had given birth previously to an infant with EOGBSI) was a more effective method than a risk-factor approach alone for reduction of EOGBSI. The rates of EOGBSI continued to fall. In 2010 the CDC published their most recent iteration.[7] This guideline continues to endorse universal screening and IAP.

Observational studies

Observational studies retrieved in our review commented on the acknowledged effectiveness of IAP prior to commencing their studies. Three studies identified a positive association between IAP and reductions in EOGBSI,[11,23,25] finding IAP with beta lactams (penicillin or ampicillin) highly effective. The studies agreed that timing of screening and IAP administration was important when assessing effectiveness but authors could not agree on optimum timing of the intervention.

A retrospective study (Lin et. al. 2001) with matched controls involving newborns of mothers with one or more risk factors for GBS found administration of IAP was 86% (CI 66% to 94%) effective if given two hours or more before birth.[25] The study period occurred prior to the 2002 CDC guidelines so an RFA was used for screening. A later study, again using matched controls but undertaken after the 2002 CDC iteration, found IAP to be 91% (CI 22% to 95%) effective if given at least four hours before birth.[23] In this study, the authors found effectiveness dropped to 47% (CI 16% to 76%) if IAP was given less than four hours before birth. Of note, the effectiveness of clindamycin as an alternative to penicillin for women with penicillin allergy was significantly lower in this study at 22% (CI 53% to 60%).

Effectiveness of IAP was found to be undermined by difficulties in screening and timely identification of women with GBS risk. Reasons for "missed opportunities" for the administration of IAP were described in retrieved studies as multifactorial. A study published in 2003 considered barriers and limitations to timely administration of IAP.[26] The authors concluded that errors including poor specimen collection and processing plus misinterpretation of protocols were limitations to timely administration and therefore effectiveness of IAP.

Less than optimal positive and negative predictive values of the universal screening approach was assessed as a reason for missed opportunities in the administration of IAP.[11] Lin and colleagues (2011) identified women as GBS positive or negative by culture based screening and found IAP to be 83.7% (CI 77.6% to 88.1%) effective.[11] However their results showed ~10% of women with negative GBS carriage were positive during labour and missed IAP while ~50% of women with positive antenatal GBS carriage were negative during labour yet received IAP.

A study undertaken in the same year found that of 79 cases of culture proven EOGBSI, 85.8% were born to women who received no IAP. A combination of universal screening and risk factors was used to select women for IAP and it was noted that clinicians commonly missed risk factors, but where women received the correct IAP medication, the correct dose of medication and timely administration, incidences of EOGBSI were unlikely.[24] These studies illustrate that some women received IAP unnecessarily and cases

of EOGBSI occurred in babies of women who had a risk factor for GBS but received no IAP.

Although authors stated that when IAP was administered correctly, EOGBSI was unlikely, babies continued to be diagnosed with EOGBSI even when their mothers were negative to GBS. This was illustrated in the study by Pinto and colleagues (2003). Of the 92 newborns in this study with EOGBSI, 18 were born to women who were GBS negative on antenatal culture. The authors noted 15 cultures were obtained using sub- optimal techniques or were collected more than six weeks before birth.[26]

As well as a false negative maternal GBS status, other possible explanations of EOGBSI in spite of adequate IAP include idiosyncrasies in drug distribution or pharmokenetics, unusually large quantities of circulating bacteria, micro-environmental characteristics at colonised sites that interfere with antimicrobial activity or the presence of fetal systemic infection before the receipt of IAP.[26]

Discussion

Three RCTs providing level-1 evidence, retrieved for our integrative review found IAP to be effective in the reduction of EOGBSI in a controlled, clinical environment. The 2014 Cochrane systematic review found, when the three RCTs, involving 488 newborns were combined in a meta-analysis, the incidence of EOGBSI was reduced when using IAP compared to no treatment, with a risk ratio of 0.17 (CI 0.04 to 0.74).[7]

RCTs are considered the gold standard in evaluating healthcare interventions but they can yield biased results if lacking methodological rigor. The three RCTs included in this integrative review, and also in the Cochrane systematic review were found to have a high risk of performance and selection bias.[2,15,22] The three small studies, which are all over 20 years old, had serious flaws and should not be relied upon as robust evidence for IAP effectiveness.

Not all researchers however have reached this conclusion. A 2013 narrative review by Schrag and Verani was at odds with our review and with the 2014 Cochrane findings.[18] Reporting on the experience of IAP in the USA, Schrag and Verani claimed that the trials conducted by Boyer and Gotoff [2] and Tuppurainen and Hallman [15]demonstrated that IAP

was highly effective, with no mention of the studies' flawed methodologies.[18] The selective reporting bias in the Boyer and Gotoff [2] trial was not cited as a methodological problem, instead the review stated "…one trial with ampicillin was stopped early due to overwhelming efficacy."[18] Clearly authors have reached different conclusions, when considering both screening methods[12] and the validity of RCTs, despite basing their decisions on interpretation of the same data. The influential trial by Boyer and Gotoff (1986) has had significant impact on policy and guidelines for GBS risk and is widely cited, adding to the view that IAP is highly effective and that the intervention has been the single reason for reduction of EOGBSI. The trial by Tuppurainen and Hallman (1989)[15] informed the 3 gram dosage of penicillin recommended by the CDC since 1996 and remains the only clinical trial to support this recommendation. Our integrative review found both these trials have serious methodological flaws.

Observational studies, which provide level-2 evidence[7] found IAP to be effective against EOGBSI in everyday maternity care with maximum effect achieved when protocols for both screening and administration of IAP were correctly followed. The observational evidence described here[11,23-26] concludes that for IAP to reduce rates of EOGBSI most effectively, women at risk of transmitting GBS to her newborn must be accurately identified and IAP administered in a timely manner. Studies revealed that despite the CDC guidelines[7,8,28] aiming to reduce protocol failures, difficulties persisted in correct implementation of protocols and guidelines regardless of which screening strategy was recommended.

It seems remarkable that IAP has been so effective as observational studies agreed that, protocol failure and in particular, timing of IAP was important to effectiveness. The four-hour time frame between administration of IAP and birth is endorsed by the Centers for Disease Control and Prevention (2010)[7] as well as many IAP protocols worldwide including Australia. However the four hour time frame, although still debated, was often reported as not achieved.[23] Furthermore, around one fifth of women admitted for birth in advanced labour would be GBS positive and may birth before the recommended four hours between administration of IAP and birth. Effectiveness of IAP in this setting may be limited.

Positive and negative predictive values of universal screening were shown to be sub-optimal, illustrated by the birth of babies with EOGBSI whose mothers had a negative GBS screen.[11,26] These findings are consistent with other published reports. [6,7,11,26] No studies considered the longer-term effects of IAP.

A longer-term health effect of considerable concern is the impact of IAP on the baby's microbiome. The human microbiome encompasses an ecosystem of approximately 90 trillion microbes that impact on host physiology and are known to protect the host from pathogens. During vaginal birth, and maybe even in utero, the baby begins the process of seeding a founding microbiome.[29] It appears that this founding group of commensal microbes together with exclusive breastfeeding is important in optimising newborn immune and epigenetic health. Both in adults and children, microbial diversity can be disrupted by the administration of antibiotics causing dysbiosis of the host microbiome. Dysbiosis of the neonatal microbiome may occur indirectly by the administration of IAP to the mother in labour.[30] New technologies have enabled studies linking a reduction in the diversity of the human microbiota to diseases such as obesity, inflammatory bowel disease, autoimmune disease and, more recently, neurological disease.[31] Interactions between a newborn and her/his microbiome appear crucial for normal development, but how host–microbe symbiosis is established and maintained remains under explored. We noted a lack of consideration given to effects of antibiotics on the longer-term health of the newborn in all retrieved studies.

It would seem likely that we are unnecessarily exposing mothers and babies to an intervention whose longer-term adverse effects may outweigh short-term effectiveness. One Australian study has calculated that 1191 women must to be exposed to IAP and 5704 screened to prevent one case of EOGBSI.[32]

If enough women and babies are exposed to antibiotics that are highly effective at reducing GBS bacteria, it is likely that the reported incidence of culture proven EOGBSI, will reduce. It is unlikely that this simple equation reveals the whole story. If inherent limitations and reduced protocol compliance as discussed here is widely reflected across maternity settings, we consider the global claim that the reduction in EOGBSI is solely due to IAP is questionable.

Furthermore, as well as lack of discussion around the potential longer-term effects of IAP, studies retrieved for our review have not considered the idea that rates of EOGBSI may have been reducing for reasons other than widespread IAP. As well as the difficulty of assessing true rates of EOGBSI in the community, changes in population (herd) immunity, diverse changes in living circumstances and processes of care or unexplained waxing and waning of bacterial serotypes may have caused variations in rates that were not considered in any of the studies.[33]

Researchers have explored alternative methods aimed at reducing the risk of EOGBSI. Chlorhexidine (CHX) douche is a non-systemic approach for the management of IAP. A 2014 Cochrane review analysed three RCTs and concluded the quality of evidence for the effectiveness of chlorhexidine was low and risk of bias high.[34]. In the absence of adequately powered RCTs, the Cochrane review does not support the use of chlorhexidine for preventing EOGBSI. These findings contrast with a systematic review by Goldenberg et al. (2006). These researchers reviewed studies published in English between 1950 and 2005 in which chlorhexidine was used as a vaginal treatment. The authors ultimately focused on two observational studies which concluded that although this intervention does not appear to be effective against EOGBSI in high resource countries, it may be useful in low resource settings.[35]

Since evidence for alternative prophylaxis is poor, we consider that there is currently a place for IAP in the management of GBS risk. However, as antibiotic prophylaxis also has significant limitations and was never intended to be a long-term solution for the reduction of EOGBSI, new methods for management of GBS risk are being explored.

To date alternatives remain theoretical. They include serological screening, vaccination and rapid point of care testing. A serological screening option for women to assess whether a protective antibody against specific GBS serotypes is present may be a solution since serotype specific antibodies are associated with protection from EOGBSI in term neonates.[36] Another alternative is vaccination which, in the future, may be a choice for some women. Research into GBS vaccine is ongoing [37] and a recent phase 1b/2 RCT completed in 2016 concluded a vaccine was well tolerated in pregnant women and led to higher GBS serotype-specific antibody concentrations in babies than a placebo, with both interventions resulting in similar safety profiles.[38] Recently, screening for GBS using a

point of care test has been put forward as an option enabling clinicians to obtain rapid intrapartum maternal GBS colonisation results. Whilst this method sounds appealing and was proposed as a strategy at a recent consensus conference on GBS screening and IAP, the technology is expensive and logistics, provision and maintenance are problematic.[39]

There will always be women who choose to decline screening and IAP. Clinicians need to be well-informed about the effectiveness of current screening methods and management of GBS risk in order to provide women with sufficient information to make an informed choice. Working within existing guidelines means that many women and babies will be over managed with IAP and some cases of EOGBSI will be missed. Future research will need to explore whether the widespread use of IAP is as detrimental to the baby's microbiome as current literature suggests.[40]

Conclusion

An integrative review framework enables a high-quality review which may influence changes and initiatives in maternity care. Information necessary to inform health care decisions is often incomplete or unavailable. As a result, some interventions used in maternity care, including IAP are delivered without clear evidence of their effectiveness.

The study of EOGBSI is complex. The true rates of EOGBSI are difficult to assess across jurisdictions. Maternal GBS colonisation is relatively common. The bacteria is usually asymptomatic, harmless and transient. Neonatal infection caused by maternal GBS carriage, is very uncommon. Therefore, many women and babies are exposed to IAP for an infection that is rare. Little is known about why GBS carriage is relatively common in pregnancy. This common bacteria, may even have unknown benefit to the woman and her child. Rarely, and often for reasons as yet unclear, a baby succumbs to EOGBSI, a serious and sometimes fatal condition. Historically, mortality from EOGBSI was high, up to 50%.[41] It made sense then to use an easily available, narrow spectrum antibiotic to prevent transmission from mother to baby of this potentially pathogenic bacteria. Since the 1980s mortality from EOGBSI has reduced substantially and today mortality is estimated to be around 10% of all babies with the infection and EOGBSI is treatable.[10]

If enough women are given IAP it is likely that the reported incidence of reported EOGBSI will reduce, but at what cost to women and babies? The longer-term health

effects of exposing many thousands of women and babies to large doses of intravenous antibiotics have not been explored. We consider that the inherent limitations of current CDC recommendations of universal screening and IAP, the inability to calculate the true rate of EOGBSI, together with a lack of evidence of the longer-term health effects of IAP, raises questions about the widespread use of this intervention.

Although retrieved studies agreed on the short-term effectiveness of IAP, it was clear from our integrative review that both standard methods of screening for IAP were imprecise and captured many women that, although presenting with an antenatal diagnosis of GBS colonisation or other risk factors, would not have a baby with EOGBSI. As there is no practical method to determine which mothers are at the greatest risk, many women and babies are exposed to IAP unnecessarily.

Notwithstanding the methodological limitations of studies discussed, are we able to translate findings into maternity practice today? The three RCTs, although undertaken in high-income countries, are more than 20 years old (1986-1991).[2,15,22] Generalising findings into contemporary practice from decades-old care environments to modern day maternity and neonatal care is potentially problematic and may not lead to valid conclusions. Rather, high-quality studies are required to reliably guide current practice. Due to the widespread use of IAP, at least in high income settings, the opportunity for further clinical trials is likely lost.

Currently, there remains a place in maternity care for IAP for the management of EOGBSI risk but clinicians and policy makers must consider the cost to the majority of mothers and babies who receive no benefit and possibly incur harm. In light of this, we must question the use of widespread screening and IAP and be equipped to discuss and document a realistic assessment of the evidence in our policies, guidelines and discussions with women. We do not have a simple means of quantifying and communicating relative risk to women. However, women and their families should be given access to current knowledge so that they can decide what risk they are prepared to embrace. Investigation into potentially harmful longer-term effects of intrapartum antibiotics needs to be commenced and further investigation of alternatives is warranted.

References

1. Kwatra G, Cunnington M, Merrall E, et al. Prevalence of maternal colonisation with group B streptococcus: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; **16**: 1076-84.
2. Boyer K, Gotoff S. Prevention of group B streptococcal disease with selective chemoprophylaxis. *The New England Journal of Medicine* 1986; **314**(26): 1665- 9.
3. Edmond K, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet* 2012; **379**(9815): 547-56.
4. Ohlsson A, Shah V. Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review). *Cochrane Database Syst Rev* 2014; **6**: CD007467.
5. Tudela CM, Stewart RD, Roberts SW, et al. Intrapartum evidence of early-onset group B streptococcus. *Journal of Obstetrics and Gynecology* 2012; **119**(3): 626-9.
6. UK National Screening Committee. Screening for Group B streptococcal infection in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2012.
7. Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines *Mortality and Morbidity weekly report (MMWR) Recommendations and reports* 2010; **59**(1): 1-36.
8. Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines. *Mortality and Morbidity weekly report (MMWR) Recommendations and reports* 2002; **51**(1): 1-36.
9. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Maternal Group B Streptococcus in pregnancy: screening and management .C-Obs 19. 2016.
10. Royal College of Obstetricians and Gynaecologists (RCOG). The Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. 2nd ed. London: Royal College of Obstetricians and Gynaecologists; 2012.

11. Lin F, Weisman L, Azimi P, et al. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. *Pediatr Infect Dis J* 2011; **30**(9): 759-63.
12. Kurz E, Davis D. Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review. *Joanna Briggs Institute Database System of Reviews and Implementation Reports* 2015; **13**(3): 206-46.
13. Van Dyke M, Phares C, Lynfield R, Thomas A, Arnold K, Craig A. Evaluation of universal antenatal screening for group B streptococcus. *N Engl J Med* 2009; **360**: 2626-36.
14. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. *Pediatrics* 2016; **138**(6).
15. Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients. *Obstet Gynecol* 1989; **73**(4): 583-7.
16. Royal College of Obstetricians and Gynaecologists. Prevention of early-onset neonatal group B streptococcal disease. Green-top guideline No. 36. 2017.
17. Azad M, Konya T, Maughan H, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at four months. *Can Med Assoc J* 2013; **185**: 385-94.
18. Schrag SJ, Verani JR. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine. *Vaccine* 2013; **31**: 20-6.
19. Whittemore R, Knafl K. The integrative review: updated methodology. *J Adv Nurs* 2005; **52**(5): 546-53.
20. Critical Appraisal Skills Programme. CASP Checklist. 2014. http://www.casp- uk.net/index.htm (accessed 9 June 2015.
21. Glasgow R, Lichtenstein E, Marcus A. Why Don't We See More Translation of Health Promotion Research to Practice? Rethinking the Efficacy-to-Effectiveness Transition. *Am J Public Health* 2003; **93**(8).

22. Matorras R, Garcia-Perea A, Omenaca F, Diez-Enciso M, Madero R, Usandizaya J. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1991; **40**(1): 57-62.
23. Fairlie T, Zell ER, Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. *Obstet Gynecol* 2013; **121**(3): 570-7.
24. Berardi A, Lugli L, Rossi C, et al. Intrapartum antibiotic prophylaxis failure and group-B streptococcus early-onset disease. *J Matern Fetal Neonatal Med* 2011; **24**(10): 1221-4.
25. Lin FY, Brenner RA, Johnson YR, et al. The effectiveness of risk-based intrapartum chemoprophylaxis for the prevention of early-onset neonatal group B streptococcal disease. *Am J Obstet Gynecol* 2001; **184**(6): 1204-10.
26. Pinto NM, Soskolne EI, Pearlman MD, Faix R. Neonatal Early-onset Group B Streptococcal Disease in the Era of Intrapartum Chemoprophylaxis: Residual Problems. *J Perinatol* 2003; **23**: 265-71.
27. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *J Am Med Assoc* 1996; **276**(8): 637-9.
28. Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. *Mortality and Morbidity weekly report (MMWR) Recommendations and reports* 1996; **45**(RR-7): 1-24.
29. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. *Sci Transl Med* 2014; **6**(237).
30. Azad MB, Konya T, Persaud RR, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *Br J Obstet Gynaecol* 2015; **123**: 983- 93.
31. Chu D, Antony K, Ma J, et al. The early infant gut microbiome varies in association with a maternal high-fat diet. *Genome Med* 2016; **8**(1): 77.

32. Angstetra D, Ferguson J, Giles W. Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. *Aust N Z J Obstet Gynaecol* 2007; **47**: 378-82.
33. Flores AR, Galloway-Peña J, Sahasrabhojane P, et al. Sequence type 1 group B Streptococcus, an emerging cause of invasive disease in adults, evolves by small genetic changes. *Proc Natl Acad Sci U S A* 2015; **112**(20): 6431-6.
34. Ohlsson A, Shah V, Stade B. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. *Cochrane Database Syst Rev* 2014; **12**: CD003520.
35. Goldenberg RL, McClure EM, Saleem S, Rouse D, Vermund S. Use of vaginally administered chlorhexidine during labor to improve pregnancy outcomes. *Obstet Gynecol* 2006; **107**(5): 1139-46.
36. Dangor Z, Kwatra G, Izu A, et al. Correlates of protection of serotype-specific capsular antibody and invasive Group B Streptococcus disease in South African infants. *Vaccine* 2015; **33**(48): 6793-9.
37. Madhi SA, Dangor Z, Heath PT, et al. Considerations for a phase-III trial to evaluate a group B Streptococcus polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young infants. *Vaccine* 2013; **31 Suppl 4**: D52-7.
38. Madhi SA, Cutland CL, Jose L, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. *Lancet Infect Dis* 2016; **16**: 923-34.
39. Di Renzo G, Melin P, Berardi A, et al. Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference. *Journal of Maternal-Fetal and Neonatal Medicine* 2014: 1-17.
40. Seedat F, Stinton C, Patterson J, et al. Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: a systematic review. *BMC Pregnancy Childbirth* 2017; **17**(1): 247.
41. Schuchat A. Group B streptococcus. *The Lancet* 2001; **353**(9146): 51-6.

Chapter 3

Epidemiology of neonatal early-onset sepsis in a geographically diverse Australian health district 2006-2016

Chapter preface

This manuscript was published in *PLoS ONE* in 2019. *PLoS ONE* was chosen because of the journal's broad scope and interdisciplinary focus. As my research crosses the professional boundaries of maternity and neonatal care, *PLoS ONE* offered an ideal platform for discussion and debate between different specialties. Pathogens causing neonatal infections and their antibiotic susceptibility patterns may change over time and differ between countries. It is therefore important to maintain contemporary epidemiological knowledge of rates and trends of EOS to inform policy and clinical practice. Chapter 3 presents the manuscript 'Epidemiology of neonatal early-onset sepsis in a geographically diverse Australian health district 2006-2016' in its original form using the *Vancouver* output referencing style. The manuscript is provided in its published form (Appendix 2). References for this manuscript are also presented in the 'Thesis references' section using the university's recommended referencing style *(Harvard_UTS).* Results of this study informed the background to the next study presented in Chapter 4.

Abstract

Aim

To describe the epidemiology of EOS including blood culture utilisation, across a large and geographically diverse Australian health district.

Background

Sepsis in the first three days of life remains a leading cause of death and morbidity. In high-income countries, group B Streptococcus (GBS) and Escherichia coli *(E. coli)* have dominated as causes of EOS for five decades.

Method

An 11-year retrospective cohort study to determine the epidemiology of EOS. Incidence rates were calculated per 1000 live births. Logistic regression with linear temporal trend and covariates for potential effect modifiers were employed. Blood culture utilisation was determined by examining the rate of babies undergoing blood culture within 72 hours of birth.

Results

Among 93,584 live born babies, 65 had confirmed EOS (0.69/1000 live births); 22 term, 43 preterm. Across the 4 largest birth units, the proportion of babies having blood culture within 72 hours of birth varied from 1.9-5.1% for term and 21-35% for preterm babies. The annual change in the EOS rate was significant, (p=0.03, OR= 0.91, 95% CI, 0.84 - 0.99%). Group B Streptococcus was the most common cause of EOS in term neonates at 0.35/1000 live births (95% CI, 0.07-0.63%) in 2006 and 0.1/1000 live births (95% CI, 0-0.2%) in 2016. Escherichia coli was the most common cause in preterm babies at 3.4/1000 (95% CI, 0.11-6.76%) in 2006 reducing significantly to 1.35/1000 live births (95% CI, -0.07-2.78%) by 2016.

Conclusion

Escherichia coli and GBS were the most common causes of EOS in preterm and term babies respectively. Rates of all cause term and preterm EOS declined significantly as did preterm sepsis due to *E.coli*. While rate of sepsis due to early-onset GBS declined, this did not reach significance. Given the high proportion of preterm babies undergoing blood culture, it is unlikely that any EOS events were missed.

Introduction and Background

Neonatal EOS refers to culture-proven bloodstream and/or central nervous system infection occurring in live born neonates soon after birth. It remains a significant cause of infant morbidity and mortality in both high and low-income countries [1]. Most events occur in the first 48 hours of life [2]. Based on varying definitions, recent reported estimated incidences of culture proven EOS range from 0.01 to 0.53/1000 live births in Europe [3], 0.77/1000 in the USA [4, 5] to 0.83/1000 in Australia [6]. Recorded mortality

has been as high as 30% in high-income and 60% in low-income countries[3] but has reduced in high-income jurisdictions in recent years to around 10% of all babies with EOS [3, 7]. Preterm babies continue to suffer a much higher mortality than term infants [8]. Neonatal EOS is almost always due to pathogenic microorganisms acquired from the mother, either during or preceding birth [2,5]. Infection may be trans-placental (haematogenous) but is more commonly thought to occur by an ascending route from the mother's genitourinary tract [9].

Risk factors for early-onset sepsis

Perinatal maternal risk factors reported to be associated with EOS include recto-vaginal GBS colonisation, rupture of membranes (ROM) ≥18 hours, prematurity, and intrapartum fever [3]. Recently authors have questioned the value of including fever as a surrogate for chorioamnionitis [10]. However currently, maternal fever (≥38°) remains a risk factor for EOS in most jurisdictions [8, 11-13]. Other risk factors include bacteriuria in the index pregnancy and having a previous child diagnosed with early- onset group B streptococcal infection (EOGBS) [11].

Pathogens

Early-onset sepsis due to *E. coli* is associated with high rates of mortality and morbidity, especially in preterm newborns [5]. The rate of multiple resistant *E. coli* has been described as stable overall but increasing in very low birth weight neonates (<1.500g) [14]. In term babies, population-based neonatal infection surveillance studies demonstrate that GBS remains the pathogen most frequently associated with term EOS [6, 15-17].

Early-onset group B streptococcal sepsis

Whilst there is a decline in early-onset GBS (EOGBS) sepsis whenever any maternal intrapartum antibiotic prophylactic (IAP) is provided [18] and others have noted evidence for IAP to be strong [6, 19], the most recent Cochrane review on the effectiveness of IAP concludes that whilst IAP appeared to reduce EOGBS, this may be due to bias. The Cochrane reviewers found a high risk of bias for one or more key domains in the methodology and execution of the studies included in their analysis [20]. Therefore, Cochrane states there is a lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBS. More recently we undertook a broader,

integrative review and concluded the evidence that the incidence of EOGBS can be reduced by widespread administration of maternal IAP is not robust [20].

Aim

To describe the epidemiology of EOS including blood culture utilisation, across a large and geographically diverse Australian health district.

Materials and Methods

A retrospective cohort study design was employed using data from a cohort of live born babies and their mothers birthing in the Hunter New England local health district (HNELHD) in New South Wales (NSW), Australia over the period 2006-2016.

Study setting and population

New South Wales is the largest and most populous state in Australia covering a region of 131,785 square kilometres, equivalent to the size of England. In 2008 the state was divided into 15 local health districts (LHDs). The HNELHD is geographically and socially diverse. As of 2016, the health district had 873,741 residents. Aboriginal and Torres Strait Islander people account for 4.0% (equating to 21% of NSW's Indigenous population) and 19% of residents were born overseas [21]. The health district spans 25 local government areas and is the only regional health district in NSW with a metropolitan hospital and level three neonatal intensive care unit (NICU), an along-side birth centre and a freestanding birth centre nearby. In total, these centres support around 4000 births per year. The district also includes a mix of several large regional hospitals providing care for 500 to 1,500 births per year through to 11 rural units servicing a small percentage of people located in more remote settings supporting <250 births per year.

Our study population included women from the original Hunter area birthing in 2006 to 2007. From 2008 onwards when HNELHD was formed, the cohort of women increased to include the 16 units mentioned above. The study population included women and babies of all risk categories, birthing within all publicly funded maternity services in the HNELHD including hospital, birth centre and planned births at home. From 2006 onwards women in the Hunter area/HNELHD were offered universal screening for GBS risk.

In this paper the term ‘pregnancies’ better describes the total cohort of women as one woman could have been pregnant more than once during the study period, however, the term ‘women’ represents all women and each of her pregnancies resulting in a live birth(s) from 2006 to 2016.

Blood Culture utilisation

To evaluate EOS surveillance intensity, data from 2013 to 2016 were analysed to determine the proportion of babies from whom at least one blood culture was collected during the first 72 hours of life stratified by gestation (term or preterm).

Demographics

Criteria comprised live born infants and their mothers, born in the Hunter area 2006 to 2007 and expanded to include the newly formed HNELHD between 1st January 2008 and 31st December 2016. Stillborn babies, duplicate entries and entries with inadequate data were excluded Figure 3.1.

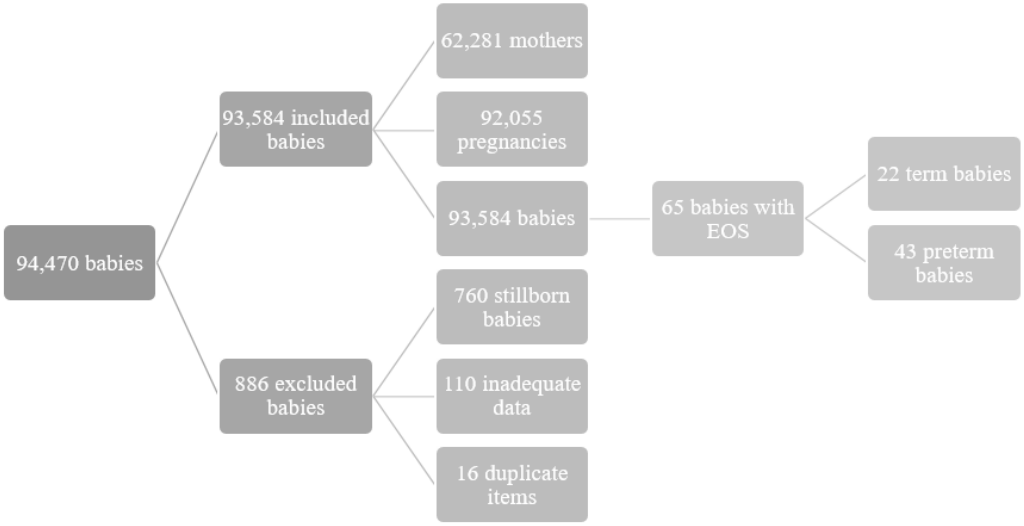


Figure 3.1 - Inclusions and exclusions

Information was obtained from medical records and the maternity ObstetriX database. ObstetriX (changed to e. Maternity in 2017) is a state wide surveillance system providing point-of-care data collection across antenatal, intrapartum, and immediate postnatal periods. Clinicians contribute information soon after birth. Local health district data custodians maintain the database.

We collected demographic data for mothers and babies, antenatal and intrapartum risk factors for EOS together with the neonatal hospital course and short-term neonatal outcomes. Maternal GBS colonisation, prematurity, and rupture of membranes (ROM) ≥18 hours, plus maternal age (age is categorical including ≤20 years versus all others), were collected and used in analysis. While history of maternal GBS bacteriuria and a previous child with EOGBS are both GBS risk factors, considered in a decision to offer IAP, we were unable to obtain information on either. Data on rates of fever were poorly transcribed into the database and therefore were not included as a risk factor for sepsis in our analysis.

Microbiological Cultures

Results of culture positive blood and cerebrospinal fluid (CSF) specimens were accessed from the publicly funded pathology service provider (Auslab) and three of four private pathology providers. Early-onset sepsis events were identified from laboratory data, when significant isolates (bacteria or fungi) were obtained from blood culture and/or CSF collected within the first 72 hours of life. Cultures yielding ≥3 bacterial species or a potential contaminant e.g. coagulase negative Staphylococci, as specified by Schrag and colleagues, 2016 were assumed to have been contaminated and were therefore excluded [5].

Definition of early-onset sepsis

Researchers use a range of time frames to define EOS ranging from 48 hours to 7 days post birth [11]. The definition used here is neonatal sepsis arising within 72 hours of birth in accord with the definition used by the UK National institute for clinical care excellence (NICE) [3, 22].

Morbidity and Mortality

Admission and short-term morbidity were reported as serious or not serious. Serious morbidity was defined as the need for significant respiratory or circulatory support requiring neonatal intensive care and/or encephalopathy or seizures. It was not possible to assess long-term morbidity. Live status of each baby with an EOS event as of December 2017 was derived from the HNELHD patient demographics system, which is linked to NSW death registration data.

Prevention of group B streptococcal sepsis

Between 2006 and 2008, starting with the metropolitan unit in HNELHD, a program of GBS screening for women reaching ≥35 weeks' gestation was commenced. Mothers with recto-vaginal GBS colonisation or certain other risk factors for EOGBS (as documented above) are offered IAP in labour, or at rupture of membranes if this occurs first in order to reduce the likelihood of EOGBS.

Ethics approval

The study was approved by the HNELHD Human research ethics committee (HREC) on 05/05/2016 with variation applied for and granted 09/03/2018 16/05/18/5/5.05 SSA. LNRSSA/16/HNE/225 and The University of Technology Sydney (HREC): No. 2014000115. This publication adheres to the provision of privacy and confidentiality of patient data and clinical information, including NSW health records and information privacy act, 2002. The purpose of our study was to describe the epidemiology of EOS rather than individual events; therefore consent from individuals was not required. All data was de-identified and password protected.

Statistical analysis

Descriptive statistics on sample characteristics are provided. Incidence rates were calculated as cases per 1000 live births per year with t-tests being used for continuous variables. Chi-squared tests were used for proportions and Wilcoxon rank sum tests for comparisons of medians. P-values >0.05 suggest a statistically detectable difference between groups, which may or may not be clinically relevant and/or meaningful. We explored temporal trends in background all-cause EOS sepsis in the individual birth data by using logistic regression with a linear temporal trend and covariates for potential effect modifiers.

Potential effect modifiers used were positive maternal GBS recto-vaginal colonisation, prematurity (<37 weeks gestation), rupture of membranes (ROM) ≥18 hours and maternal age (<20 years versus all others). We provide estimates of odds ratios, graphical visualisation, probabilities of events and the associated 95% confidence intervals and p-values. All models were checked for calibration and discrimination and we use a conventional significance level of 0.05 throughout.

Results

Study population

After exclusions, the study population included 62,281 women who had 92,055 pregnancies. These women gave birth to 93,584 babies. There was an increase in the birthing population during and after 2008 as the area restructured and HNELHD was formed. Ninety-eight per cent of live born babies (90,510) were singletons and 8,165 (8.9%) of the pregnancies were preterm resulting in 9,146 (9.8%) preterm live born babies. Eight per cent of women (9,336) identified as Aboriginal or Torres Strait Islander (ASTI).

Table 3.1 provides a descriptive statistical summary of the data. It reports various characteristics of our sample overall, stratified by EOS and No EOS. The p-values correspond to statistical comparisons between the No EOS and EOS strata. Table 3.1 suggests statistically significant differences between the No EOS and EOS groups for term versus preterm babies, type of pregnancy (singleton or other), ATSI mothers, rupture of membranes >18 hours and pregnancies with positive maternal GBS colonisation. These variables with the exception of the type of pregnancy (singleton versus other) and mothers that are ATSI are recognised risk factors for EOGBS Table 3.1a & 3.1b. These results suggest that risk factors for EOS appear in our sample.

Table 3.1(a) & (b) - Sample characteristics of women, their pregnancies and babies

Table 3.1(a) - Women

	Value	Overall (%)	No EOS (%)	EOS (%)	P value
Number of pregnancies		92,055	91,990 (99.9)	65 (0.1)	
Type of pregnancy	Singleton	90,510 (98)	90,453 (98)	57 (88)	<0.001
	Multiple	1,545 (2)	1,537 (2)	8 (12.3)	
Term pregnancy (%)	Term	83,890 (91)	83,868 (91)	22 (34)	<0.001
	Preterm	8,165 (9)	8,122 (9)	43 (66)	
Median maternal age [IQR]		28 [24 to 32]	28 [24 to 32]	28 [24 to 32]	0.682
Aboriginal/Torres Strait Islander	Yes	9,336 (10)	9,330 (10)	6 (9)	<0.001
	No	82,590 (90)	82,533 (90)	57 (88)	
	Not stated	103 (0.1)	103 (0.1)	0 (0)	
	Missing	26 (0)	24 (0)	2 (3)	
Rupture of membranes ≥ 18	Yes	8,881 (10)	8,847 (10)	34 (52)	<0.001
	No	83,129 (90)	83,100 (90)	29 (45)	
	Missing	45 (0)	43 (0)	2 (0)	
GBS result (total pregnancies)	Positive	13,288 (14)	13,278 (14)	10 (15)	0.028
	Negative	48,236 (53)	48,212 (52)	24 (37)	
	Unknown	30,531 (33)	30,500 (33)	31 (48)	
Alcohol consumption	1 to < 5	2,416 (3)	2,415 (3)	1 (1.5)	0.002
	1+daily	236 (0.3)	236 (0.3)	0 (0)	
	5+daily	216 (0.2)	216 (0.2)	0 (0)	
	None	88,406 (96)	88,344 (96)	62 (95)	
	Unknown	522 (0.6)	522 (0.6)	0 (0)	
	Missing	259 (0.3)	257 (0.3)	2 (3)	

Smoking at booking	Yes	19,143 (21)	19,130 (21)	13 (20)	<0.001
	No	72,469 (79)	72,419 (79)	50 (77)	
	Unknown	184 (0.2)	184 (0.2)	0 (0)	
	Missing	17 (0)	17 (0)	0 (0)	
Prior pregnancy	Yes	66,648 (72)	66,606 (72)	42 (65)	0.369
	No	25,390 (28)	25,367 (28)	23 (35)	
	Missing	17 (0)	17 (0)	0 (0)	

Table 3.2(b) - Babies

	Value	Overall (%)	No EOS (%)	EOS (%)	P value
All babies		93,584	93,519 (99.9)	65 (0.1)	
Singleton	Yes	90,510 (97)	90,453 (97)	57 (88)	
Term	Yes	84,438 (90)	84,416 (90)	22 (34)	<0.001
	No	9,146 (10)	9,103 (10)	43 (66)	
Mean birth weight (SD)		3,360 (641)	3,360 (640)	2217 (1135)	<0.001
Median gestational age [IQR])		40 [38, 41]	40 [38, 41]	33 [29,39]	<0.001

Legend: EOS= early-onset sepsis, [IQR]=interquartile range, ASTI= Aboriginal or Torres Strait Islander, 1 to <5-= one drink daily and not more than 5 at one sitting, eligible= a pregnancy ≥ 35 weeks gestation, ROM= rupture of membranes, GBS= group B streptococcus

Early-onset sepsis

In total, 65 culture-proven EOS events were identified Figure 3.2. Over 80% of EOS was evident within 48 hours of birth 82, and 88% for term and preterm groups respectively. Most, but not all, babies subsequently diagnosed with EOS were born at the metropolitan unit 50/65 (77%). The annual change in the background rate of all-cause EOS was significant at the 0.05 level with a multiplicative change in the odds of EOS reducing by approximately 9% per year over the study period as indicated by an (p=0.03, OR= 0.91, 95% CI, 0.84 to 0.99%). Six women who identified as ATSI mothers had babies with EOS Table 3.1a & 3.1b.

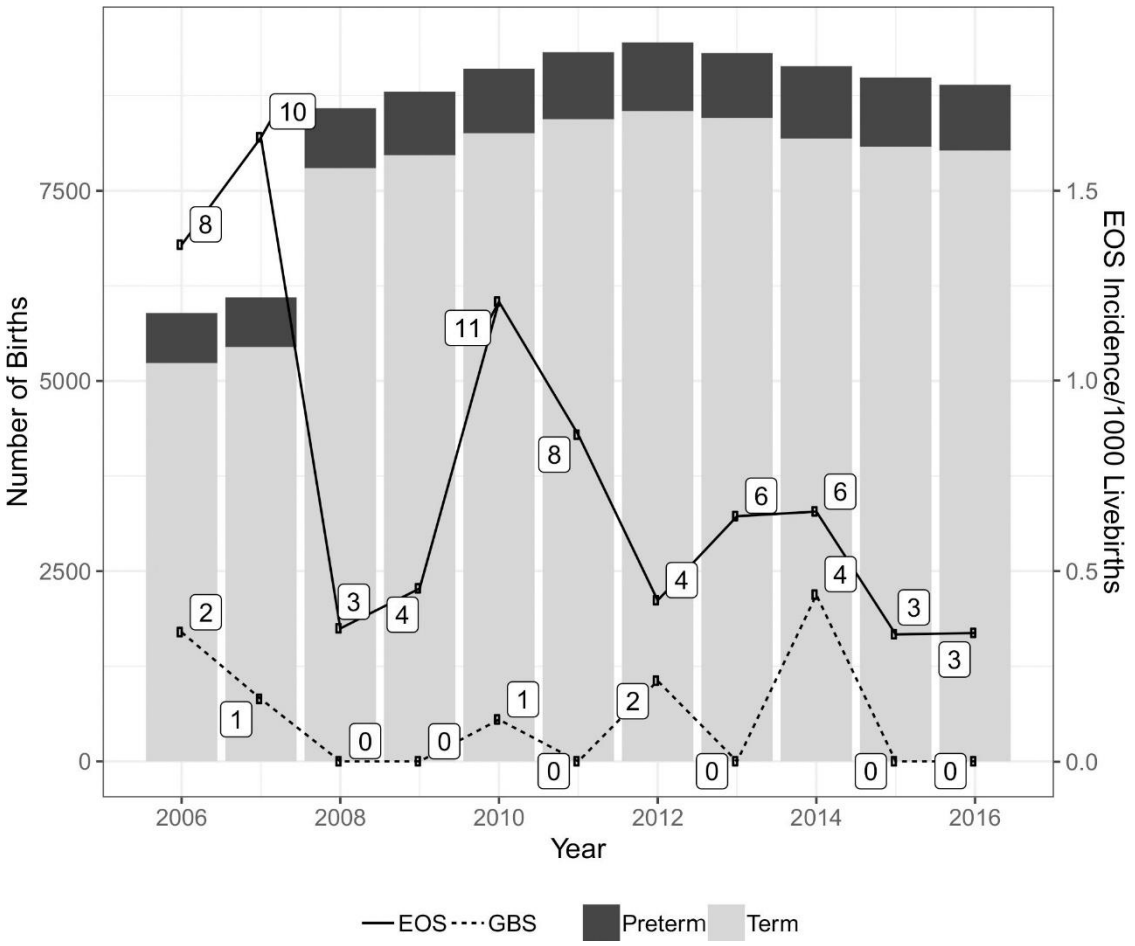


Figure 3.2 - Early-onset sepsis events per 1000 live births

Term babies with early-onset sepsis

Twenty-two, (34%) of the 65 babies with EOS were term gestation. Baseline (2006) incidence of EOS in term infants was estimated with adjustment for gestation, birth weight, maternal GBS carriage, ROM ≥18 hours and maternal age to be approximately 0.5 (95% CI, 0.02 to 0.97)/1000 live births. By 2016, the rate was 0.19 (95% CI, 0 to 0.4).

Preterm babies with early-onset sepsis

Forty-three babies who developed EOS were preterm. Baseline incidence of preterm EOS was estimated with adjustment for gestation, birth weight, maternal GBS colonisation, ROM ≥18 hours and maternal age to be approximately 22/1000 live births (95% CI, 1.3 to 42.7) in babies with gestations <30 weeks and 3.4/1000 live births (95% CI, 0.1 to 6.8)

in babies with gestations 30 to 36 weeks and 6 days. By 2016, the respective rates had fallen significantly to 8.8/1000 live births <30 weeks (95% CI, -0.5 to 18) and 1.4/1000 live births between 30 and 36 and 6 days (95% CI, -0.1 to 2.8) Figure 3.2.

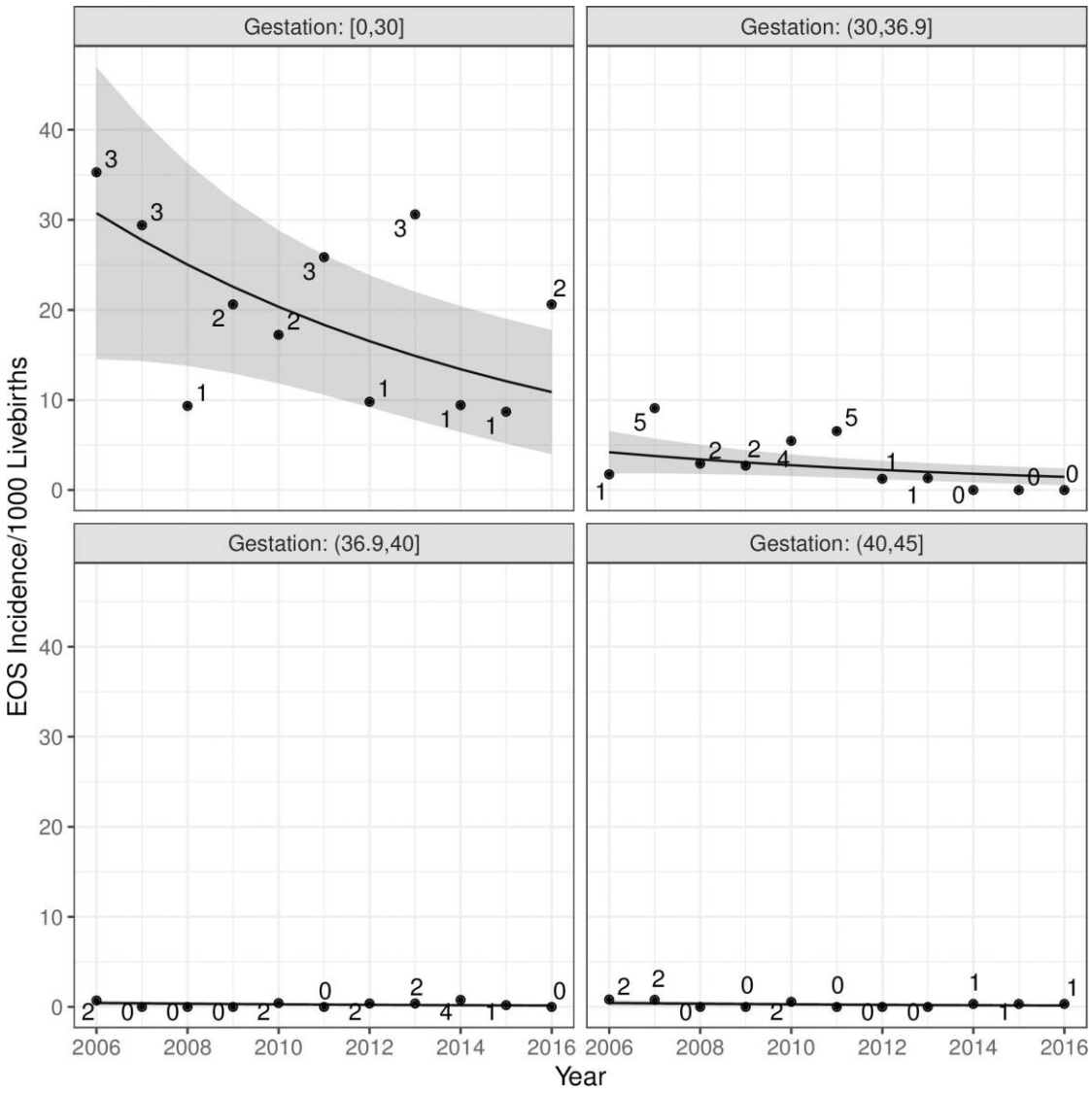


Figure 3.3 - Early-onset sepsis events by gestation

EOS surveillance intensity 2013-2016

Across the 4 largest birth units, the proportion of babies having at least one blood culture within 72 hours of birth varied from 1.9 to 5.1% for term and 21 to 35% for preterm

babies with large year-to-year variation. Across the smaller units that do not care for preterm babies, the proportion of babies cultured was 1.1% or less, with a mean of 0.7%.

Diagnosis

All EOS events were diagnosed by blood culture. Forty-one (63%) babies also underwent lumbar puncture; 11/41 (27%) term and 30/41 (73%) preterm. Lumbar punctures were taken within two days of a positive blood culture in 31/41 (76%) cases. Of the 41 lumbar puncture tests taken, four (10%) were positive and results were in accord with the blood culture.

Gram-negative species predominated significantly in preterm EOS events, 24/43 (55%) and (4/23) 17% in term babies (p=0.006); *E. coli* and other *Enterobacteriaceae* were the leading causes in 20/43 (45%) of the preterm cohort Table 3.2. The rate of EOS due to *E. coli* over the study period was 0.19/1000 live births (n=18); 0.02/1000 live births (n=2) in the term cohort and 1.75/1000 live births (n=16) in the preterm cohort.

Gram-positive species were responsible for most EOS cases in term babies 18/22 (82%) versus 18/43 (42%) in preterm babies Table 3.2. Group B Streptococcus constituted almost half of EOS events in term babies at 10/22 (45%). The overall rate of EOGBS was 0.19/1000 (n=18) live births.

Table 3.2 - Term and preterm early-onset sepsis by organism

Fungi	Term	Preterm	Total
Candida glabrata		1	**1**
Gram negative bacteria			
Acinetobacter baumannii complex	1		**1**
Escherichia coli*	**2**	**16**	**18**
Haemophilus influenzae		4	**4**
*Klebsiella pneumoniae**		1	**1**
*Morganella morganii**		1	**1**
Pseudomonas aeruginosa		1	**1**
Salmonella species*	1		**1**
*Serratia marcescens**		1	**1**
Gram positive bacteria			
Enterococcus faecalis	2		**2**
Enterococcus faecium	1		**1**
***Streptococcus agalactiae* (GBS)**	**10**	**8**	**18**
Streptococcus pneumoniae	2	4	**6**
Streptococcus species (other)	2	4	**6**
Staphylococcus aureus (methicillin-susceptible)	1	2	**3**
Total	**22**	**43**	**65**

*These species are from the Enterobacteriaceae family.
No events due to methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococci were detected. Of the events due to E. coli, 67% were ampicillin resistant.
No Gram-negative isolates producing extended spectrum betalactamases or carbapenemases were detected

Neonatal clinical course

Of the 14 babies born outside the metropolitan unit, the majority 11/14 (79%) remained in their regional unit of birth for on-going care. Two babies were transferred to the local metropolitan unit and one was transferred out of the LHD. We were unable to follow up babies transferred out of area, excluding mortality. Most babies with EOS are referred to one of the public facilities for management and would have been captured within our data set. Furthermore, given the high proportion of preterm babies undergoing blood culture in our district (21 to 35%), it is unlikely events were missed.

All of the 65 babies were transferred to a neonatal intensive care unit/ special care unit

(NICU) but only 14/65 (22%) were admitted with a primary presumptive diagnosis of sepsis. Other common reasons for admission were prematurity and/or respiratory distress.

All babies (except one unknown) subsequently diagnosed with EOS received antibiotics. Empiric treatment was reported as intravenous penicillin and gentamicin in 61/64 cases (95%). Term infants remained on antimicrobials for a median of seven days [IQR, 7.5, 5.0 to 12.5], and remained in hospital (NICU and/or ward) for a median of 7.5 days [IQR, 7.5, 3.5 to 11.0]. Forty-one (95%) preterm babies were known to have antibiotics. Preterm babies with EOS also remained on antimicrobials for a median of seven days [IQR, 13.0, 3.3 to 16.3] and remained in hospital for a median of 19 days [IQR, 34.0, 3.8 to 37.85].

Morbidity and mortality

Thirty-three (50%) babies had serious short-term morbidity, in particular, ventilatory support requiring neonatal intensive care. Serious, short-term morbidity occurred in 8/13 (62%) term babies with non-EOGBS sepsis and 4/10 (40%) term babies with EOGBS. It was not possible to report on long-term morbidity.

Overall, 10/65 (17%) babies with EOS died; all were preterm. The rate of preterm mortality was 1.1/1000 preterm births and rate of mortality per total live births was 0.1/1000. Gestation ranged from 24 to 34 weeks and weight from 630 to 2440 grams. Six of the 10 babies that died had early-onset *E. coli* infection. Mortality occurred at a median of three days after birth [range 6 hours to 44 days]. All deaths occurred at the metropolitan hospital**.**

Discussion

This study provides an eleven-year, "real world" view of the epidemiology of EOS in a geographically and socially diverse setting. The EOS surveillance intensity varied with up to a two-fold difference in the proportion of term babies undergoing blood culture testing across the four largest neonatal units. Aside from the variation caused by different case mix, there are likely to be significant differences in clinician thresholds for blood culture collection, which will impact on measured culture proven EOS rates. Blood culture utilisation should be included in future studies in accord with best epidemiological practice.

All-cause EOS events declined significantly with a multiplicative change in the odds of EOS reducing by approximately 9% per year over the study period. *Escherichia coli* (n=18*)* and GBS (n=18) were the most common bacteria causing EOS events. The very low frequency of EOS events limited what could be established statistically, however, the modelling showed a significant reduction in *E. coli* but no evidence of a significant change in EOGBS over time.

Historically, babies of ATSI mothers have been over-represented in early-onset sepsis data. In our study, there were six babies whose mothers were identified as ATSI. These babies represent 9% of all infants with EOS. This finding is similar to the proportion of ATSI women in our total cohort Table 3.1a & 3.1b and agrees with Singh et al whose work suggests the rate of EOS in babies of ATSI mothers may be decreasing [5].

The estimated incidence in 2016 of all-cause EOS in term babies was 0.19/1000 live births (95% CI, 0, 0.4) at the overall median birth weight of 3.42 kg. After adjustment was made for gestation, birth weight, positive maternal GBS, ROM ≥18 hours and maternal age, this represented a non-significant decline from 0.5/1000 live births (95% CI, 0.02, 0.97) in 2006 Figure 3.2. This result is consistent with other studies [5, 6].

As expected, EOS was highest in preterm infants with two-thirds of events occurring in this group. All-cause EOS events in preterm babies showed a significant decline over the years. Adjusted rates were 3.4/1000 live births in 2006 (95% CI, 0.11, 6.76) to 1.35/1000 live births in 2016 (95% CI,-0.7, 2.78). The most dramatic reduction occurred in babies <30 weeks gestation. After adjustment, rates in this group fell from 22/1000 live births (95% CI, 1.3, 42.7) in 2006 to 8.8/ 1000 (95% CI, -0.5,18) in 2016. Preterm events that occurred from 2014-2016 were confined to babies of gestation <30 weeks Figure 3.2.

The decline in incidence of all preterm EOS events possibly represents the effect of local changes in the management of preterm birth which, since 2011, has included routine pre-emptive antibiotic treatment upon presentation of mothers in preterm, or suspected preterm labour (Murray, H., personal communication, 2018) and advances in neonatal intensive care provision over the study period.

A universal screening approach was recommended in our LHD across the study years, with risk factors considered if a woman was GBS unknown. The crude incidence of EOGBS across term and preterm groups in our study was low at 0.19/1000 live births

and, despite minor fluctuations, did not change significantly over time. Whilst we acknowledge that EOGBS rates have increased and decreased across various jurisdictions during our study period, our results compare favourably with the contemporary incidence of EOGBS recorded by the English Neonatal Infection Surveillance unit, 0.57/1000 live births, using a risk-factor approach [23]; a large, multi-centre study from the US, 0.2/1000 live births, using a universal screening approach [5] and 0.33/1000 live births in a recently published Australasian study [17]. In Australia either a universal or risk-factor approach is used. New Zealand recommends a risk-based approach [24].

The use of IAP in our cohort has not been associated with a detectable increase in antimicrobial resistance or EOS due to non-GBS causes. However, increasing community colonisation with extended spectrum betalactamase-producing *E. coli* (7.5% in 2015) is documented in Australia and may, in future lead to increasing EOS events due to such strains [25] Table 3.2. In the tertiary facility, there have been two multi-resistant *E. coli* EOS events subsequent to this study's time period with isolates that were both resistant to gentamicin. One isolate was also resistant to ceftriaxone (*CTX-M-1* extended spectrum betalactamase gene detected).

Limitations of this study include the focus on reported culture-proven EOS events, which may have under-estimated the true burden of EOS due to false negative culture results. While our models adjusted for relevant variables, we were unable to use all EOS risk factors, as history of GBS bacteriuria and having a previous child with EOGBS were not available from the database. Fever is currently stated as a risk factor for EOS but was poorly documented and therefore not used in our analysis. The observational design may limit generalisability and is unable to rule out all possible biases. Our study is however, generalisable to other diverse jurisdictions that can link pathology data with a maternity outcomes database such as ObstetriX or eMaternity.

We believe strengths of this study are the inclusion of women with low and high-risk pregnancies across a geographically and socially diverse region, over a long period of time, in a setting where maternal universal screening for GBS was in place throughout the study period. Further, unique to our study, the inclusion, and evaluation of EOS surveillance intensity by studying blood culture utilisation.

Future Direction

Neonatal sepsis is an important issue in both low and high-income countries. At best, these invasive infections separate mothers and babies and strongly impact on the health care budget. At worst, invasive sepsis increases preterm birth, stillbirth, neonatal morbidity, and mortality. Although rates of GBS, the most common bacteria affecting term babies, remained low throughout our study, the potential for a vaccination to reduce risk of EOS due to GBS is attractive. In a recent multi-centre trial, GBS CPS III-TT conjugate vaccine significantly delayed maternal vaginal and rectal GBS serotype III colonisation [26].

However, a significant proportion of EOS occurs before a pregnancy is term and is due mainly to non-GBS causes. Most preterm babies do not benefit from maternal third trimester GBS screening and may not benefit from GBS vaccination. Whilst antenatal and intrapartum vigilance for signs of sepsis is crucial, a more upstream prevention such as optimisation of maternal factors that influence the neonatal and vaginal microbiome is worth consideration.

Finally, a tool that can assist clinicians in predicting the probability of EOS based on maternal risk factors as well as the baby's clinical presentation is being used in West Australia. Using this tool, the risk of EOS can be calculated in a baby born $\geq$34 weeks gestation [27]. The interactive calculator produces the probability of EOS per 1000 births. As well as reducing the proportion of newborns undergoing laboratory testing and receiving empirical antibiotic treatment [28], clinical care algorithms can assist a family's decision making around GBS screening and IAP provision, thereby possibly reducing the number of women and babies unnecessarily exposed to this intervention [29]. Such public health initiatives are best implemented, guided and audited by a multi-disciplinary maternity and neonatal care team.

References

1. Heron M. Deaths: leading causes for 2016. National Vital Statistics Report. US department of Health and Human Services. Center for Disease Control and Prevention; National Center for Health Statistics; 2016.
2. Tudela CM, Stewart RD, Roberts SW, Wendel GD, Jr., Stafford IA, McIntire DD, et al. Intrapartum evidence of early-onset group B streptococcus. Obstet and gynecol. 2012;119(3):626-9.
3. van Herk W, Stocker M, van Rossum A. Recognising early onset neonatal sepsis: An essential step in appropriate antimicrobial use. J Infect. 2016.
4. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005- 2008. Pediatr Infect Dis J. 2011;30(11):937-41.
5. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016;138(6).
6. Singh T, Barnes EH, Isaacs D, Australian Study Group for Neonatal I. Early-onset neonatal infections in Australia and New Zealand, 2002-2012. Arch Dis Child Fetal Neonatal Ed 2018.
7. Royal College of Obstetricians and Gynaecologists. The Prevention of Early- onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. 2nd ed. London: Royal College of Obstetricains and Gynaecologists; 2012.
8. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines MMWR 2010;59(1):1-36.
9. Brown RG, Marchesi JR, Lee YS, Smith A, Lehne B, Kindinger LM, et al. Vaginal dysbiosis increases risk of preterm fetal membrane rupture, neonatal sepsis and is exacerbated by erythromycin. BMC Medicine. 2018;16(1):9.
10. Sung JH, Choi SJ, Oh SY, Roh CR, Kim JH. Revisiting the diagnostic criteria of clinical chorioamnionitis in preterm birth. BJOG. 2017;124(5):775-83.

11. UK National Screening Committee. Screening for Group B streptococcal infection in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2012.
12. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Maternal Group B Streptococcus in pregnancy: screening and management. C-Obs 19. 2016.
13. Heath P, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol. 2007;21:411-24.
14. Mendoza-Palomar N, Balasch-Carulla M, Gonzalez-Di Lauro S, Cespedes MC, Andreu A, Frick MA, et al. Escherichia coli early-onset sepsis: trends over two decades. Eur J Pediatr. 2017;176(9):1227-34.
15. Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland
16. M. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed. 2011;96(1):F4.
17. Klinger G, Levy I, Sirota L, Boyko V, Reichman B, Lerner-Geva L, et al. Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants. Am J Obstet Gynecol. 2009;201(1):38 e1-6.
18. Chen JC, Jenkins-Marsh S, Flenady V, Ireland S, May M, Grimwood K, et al. Early-onset group B streptococcal disease in a risk factor-based prevention setting: A 15-year population-based study. Aust N Z J Obstet Gynaecol. 2018:1-8.
19. Edmond K, Kortsalioudaki C, Scott S, Schrag S, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet. 2012;379(9815):547-56.
20. Isaacs D. Evidence-based neonatal infections. United Kingdom: John Wiley & Sons Ltd; 2014.
21. Ohlsson A, Shah V. Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review). Cochrane Database Syst Rev. 2014;6:CD007467.
22. Australian Bureau of Statistics. Hunter New England Local Area Health District: Healthstats: NSW Health; 2016 [updated 2016. cited 2019 Jan 16]. Available from http://www.healthstats.nsw.gov.au

23. National Institute for Health and Clinical Excellence. Antibiotics for early-onset neonatal infection. NICE clinical guideline No149. London. 2012.
24. Seedat F, Taylor-Phillips S, Geppert J, Stinton C, Patterson J, Brown C, et al. UK National Screening committee (UK NSC). Universal antenatal culture-based screening for maternal GBS carriage to prevent EOGBS disease. Review update. 2016.
25. NZ consensus guideline. The prevention of early-onset neonatal group B streptococcus infection. 2014.
26. Antimicrobial use and resistence in Australia: AURA report 2017 [cited 2018 Aug 8. Available from https://www.safetyandquality.gov.au/our-work/national- standards-and-accreditation.
27. Hillier SL, Ferrieri P, Edwards MS, Ewell M, Ferris D, Fine P, et al. A Phase II Randomized, Control Trial of Group B Streptococcus (GBS) Type III Capsular Polysaccharide -Tetanus Toxoid (GBS III-TT) Vaccine to Prevent Vaginal Colonization with GBS III. Clin Infect Dis. 2018.
28. Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early- Onset Sepsis. JAMA Pediatr. 2017;171(4):365-71.
29. Lebedevs T, Sajogo M. Effect of the neonatal early onset sepsis calculator on pharmacy-prepared empirical antibiotics. J Pharm Pract Res. 2018;48(5): 450- 453
30. Kaiser Permanente Division of Health. Neonatal early-onset sepsis calculator. [cited 2019 Jan 08]. Available from https://neonatalsepsiscalculator.kaiserpermanente.org/2018

Chapter 4

Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district: 2006-2016

Chapter preface

Study 2 is a companion to Study 1 and was also published in the journal *PLoS ONE*. Similar to Study 1, the published version of Study 2, Chapter 4 presents the manuscript 'Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district: 2006-2016**'** in its original form using the *Vancouver* output referencing style. My integrative literature review (Chapter 2) revealed a lack of robust evidence for the effectiveness of the intervention IAP, to reduce the likelihood of EOGBS. Despite widespread use of IAP, Study 1 (Chapter 3) revealed GBS as the leading cause of term EOS. As a result of this finding, in Study 2, I investigated the rates of maternal GBS colonisation, screening and IAP provision, and neonatal outcomes in one local area health district over an eleven- year period. The manuscript is provided in its published form (Appendix 3). References for this manuscript are also presented in the 'Thesis references' section using the university's recommended referencing style (*Harvard_UTS*).

Abstract

Background

Intrapartum antibiotic prophylaxis (IAP) to reduce the likelihood of neonatal early- onset group B streptococcal infection (EOGBS) has coincided with major reductions in incidence. While the decline has been largely ascribed to IAP following either universal screening or a risk-based approach to identify mothers whose babies may most benefit from IAP, there is a lack of high quality evidence to support this view.

Aims

To describe management of maternal GBS colonisation in one local health district using universal screening and assess rates of EOGBS over time.

Methods

A retrospective cohort study was undertaken to describe compliance with GBS management, to determine the incidence of EOGBS and association between rates and maternal screening. Linking routinely collected maternity and pathology data, we explored temporal trends using logistic regression and covariates for potential effect modifiers.

Results

Our cohort included 62,281 women who had 92,055 pregnancies resulting in 93,584 live born babies. Screening occurred in 76% of pregnancies; 69% had a result recorded, 21.5% of those were positive for GBS. Prophylaxis was used by 79% of this group.

Eighteen babies developed EOGBS, estimated incidence/1000 live births in 2006 and 2016 was 0.35 (95% CI, 0.07 to 0.63) and 0.1 (95% CI, 0 to 0.2) respectively. Seven of 10 term babies with EOGBS were born to mothers who screened negative. Data were unable to provide evidence of difference in rates of EOGBS between screened and unscreened pregnancies. We estimated the difference in EOGBS incidence from crude and weighted models to be 0 (95% CI, -0. 2 to 0.17) and -0.01 (95% CI, -0.13 to 0.10) /1000 live births respectively.

Conclusion

No change was detected in rates of EOGBS over time and no difference in EOGBS in babies of screened and unscreened populations. Screening and prophylaxis rates were modest. Limitations of universal screening suggest alternatives be considered.

Introduction

Early-onset group B streptococcal infection (EOGBS) is a high impact event that, despite its low frequency, remains a significant cause of early infant morbidity and mortality [1].

To reduce the likelihood of EOGBS, intrapartum antibiotic prophylaxis (IAP) was introduced in the 1980s and offered to women whose babies were thought to be most at risk. In the USA, widespread use of IAP coincided with a decline in reported EOGBS rates; from 0.7/1000 live births in 1997 [2] to 0.22/ 1000 in 2016 [3]. However, since the pre-prevention era, the proportion of women and babies exposed to IAP has more than doubled (from 12% to 30%) in the USA and other high-income countries [4].

Antibiotics have saved millions of lives, but they are not without risk. Most recently concerns have been raised about the possible link between IAP exposure and dysbiosis of the infant's founding microbiome, which may lead to adverse health effects in later life [5-9]. Research which highlights benefits, risks and limitations of GBS screening and IAP provision is therefore warranted.

Background

Neonatal group B streptococcal colonisation and infection

Prior to the implementation of screening and IAP provision, it was believed that up to 50% of babies born vaginally to mothers with GBS colonisation would be colonised by the bacterium as part of their founding microbiome. Most of these babies were not compromised by GBS colonisation and remained well [10, 11]. In the absence of IAP, it is reported that 1-3% of babies colonised with GBS will develop EOGBS [12]; however, this proportion is difficult to quantify in the era of widespread IAP. In a global systematic review and meta-analysis, the incidence of EOGBS was 0·43/ 1000 live births (95% CI, 0·37, 0·49) and global case fatality 12·1%, (6·2,18·3) [1].

Screening approaches

In 1996 the Centers for Disease Control and Prevention (CDC) published guidelines recommending that clinicians select women whose babies may benefit from IAP and offer prophylaxis to reduce the likelihood of EOGBS. The selection criteria were based on certain risk factors including maternal recto-vaginal GBS colonisation, rupture of membranes (ROM) ≥18 hours, intrapartum fever and prematurity [12-14]. History of bacteriuria in the index pregnancy and having a sibling diagnosed with EOGBS are also risk factors [12, 13].

In 2002, based on a large retrospective study in the USA [15], the CDC recommended universal screening for recto-vaginal GBS colonisation of all pregnant women at 35–37 weeks' gestation as the best method for GBS management [16]. When GBS status was unknown, a risk-based based approach for IAP was recommended. In 2010 the CDC continued to recommend universal screening [12] although globally, countries remain divided regarding optimal GBS management.

In Australia the evolution of GBS management strategies began in the late 1970s, based on the observation of an unexpectedly large number of EOGBS reported in one city. As a consequence of a review into local EOGBS rates in a large metropolitan Melbourne hospital, policy recommended a universal GBS screen for pregnant women and provision of IAP to those at risk [17]. This review influenced GBS management throughout the country. However, Australia has never had a national GBS policy and Australian states and territories recommend different approaches for selecting women for IAP. Queensland, for example, recommends a risk-based approach [18] and NSW recommends either universal screening or a risk-based approach [19]. The latest guidelines from the Royal Australian and New Zealand college of Obstetricians and Gynaecologists (RANZCOG) [13] also recommend either approach. Conversely, New Zealand has undertaken local research [20-22] and continues to offer a risk-based approach to manage GBS risk. A recent Australian systematic review concluded that the odds of EOGBS in infants of any gestation were significantly lower with universal screening compared with risk-based screening (OR 0.45, 95% CI, 0.37 - 0.53). However the authors noted the quality of the studies critiqued was low [23].

Incidence of early-onset group B streptococcal infection

Reported rates of neonatal EOGBS vary markedly, particularly in areas with limited access to laboratory diagnosis. Variation in rates may reflect changes in reporting of cases and/or natural fluctuation, a true increase or decrease in incidence, or less than optimal implementation of prevention strategies. Rates of EOGBS are often reported on a voluntary basis and therefore may not represent all confirmed cases. Our data include live births only. Although it is probable that GBS was a contributing factor in a proportion of stillborn babies in our district [24], it was not possible to obtain data on these babies.

Reported live birth rates of EOGBS in the USA, and other high-income countries

including Australia, have remained stable for nearly two decades, at below 0.5/1000 live births [12, 25, 26]. Exceptions include New Zealand, where researchers compared 1998-99 EOGBS rates which were estimated at 0.5/1000 live births (95% CI, 0.38, 0.65) [22] to rates five years later after instituting a national consensus risk-based approach. In 2009-11 EOGBS rates had halved to 0.26/1000 live births (95% CI, 0.18, 0.37) [21]. Other countries have reported an increase in rates. The UK from 0.48/1,000 live births (95% CI, 0.43, 0.53) in 2000-2001 to 0.57/1,000 live births in 2014/2015 (95% CI, 0.52, 0.62), and [14] the Netherlands 0·11/1000 live births to 0·19/1000 live births ($p<0·001$) [16].

Local practice

In 2005, our local health district, now called Hunter New England Local Health District (HNELHD), changed GBS management from identification of risk factors to universal culture based screening and provision of IAP in line with the CDC guidelines of the time [16]. A local study, reported a dramatic decline in EOGBS (84%) when universal screening was employed to select candidates for IAP. The study reported that to prevent one case of the infection 5,704 women needed to be screened and 1,911 women with a positive GBS result would be required to have IAP [27]. The regime for IAP was set locally at 1.2-grams of penicillin followed by 600mg four hourly until birth [28] and, due to our very low EOGBS rates, this regime has not changed despite the Australian therapeutic guidelines [29] and CDC [30] recommendations of 3-grams of penicillin followed by 1.5-1.8 grams four hourly until birth. Over a decade has passed since this local study and the change from a risk-based approach to universal screening. We were interested to assess compliance with universal GBS screening and IAP protocols and EOGBS rates in this population.

Aims

To describe compliance with GBS management in an era of universal screening and to assess rates of neonatal EOGBS over time in a diverse Australian local health district.

Methods

Study setting and population

A retrospective cohort study was employed using data from pregnancies that resulted in live born babies in the Hunter New England local health district, New South Wales (NSW) Australia, over the period 2006-2016. The study population included women whose pregnancies resulted in live born babies birthing in all publicly funded maternity services within HNELHD and their babies. The term 'pregnancies' or 'women whose pregnancies' is used in this paper as around one third of women had more than one pregnancy during the study period. Included births occurred in hospitals, alongside and freestanding birth centres and at home, between 1st January 2006 and 31st December 2016 (See Table 4.1).

Table 4.1 - Pregnancies resulting in live born babies per unit 2006-2016

Birthing unit	Pregnancies	Babies
John Hunter Hospital	41,946	42,964
Maitland	17,285	17,472
Tamworth	8,058	8,194
Manning	6,379	6,459
Armidale	3,849	3,913
Inverell	2,283	2,314
Muswellbrook	2,180	2,184
Belmont Midwifery Group Practice	1,996	1,996
Singleton	1,795	1,795
Moree	1,708	1,714
Gunnedah	1,628	1,628
Narrabri	1,234	1,235
Scone	880	882
Glen Innes	662	662
Gloucester	121	121
Manilla	51	51
TOTALS	**92,055**	**93,584**

Information concerning babies and their mothers was obtained from the maternity ObstetriX database and the NSW Health Pathology database (Auslab). ObstetriX (now e Maternity) is a state wide surveillance system providing point-of-care data collection across antenatal, intrapartum and immediate postnatal periods. Clinicians contribute information soon after birth. The database is maintained by local health district (LHD) data custodians. The medical records of babies affected by EOGBS and their mothers were also scrutinised. Provision of IAP was documented in the medical record with two clinicians signing for receipt and timing of the medication.

We collected data on maternal antenatal and intrapartum risk factors, together with neonatal outcomes for the 18 babies with confirmed EOGBS. Maternal GBS colonisation, prematurity, ROM≥18 hours and maternal age were collected and used in analysis. While intrapartum fever, history of maternal GBS bacteriuria and history of a previous child with EOGBS are risk factors, and therefore considered in a decision to offer IAP, we were unable to obtain information on these variables at a population level.

Microbiological cultures

Neonatal EOGBS can be defined as culture proven GBS bacteria found in a normally sterile site; either blood, causing sepsis or cerebrospinal fluid (CSF) causing meningitis, or both [31]. Researchers use a range of time frames to define early-onset; from 48 hours to 7 days post birth. We applied the definition used by the National Institute for Health Care and Excellence (NICE) guidelines. This guideline defines EOS as sepsis occurring ≤72 hours after birth [31].

Neonatal cultures positive for GBS were accessed from the NSW health pathology database used for most public health pathology across HNELHD. Blood and CSF culture data were also accessed from 3 of 4 private providers who service small facilities in the north-western region of HNELHD.

Gestation and eligibility for group B streptococcal screening

Term gestation was defined as ≥37 weeks gestation, preterm <37 weeks gestation. Eligibility for GBS screening applied to all women whose pregnancies were ≥35 weeks gestation, which includes a small number of women whose pregnancies were preterm. Pregnancies that reached ≥35 weeks but <37 weeks gestation were classified as “eligible

preterm pregnancies". Screening should occur within five weeks of birth to maximise accuracy [26].

Definition of screened and not screened

Identification of women whose pregnancies were screened or not screened required the combination of several fields within the obstetric database. Eligible pregnancies were regarded as 'screened' if they met either of two categories: 'screened with a result' available intrapartum or at ROM (n=60,674 69%) or 'Screened with no result' where screening results were not available or pending at the time of birth or ROM. Women whose pregnancies were regarded as 'not screened' occurred if there was no entry in the ObstetriX database or a text entry that stated either 'screening declined' or 'not screened'.

Definition of adequate intrapartum antibiotic prophylaxis

Intrapartum antibiotic prophylaxis was defined as adequate when the initial dose of IAP was given at least four hours prior to birth in line with current CDC and RANZCOG guidelines [12, 13].

Mortality and morbidity

Live status (as of December 2017) for each baby who had experienced an EOGBS event was derived from the HNELHD patient demographics system linked to NSW death registration data. Admission and short-term morbidity were reported as serious or not serious. Serious morbidity was defined as the need for significant respiratory support requiring neonatal intensive care; or circulatory support and/or encephalopathy or seizures. It was not possible to assess long-term morbidity in our study.

Ethics approval

The study was deemed by the chair of Hunter New England (HNE) human research ethics committee (HREC) not to require formal approval by the ethics committee. The study conforms to the obligations of the provision of privacy and confidentiality of patient data and clinical information, including NSW Health records and Information Privacy Act 2002 as requested in our letter of approval from HNE research Ethics and Governance unit. University of Technology Sydney, HREC, ratified this decision. No. 2014000115.

Data were de-identified for the purposes of this study. Individual consent was not required.

Statistical analysis

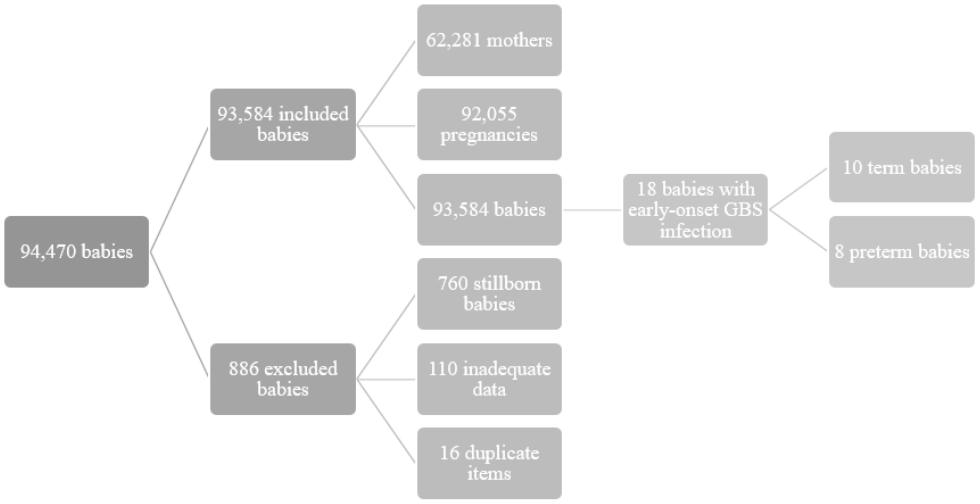
Descriptive statistics for women, their pregnancies, and live born babies are provided Table 4.1. Early-onset GBS incidence rates were calculated as events/1000 live births per year. We explored EOGBS in the babies of all women whose pregnancies reached ≥35 weeks gestation and were therefore eligible for GBS screening. Given the low number of EOGBS events we report both crude and inverse probability weighting to balance groups. The inverse probability weights were estimated using a separate logistic regression model with screening status as the outcome regressed on variables plausibly related to EOGBS and/or screening including gestation, birth weight, positive maternal GBS screening, ROM ≥18 hours and maternal age at each pregnancy (categorical indicating <20 years or all others). We also used logistic regression to model trends in EOGBS incidence over time. All models were checked for calibration and discrimination and we used a conventional significance level of 0.05 throughout.

Results

Study population

Sixteen publicly funded birthing units were included in Table 4.1 ranging from one metropolitan facility with an alongside birth centre and an associated freestanding birth centre nearby (in total around 4,000 births per year), several regional units (700 to 1,500 births per year) through to small rural units (<250 births per year).

After exclusions, (babies who were stillborn and entries with inadequate or duplicate data) the study population included 62,281 women who had 92,055 pregnancies over the study period resulting in 93,584 live born babies. Ninety-eight per cent of babies (90,510) were singletons and 9.7% (9,146) of babies were preterm. Sixty-five babies had confirmed EOS. We found 18 babies with EOGBS, 10 term and eight preterm (0.19/1000 live births) Figure 4.1. Half of the term babies with EOGBS were born in the metropolitan unit and half in regional units. One was transferred from a regional unit to a higher level of care. All preterm babies with EOGBS were born at the metropolitan unit.



EOGBS = early-onset group B streptococcal infection

Figure 4.1 - Inclusions and exclusions

Maternal GBS screening, colonisation and antibiotic prophylaxis

Nearly all women (96%) in our study had pregnancies ≥ 35 weeks and therefore were eligible for GBS screening. Seventy-six per cent of those eligible were reported to have a GBS screen. Of those, 69% had a result recorded in the database and 21.5% of those pregnancies were positive for GBS (see Table 4.2). Antibiotic prophylaxis was received by 79% of these women. Rates of positive maternal GBS colonisation in the cohort neither changed significantly from year to year nor materially between 2006 and 2016 (see Figure 4.2). Twelve per cent of women whose pregnancies were reported as GBS negative also received IAP Table 4.2. Reasons for administration of IAP to these women were not collected. Whether adequate IAP was given (≥4 hours before birth) could not be determined at a population level but was identified in individual cases.

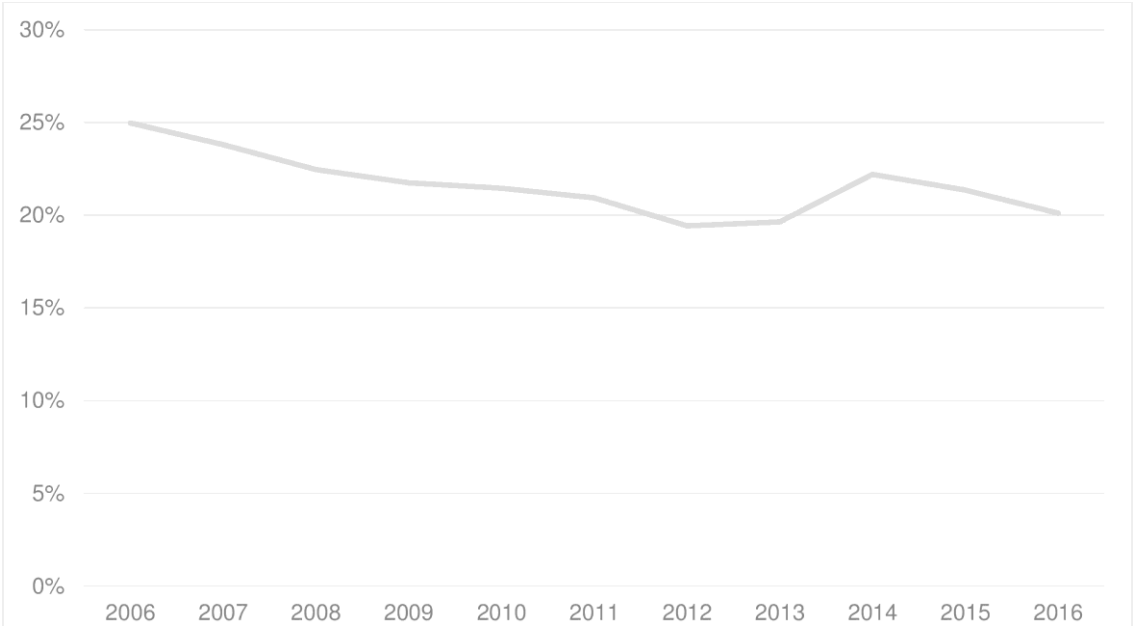


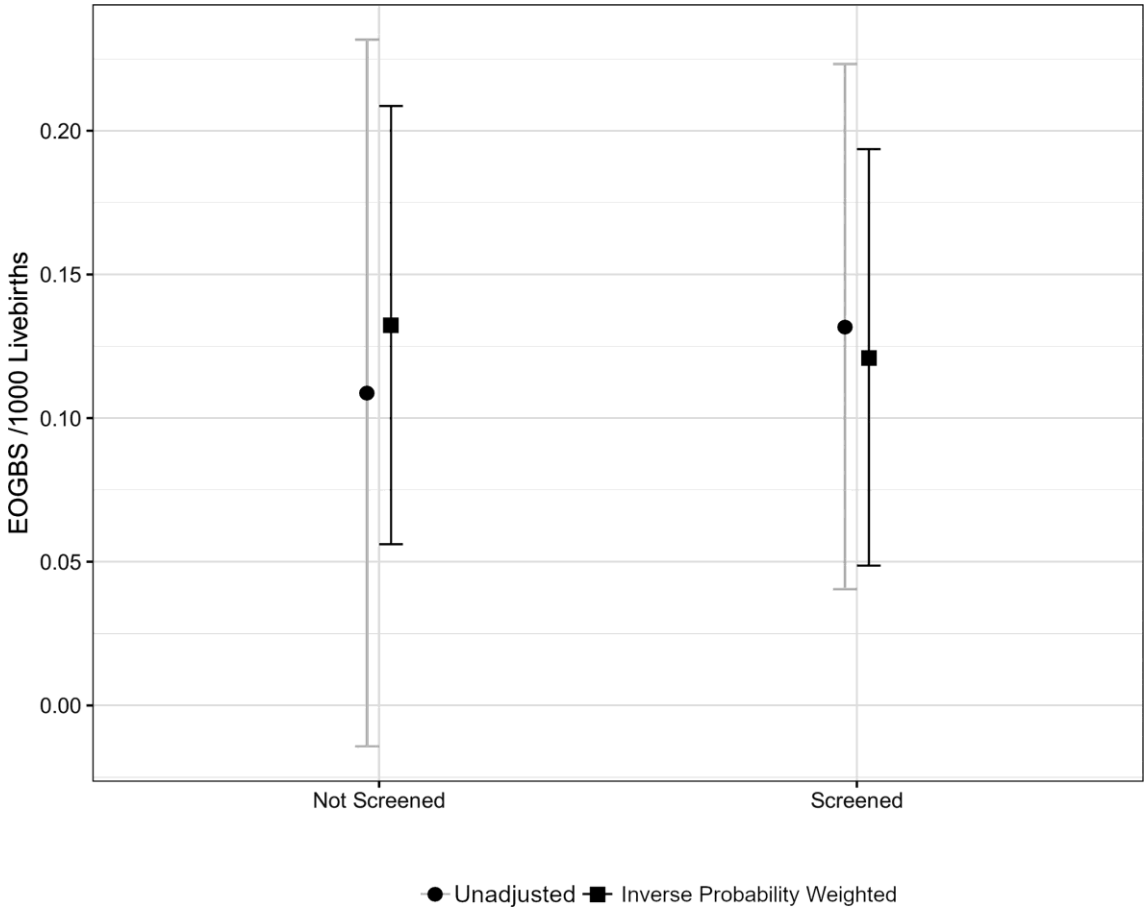
Figure 4.2 - Maternal GBS colonisation

Table 4.2 - Eligible pregnancies, maternal GBS screening and colonisation rates, and IAP provision

Birthing unit	Eligible pregnancies	Eligible pregnancies Screened (%)	Result recorded Pos/Neg (%)	GBS pos (%)	IAP given for GBS pos pregnancies	IAP given for eligible not screened
John Hunter Hospital	38,885	32,011 (82)	29,529 (76)	7,089 (24)	5,600 (79)	825 (12)
Maitland	17,051	11,494 (67)	10,954 (64)	2,407 (22)	1,918 (80)	527 (9)
Tamworth	7,873	5,178 (66)	4,764 (61)	827 (17)	695 (84)	390 (14)
Manning	6,235	4,615 (74)	3,453 (55)	632 (18)	501 (79)	156 (10)
Armidale	3,781	2,411 (64)	2,148 (57)	401 (19)	359 (90)	202 (15)
Inverell	2,257	1,918 (85)	1,584 (70)	272 (17)	227 (83)	67 (20)
Muswellbrook	2,167	1,885 (87)	1,856 (86)	353 (19)	280 (79)	35 (12)
Belmont Midwifery Group Practice	1,996	1,479 (74)	1,417 (71)	297 (21)	24 (8)	4 (1)
Singleton	1,785	1,403 (79)	1,222 (68)	216 (18)	193 (89)	45 (12)
Moree	1,684	1,318 (78)	1,036 (62)	95 (9)	88 (93)	111 (30)
Gunnedah	1,621	1,432 (88)	996 (61)	164 (16)	148 (90)	66 (35)
Narrabri	1,223	816 (67)	583 (48)	64 (11)	44 (69)	71 (17)
Scone	876	673 (77)	646 (74)	140 (22)	127 (91)	27 (13)
Glen Innes	660	436 (66)	366 (55)	82 (22)	78 (95)	49 (22)
Gloucester	121	100 (83)	91 (75)	15 (16)	13 (87)	7 (33)
Manilla	51	33 (65)	29 (57)	4 (14)	3 (75)	0 (0)
TOTALS	**88,266**	**67,202 (76)**	**60,674 (69)**	**13,058 (22)**	**10,298 (79)**	**2,582 (12)**

Eligible pregnancy≥35 weeks gestation, Pos=positive, Neg=negative, IAP=intrapartum antibiotics prophylaxis

None of our models gave evidence that the screened and unscreened cohorts had differing rates of EOGBS Figure 4.3. We estimated the difference in EOGBS incidence across reported screening status from the crude and weighted models to be 0 (-0.2, 0.17) /1000 live births and -0.01 (95% CI, -0.13, 0.10) /1000 live births respectively. Adjusting for a temporal trend did not materially impact the estimates.



EOGBS=early-onset group B streptococcal infection

Figure 4.3- Screened versus unscreened pregnancies and rates of EOGBS

Early-onset group B streptococcal infection over time

The odds ratio for the annual temporal trend of EOGBS obtained from the exponentiated parameter estimates was 0.88 (95% CI, 0.75, 1.03, p= 0.11). Model estimates for incidence per /1000 live births in 2006 and 2016 were 0.35 (95% CI, 0.07, 0.63) and 0.1 (95% CI, 0, 0.2) respectively Figure 4.4. A bootstrapped estimate for the difference between the 2006 and 2016 incidence of EOGBS was -0.28 (95% CI, -0.04, 0.74) suggesting negligible support for a change even over the 10-year interval.

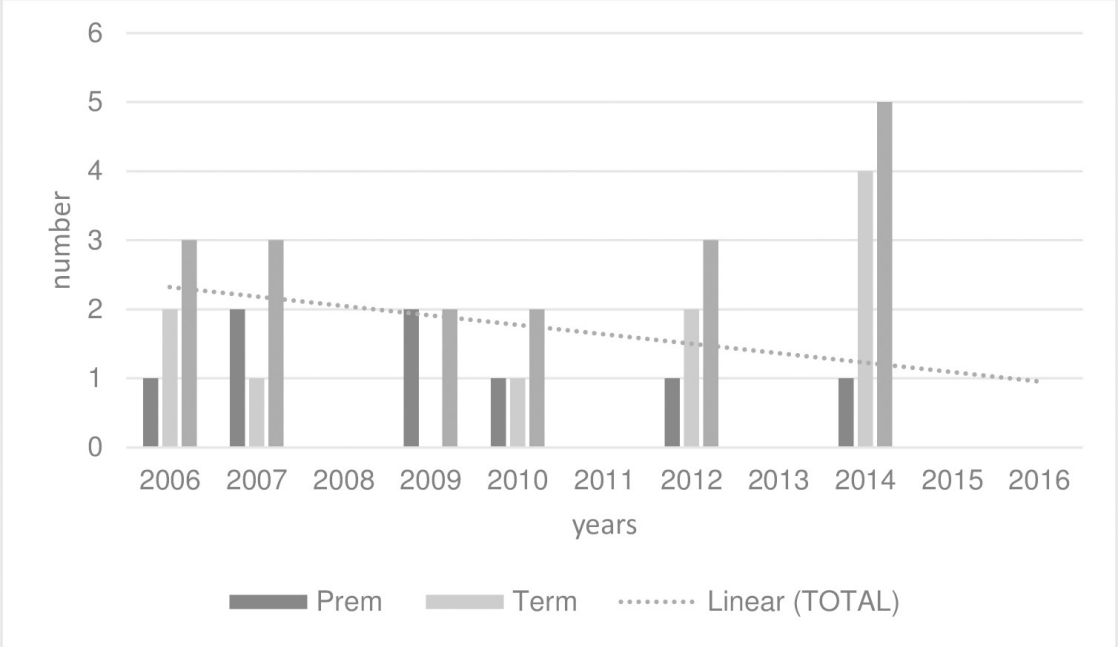


Figure 4.4 - Incidence of term and preterm EOGBS 2006 - 2016

Eligible babies with early-onset group B streptococcal infection

Ten term (therefore eligible) babies had EOGBS, a crude rate of 0.12/1000 term live births. All of these babies had mothers who were screened for GBS. These babies either had an eligible mother with a negative antenatal GBS screen (n=7) or a mother with a positive GBS result that was unknown in labour and thus was unable to trigger IAP (n=3). Six of the seven negative cultures were taken within five weeks of birth.

A further preterm baby, whose mother was eligible for GBS screening (≥ 35 weeks gestation) and had a positive result known in labour and was subsequently diagnosed with EOGBS.

Six of these 11 babies had additional risk factors documented (prematurity and/or maternal GBS colonisation, ROM ≥ 18 hours, fever), which would qualify for IAP using

a risk-factor only approach. Two mothers in the eligible group received some IAP, however neither of these women received a dose ≥4 hours before birth.

Preterm babies with early-onset group B streptococcal infection

Eight babies with EOGBS were preterm (0.87/1000 preterm live births). Gestations ranged from 24 to 36 weeks. Two mothers in the preterm group received IAP (including the mother who was 36 weeks gestation and therefore eligible preterm), but neither dose was provided ≥ four hours before birth.

Morbidity and mortality

Four of 10 term babies with EOGBS had serious short-term morbidity. All required neonatal intensive care and significant continuous positive airways pressure therapy, one baby had seizure activity. All four were discharged home in a well state and were recorded as living as of December 2017, as were the other six. One preterm baby born <32 weeks gestation died (0.11/1000 live born preterm births) a combined term and preterm crude fatality rate of 0.01/1000 live births.

Discussion

This cohort study describes the management of GBS risk in our LHD in an era of universal screening and describes analysis of the rates and trends of EOGBS in an 11- year period in a diverse range of birth settings. We found no evidence to conclude a difference in rates of EOGBS between women reported as screened or not screened for GBS. Our findings, along with others [32, 33, 34], highlight the logistical difficulty of mounting a sustained, consistent screening program across a large LHD. Furthermore, 12% of women who were not screened received IAP Table 4.2. The reasons for this were not analysed in this study.

Incidence of EOGBS in this population was low, at 0.19/1000 live births. The low frequency of EOGBS events limited our ability to explore time trends in incidence rates however our model did not provide evidence of a change in incidence over time. Our data align with the contemporary incidence rates recorded by a large, multi-centre study from the US, (0.2/1000 live births) [35].

It is possible and widely reported, that the rates of EOGBS may have remained low since

the early 2000s because of screening and IAP provision [1, 34-36]. We found 21.5% of the 69% of pregnancies who were screened and had a result documented in the database, were positive for GBS. A modest 79% of women, who were positive for GBS at the end of their pregnancy, received some IAP Table 4.2. This finding is similar to the results found in a recent Australian integrative review [37]. The review found that although screening and IAP appeared to be very effective in reducing rates of EOGBS, the rate of IAP provision in the clinical setting was not optimal suggesting there may be other reasons for very low EOGBS rates. The database in our study did not specify the dose or frequency of IAP provision, so we could not establish if the IAP provided was assessed as adequate at a population level. At an individual level, to explore the experience of babies who had EOGBS, we examined individual medical records to obtain data not entered onto the ObstetriX database. None of the babies with EOGBS had mothers who were provided with adequate IAP.

In this era of universal screening and IAP provision there is no way of knowing what the rates of EOGBS in high-income countries would be in babies whose mothers had GBS risk factors but no exposure to IAP. When data are compared from jurisdictions that use universal screening and IAP, versus a method based on risk factors, reported EOGBS rates are mixed, with either no change [25], increases in some jurisdictions [26,38], and decreases in others [21]. It should be noted, however, that some clinicians use a combination of the two standard methods of selecting women most at risk of having a baby affected by this infection [39], so comparison between countries, and even areas within countries, is problematic.

Seven out of the ten term babies with EOGBS had mothers who were screened negative for GBS. These data concur with others reporting on EOGBS in the era of widespread IAP provision, finding rates of infection occurring among babies born to women with pregnancies negative for GBS were higher than previously reported [35, 40]. There are several reasons why this may be the case. These false negative results may be due to the modest predictive values of current screening protocols; which are influenced by intermittent maternal GBS colonisation [26]. Further, in some jurisdictions, swabs may be incorrectly taken and /or transported, or incorrectly processed [14].

Five of the seven term women whose pregnancies screened negative for GBS had another

risk factor for infection (ROM ≥18 hours) warranting consideration for IAP using a risk-based approach. Even though the most common risk factor for EOGBS in our study and others [41, 42] was ROM ≥18 hours, numbers were too small (5/7 term women) to draw any conclusion. IAP was not administered to the five women with ROM ≥18 hours and a negative GBS result, in accord with local guideline recommendations at the time. Early-onset infection due to GBS occurring in babies born to women whose pregnancies have screened negative for GBS, further reflects the limitations of current methods of assessing GBS risk in our area.

As well as the protocol of screening and IAP provision that was offered to most, but not all, women with pregnancies that had a GBS positive result, it is likely that the low rates of EOGBS in our cohort maybe related to other factors. It is true that the crude rates of maternal GBS colonisation in the cohort neither changed significantly from year to year nor materially between 2006 and 2016. However, shifts in GBS serotypes and/or virulence of the bacteria may have occurred. Furthermore, population differences in exposure to GBS, maternal immunity, and fetal/neonatal susceptibility may also play a role in the reduction of infection rates [43]. Our low incidence of EOGBS in term babies cannot be exclusively ascribed to the protocol of offering women universal GBS screening and IAP.

Term babies in our study, diagnosed with EOGBS, were promptly treated and all survived. Case fatality in preterm babies with EOGBS was 0.01/1000 preterm live births. Reduction in mortality since the 1970s, which was then as high as half of both term and preterm babies with EOGBS, is thought to be largely due to advances in maternity and neonatal care [14].

Limitations

Like many before, this study underestimates the true burden of EOGBS because it focuses on live born babies with culture-proven events, missing stillbirths and cases of clinical infection. Due to the rarity of EOGBS small case numbers prevented a more in- depth analysis; particularly of screened versus non-screened pregnancies. We were unable to accurately record incidences of intrapartum fever and some other risk factors; a previous baby with EOGBS or bacteriuria in the index pregnancy and we were unable to access information for babies who were term and otherwise well but may have received

antibiotics because of deemed inadequate chemoprophylaxis. Our study uses a retrospective ascertainment of screening results, which may suffer from reporting bias. The high rate of undocumented GBS results in the database is a limitation and may be due, in part, to substandard data entry.

Strengths

This retrospective study covering 11 years includes regional, rural and some remote birthing populations using a range of birthing options; from a metropolitan unit, to smaller regional units, birth centres and planned homebirth. Our study is generalisable to other jurisdictions with similar demographics and can be replicated in areas where researchers are able to collect pathology data and link these with a maternity and neonatal database such as ObstetriX or eMaternity.

Future direction

Three decades ago, IAP was introduced as a safe but interim solution to manage GBS risk [35]. Mortality rates since the 1970s have dropped markedly and EOGBS is now a rare and treatable infection, even in babies who are not exposed to IAP as this study and others report [35]. Since the introduction of universal screening and IAP, the number of women and babies exposed to prophylactic antibiotics in labour for GBS risk has more than doubled (12% to 30%) in some jurisdictions. Most term babies exposed to IAP have negligible risk of succumbing to the infection and are therefore, arguably, exposed to IAP unnecessarily. Intrapartum antibiotic provision is not without its own set of risks. There is emerging speculative data associating intrapartum antibiotics with adverse health issues later in life [5-9]. Interventions of any kind are likely to have wider effects than acknowledged by evaluators. For ethical and methodological reasons, it is imperative that any harmful effects of interventions as well as their short-term benefits, are considered, analysed and, if relevant, alleviated. Furthermore, if universal screening continues to be recommended and used widely, high quality research to assess the relative benefits and risks of a universal screening protocol versus a risk-based approach is warranted. This will provide clinicians, women, and their families' access to high-quality evidence to enable them to discuss and make decisions about the risks they are prepared to embrace.

The potential for a maternal GBS vaccination to reduce the risk of EOGBS in term babies

is supported by studies, which demonstrate that higher maternal serotype-specific antibody concentrations are associated with a lower risk of EOGBS. However, performing field trials on protein-conjugated GBS vaccines during pregnancy is not without its challenges, with large efficacy trials versus limited immunogenic studies being considered once a correlate of protection is universally identified and accepted [44].

Apart from vaccination, there may be other methods of reducing missed opportunities to provide IAP to those who would most benefit while reducing the number of mothers and babies unnecessarily exposed to IAP. Accurate and rapid methods of intrapartum GBS testing, aimed at a specific cohort of women who experience ROM without timely onset of labour, may assist in the identification of GBS status and assist women and clinicians in subsequent GBS risk management. To ensure optimum equity in maternity care, such a test should ideally be available to women accessing a variety of birth settings. In our LHD this proposal would require a point-of-care molecular test. Logistical and expense considerations may be challenging due to the wide variety of birth settings in our region. Point-of-care testing, however, has been offered for some time at a large metropolitan hospital in an adjoining LHD and may reduce the number of women and babies at term gestation unnecessarily exposed to intrapartum antibiotics.

Following presentation of this study, decision makers in our LHD have resolved not to increase the dose of prophylactic antibiotics for maternal GBS colonisation due to our very low and stable term EOGBS rates. This HNELHD will therefore not be in line with the current Australian therapeutic guidelines and the CDC recommendations for prophylaxis, which we believe, warrant review. Based on the results of this study we, along with others strongly recommend that primary attention to risk factors for EOGBS infection and timely prophylaxis or antibiotic treatment as indicated would be a more effective strategy for reduction of EOGBS in both preterm and term groups rather than the universal screening approach which failed to identify all infants at risk.

References

1. Edmond K, Kortsalioudaki C, Scott S, Schrag S, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet. 2012;379(9815):547-56.
2. Centers for Disease Control and Prevention. Emerging Infections Program Network. Group B Streptococcus. Active Bacterial Core Surveillance Report. 1997.
3. Centers for Disease Control and Prevention. Emerging Infections Program Network. Group B Streptococcus. Active Bacterial Core Surveillance Report. 2016.
4. Van Dyke M, Phares C, Lynfield R, Thomas A, Arnold K, Craig A. Evaluation of universal antenatal screening for group B streptococcus. New Eng J Med. 2009;360:2626-36.
5. Butel MJ, Waligora-Dupriet AJ, Wydau-Dematteis S. The developing gut microbiota and its consequences for health. J Dev Orig Health Dis. 2018:1-8.
6. Azad MB, Konya T, Persaud RR, Guttman DS, Chari RS, Field CJ, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. BJOG. 2015;123:983-93.
7. Neuman H, Forsythe P, Uzan A, Avni O, Koren O. Antibiotics in early life: dysbiosis and the damage done. FEMS Microbiol Rev. 2018;42(4):489-99.
8. Örtqvist A, Lundholm C, Halfvarson C, Ludvigsson J. Fetal and early life antibiotics exposure and very early onset inflammatory bowel disease: a population-based study. Gut. 2019;68(2).
9. Miller JE, Wu C, Pedersen LH, de Klerk N, Olsen J, Burgner DP. Maternal antibiotic exposure during pregnancy and hospitalization with infection in offspring: a population-based cohort study. Int J Epidemiol. 2018;47(2):561-71.

10. Gilbert G, Hewitt M, Turner C, Leeder S. Epidemiology and predictive values of risk factors for neonatal group B streptococcal sepsis. Aust N J Z Obstet Gynaecol. 2002;45(5):497-503.
11. Heath P, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol. 2007;21:411-24.
12. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines MMWR 2010;59(1):1-36.
13. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Maternal Group B Streptococcus in pregnancy: screening and management .C-Obs 19. 2016.
14. UK National Screening Committee. Screening for Group B streptococcal infection in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2012.
15. Schrag S, Zell E, Lynfield R, Roome A, Arnold K, Craig A, et al. A population- based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. New Eng J Med. 2002;347:233-40.
16. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines. MMWR Recomm Rep 2010;59:1– 36. 2002;51(1):1-36.
17. Garland S, Fliegner J. Group B streptococcus (GBS) and neonatal infections: The case for intrapartum chemoprophylaxis. Aust N J Z Obstet Gynaecol. 1991;31(2):110-22.
18. Queensland Government department of health. Queensland clinical guidelines. Early onset group B streptococcus disease. 2015.
19. Maternal Group B Streptococcus (GBS) and minimisation of neonatal early- onset GBS sepsis. Minstry of Health. NSW government. 2016.
20. Darlow B. Early-onset neonatal Group B Streptococcal (GBS) disease in New Zealand: results of a two year surveillance study. Paediatr Child Health. 2013;24(49).

21. Darlow BA, Voss L, Lennon DR, Grimwood K. Early-onset neonatal group B streptococcus sepsis following national risk-based prevention guidelines. Aust N Z J Obstet Gynaecol. 2016;56(1):69-74.
22. Grimwood K, Darlow BA, Gosling IA, Green R, Lennon DR, Martin DR, et al. Early-onset neonatal group B streptococcal infections in New Zealand 1998- 1999. Paediatr Child Health. 2002;38(3):272-7.
23. Kurz E, Davis D. Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review. JBI Database System Rev Implement Rep. 2015;13(3):206-46.
24. Seale AC, Blencowe H, Bianchi-Jassir F, Embleton N, Bassat Q, Ordi J, et al. Stillbirth With Group B Streptococcus Disease Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S125-S32.
25. Chen JC, Jenkins-Marsh S, Flenady V, Ireland S, May M, Grimwood K, et al. Early-onset group B streptococcal disease in a risk factor-based prevention setting: A 15-year population-based study. Aust N Z J Obstet Gynaecol. 2018:1-8.
26. Seedat F, Taylor-Phillips S, Geppert J, Stinton C, Patterson J, Brown C, et al. UK National Screening committee (UK NSC). Universal antenatal culture-based screening for maternal GBS carriage to prevent EOGBS disease. Review update. 2016.
27. Angstetra D, Ferguson J, Giles W. Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. A N Z J Obstet Gynaecol. 2007;47:378-82.
28. Antibiotic expert groups. Therapeutic guidelines: antibiotic version 13. Melbourne: Therapeutic guidelines limited; 2006.
29. Antibiotic expert groups. Therapeutic guidelines: antibiotic version 14. Melbourne: Therapeutic guidelines limited; 2010.
30. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococal Disease. MMWR 1996;45(RR-7):1-24.

31. National Institute for Health and Care Excellence. Recognising risk factors for infection during pregnancy, labour and birth. 2014.
32. Lin F, Weisman L, Azimi P, Young A, Chang K, Cielo M, et al. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. Pediatr Infect Dis J. 2011;30(9):759-63.
33. Berardi A, Lugli L, Rossi C, China M, Chiossi C, Gambini L, et al. Intrapartum antibiotic prophylaxis failure and group-B streptococcus early-onset disease. J Matern Fetal Neonatal Med. 2011;24(10):1221-4.
34. Fairlie T, Zell ER, Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. J Obstet Gynecol 2013;121(3):570-7.
35. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016;138(6).
36. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005- 2008. Pediatr Infect Dis J. 2011;30(11):937-41.
37. Braye K, Ferguson J, Davis D, Catling C, Monk A, Foureur M. Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B Streptococcal infection: An integrative review. Women Birth. 2018;31(4):244-53.
38. Bekker V, Bijlsma MW, van de Beek D, Kuijpers TW, van der Ende A. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. Lancet Infect Dis. 2014;14(11):1083-9.
39. Sheehy A, Davis D, Homer CS. Assisting women to make informed choices about screening for Group B Streptococcus in pregnancy: a critical review of the evidence. Women Birth. 2013;26(2):152-7.

40. Verani J, Spina N, Lynfield R, Schaffner W, Harrison L, Holst A, et al. Early- onset Group B Streptococcal disease in the United States: potential for further reduction. Obstet and gynecol. 2014;123(4):828-37.
41. Berardi A, Rossi C, Bacchi Reggiani ML, Bastelli A, Capretti MG, Chiossi C, et al. An area-based study on intrapartum antibiotic prophylaxis for preventing group B streptococcus early-onset disease: advances and limitations. J Matern Fetal Neonatal Med. 2017;30(14):1739-44.
42. Vergnano S, Embleton N, Collinson A, Menson E, Bedford Russell A, Heath P. Missed opportunities for preventing group B streptococcus infection. Arch Dis Child Fetal Neonatal Ed. 2010;96:F72-3.
43. Kwatra G, Cunnington M, Merrall E, Adrian P, Ip M, Klugman KP, et al. Prevelance of maternal colonisation with group B streptococcus: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:1076-84.
44. Russell NJ, Seale AC, O'Driscoll M, O'Sullivan C, Bianchi-Jassir F, Gonzalez- Guarin J, et al. Maternal Colonization With Group B Streptococcus and Serotype Distribution Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S100-S11.
45. Seedat F, Geppert J, Stinton C, Patterson J, Freeman K, Johnson SA, et al. Universal antenatal screening for group B streptococcus may cause more harm than good. BMJ. 2019;364:l463.

Chapter 5

Antibiotic prophylaxis for women who screen positive for group B streptococcal colonisation: Clinician compliance with guidelines

Chapter preface

The study presented in Chapter 5 has been submitted to the journal Midwifery and is under review and is presented here in its final draft format.

Midwifery was chosen as it is a leading international journal specialising in midwifery and maternal health. The journal provides an international, interdisciplinary forum for the publication, dissemination and discussion of advances in evidence, controversies (such as GBS management) and current research. As *Midwifery* promotes continuing education through publication of scholarly research, I felt a cohort study describing the practical application of current GBS management in the journal *Midwifery* would enable exposure to midwives worldwide and therefore provide a forum for discussion, debate and generalisation of this study design to other international jurisdictions. The manuscript employs the *Midwifery* journal output style and formatting as directed by the journal. References for this manuscript are also presented in the 'Thesis references' section using the university's recommended referencing style (*Harvard_UTS*).

Abstract

Objectives

To assess adherence to guidelines which state intrapartum antibiotic prophylaxis (IAP) should be provided at or greater than four hours before birth to women whose babies are at risk of early-onset group B streptococcal infection (EOGBS). To examine associations between receipt of IAP and parity, onset of labour, time, place and mode of birth.

Design

A retrospective cohort design was employed.

Method

The study population was drawn from 4,098 women who had 4,100 babies in one Australian birth unit and its associated birth centres in 2016. According to local guidelines for the prevention of EOGBS infection, 3,808 women were eligible for universal GBS screening, with 526 women identified as GBS positive. To achieve sufficient power to provide a 5% margin of error and a 95% confidence interval, a sample of 223/526 women, positive for GBS was required for analysis. The database and medical records of 223 randomly selected women, positive for GBS, and their babies were interrogated to identify general characteristics and data specific to GBS management and were entered into Microsoft Excel and SPSS v.25 for descriptive and correlational statistical analysis.

Results

Of the 223 women, 84% (n=188) received some IAP with 79% of the 188 (176/188) receiving prophylaxis with benzylpenicillin. Prophylaxis that was in accord with local guidelines was received by 31% (54/176). The odds of receiving intrapartum antibiotic prophylaxis in accord with local guidelines were three times higher among primiparous women compared to multiparous women ($p<0.001$, OR=3.4, 95% CI, 1.7, 6.7) and were three times higher among women experiencing induction of labour compared to women who commenced labour spontaneously ($p<0.001$, OR=3.4, 95% CI, 1.8, 6.3).

Conclusions

In this setting, less than a third of women who had a documented positive GBS screening result received intrapartum antibiotic prophylaxis in accord with local guidelines. Therapeutic levels of antibiotic prophylaxis may not have been achieved. Despite this, the overall rate of EOGBS infection was low at 0.19/1000 live births in our local health district from 2006-2016, with no events identified in 2016. Women having a first baby and/or experiencing induction of labour were significantly more likely to receive IAP in accord with local guidelines than multiparous women and/or women who commenced labour spontaneously.

There is a need to understand other factors in this population that may be contributing to protection from EOGBS.

Implications for practice

The results of this cohort study should be used to reconsider guidelines in our local health district and jurisdictions that have a similar approach to the medical management of GBS risk. An alternative or a more nuanced method of selection and administration of IAP for women whose babies are deemed at risk of this infection needs to be developed.

Introduction/background

Early-onset group B streptococcus (EOGBS) infection is a high impact, low incidence event. Maternal group B streptococcal (GBS) colonisation is common. In 2016 an estimated global mean prevalence of vaginal colonisation with this bacterium was ~1 in 5 (Kwatra et al. 2016). However, neonatal infection resulting from maternal colonisation is uncommon, estimated at ~1 in 2,326 when a woman has been exposed to any IAP and ~1 in 1,333 when a woman has had no exposure to the intervention (Edmond et al. 2012). It is not entirely clear why only a minority of babies become infected with EOGBS despite relatively high maternal colonisation rates. Although international and local guidelines exist for the management of neonatal and infant infection risk, research has revealed these guidelines are poorly implemented (Berardi et al. 2017; Le Doare et al. 2017; Schrag et al. 2016).

Australian GBS guidelines

Australian GBS guidelines were developed following publication of a large retrospective cohort study undertaken in Melbourne, Australia (Garland & Fliegner 1991). This study revealed universal screening (at 28 weeks gestation), reduced the rate of EOGBS compared with an unscreened group. As a result of this early study, universal screening for GBS risk was recommended, predating the first US Centre for Disease Control and Prevention (CDC) guideline recommendations of 1996 (CDC 1996).

Although Australia has no national policy, and guidelines around the country vary, most jurisdictions have taken up this recommendation and continue to offer universal screening

(at 35-37 weeks) to select women whose babies may benefit from IAP for GBS risk (Sheehy, Davis & Homer 2013).

In addition to the study by Garland and colleagues, Australian GBS guidelines were subsequently influenced by the CDC which initially recommended selecting women who may benefit from IAP by either a universal culture based screen or a method based on risk factors (CDC 1996). The next iteration by the CDC on this topic recommended a universal screening approach with consideration of certain antenatal risk factors (CDC 2002). This change in recommendation followed a large USA based cohort study that showed the risk of EOGBS was significantly lower among babies of women screened using a universal approach than among those in the risk-based group (adjusted relative risk, 0.46, 95% CI, 0.36 to 0.60) (Schrag et al. 2002).

More recently the Australian Therapeutic Guidelines (Antibiotic expert group 2014) have had an impact on GBS management guidelines in Australia. In 2000 these guidelines proposed a regime that differed from the CDC, by recommending benzylpenicillin 1.2g IV and then 600mg four hourly until birth, as prophylaxis for GBS risk (Antibiotic expert group 2000). This recommendation remained until 2014 when the Australian Therapeutic Guidelines increased the dose of benzylpenicillin to 3g followed by 1.8g, 4-hourly until birth (Antibiotic expert group 2014). The change in recommendation was introduced in order to align with the CDC (CDC 1996, 2002, 2010) and other international guidelines (Royal College of Obstetricians and Gynaecologists (RCOG) 2017).

Our local health district (LHD) GBS guideline, issued in 2003 and current in 2016 states, "to achieve prophylaxis, IAP must be administered at least four hours prior to delivery. [The] antibiotic of choice [in the local health district] is IV benzylpenicillin 1.2g initially, then 600mg IV four hourly until delivery" (Johnson et al. 2001). The local guideline has now been updated, but unlike the majority of jurisdictions in Australia, the 1.2g benzylpenicillin regime remains (Hunter New England Local Health District 2018).

Pharmacology and pharmacokinetics

Benzylpenicillin, also known as Penicillin G, has become the mainstay of prophylaxis against GBS. It is known to be a (usually) readily available bactericidal against GBS. Although, antibiotic prophylaxis against GBS is reported as effective, the

pharmacokinetics of the drug in relation to reduction of EOGBS is unclear. The reduction in infection rates when IAP is administered could be caused by antibiotic loading of the fetus and amniotic fluid, by eradication of vaginal colonisation, or by a combination of both. Penicillins are known to enter both the fetus and amniotic fluid readily and also to decrease GBS vaginal colony counts which may partly explain the effectiveness of chemoprophylaxis. However, despite antibiotic loading of fetal and amniotic fluid compartments within minutes; the time taken to achieve optimal fetal prophylactic benefit is unclear (McNanley et al. 2007).

Due to the dearth of robust research on this topic, recommended optimal timeframes for a therapeutic dose of IAP vary. Most guidelines, including the guideline used during our study period, recommended the first dose of intravenous antibiotic should be given at least four hours prior to birth, and then repeated at 4-hourly intervals until birth, when necessary. Effectiveness falls to 43% if given <4 hours prior to birth according to one large observational study involving 7,691 births, conducted in the USA (Fairlie, Zell & Schrag 2013). In contrast, an earlier, but similar study stated that giving penicillin at least two hours before birth is sufficient to reduce neonatal colonisation (Lin et al. 2011) and therefore the likelihood of EOGBS. Early observational evidence suggests that benzylpenicillin levels in cord blood exceed the minimum inhibitory concentration for GBS as early as one hour after maternal administration, but it is not known how this relates to maternal colonisation or EOGBS infection (Barber et al. 2008).

Despite minor fluctuations, EOGBS rates in our LHD have not changed significantly over more than a decade. The rate ranged from 0.34/1000 live births in 2006 to 0.1/1000 live births in 2016 with an overall rate for the 11 year period of 0.19/1000 live births (Braye et al. 2019a). We were interested to investigate clinical compliance with current GBS management guidelines in our birth setting which has used a universal approach to screening for GBS risk since 2004 (Angstetra, Ferguson & Giles 2007).

The study had two main objectives: (1) To assess adherence to guidelines for the provision of intrapartum antibiotic prophylaxis for prevention of neonatal early-onset group B streptococcal infection for women colonised with group B streptococcus; (2) To examine associations between receipt of intrapartum antibiotic prophylaxis and parity, onset of labour, time, place and mode of birth.

Methods

Study setting

The setting for this study was a large regional maternity service in New South Wales, Australia. The service includes a major public tertiary referral hospital with ~4000 births annually occurring in a birthing unit (BU), operating theatre (OT) co-located birth centre, and a free-standing birth centre, which also offers homebirth (BC).

Study population

In 2016, 4,098 women had 4,100 pregnancies. These pregnancies resulted in 4,200 babies born in the birth units included in our study. Most women 93% (n=3,808) were eligible for antenatal GBS screening i.e., ≥35weeks gestation, in accord with guidelines at the time; 61% (n=2,322) had a result recorded with 23% (n=526) of women positive for GBS colonisation.

Inclusion criteria and exclusion criteria

Women included in the study were eligible for GBS screening (≥35 week's gestation), birthed in or with the study units in 2016 and were positive for GBS colonisation, together with their live-born babies. Women excluded were those who had an elective caesarean section (CS) and were therefore not eligible for IAP, in accord with local guidelines current in 2016.

Sample size and power

A sample size of 223 was calculated to produce results with a 5% margin of error and 95% confidence interval (CI) (http://www.raosoft.com/samplesize.html 2011). Therefore, a random sample from the 526 women positive for GBS was selected. Each woman in the cohort of 526 was assigned a sequential number. These numbers were then randomised using a Microsoft Excel random number generator. The first 223 women meeting the eligibility criteria were selected as the sample for this study.

Data Collection

Two datasets were obtained for examination; ObstetriX and NSW Health Pathology data.

The study cohort was drawn from a larger dataset used in previous related studies (Braye et al. 2019a; Braye et al. 2019b). Data were de-identified and are available, after ethics clearance, to other researchers from the University of Technology Sydney institutional data repository (Foureur et al. 2019). The ObstetriX database, subsequently superseded by eMaternity, is completed by maternity staff and gathers antenatal, intrapartum and postnatal information on the mother and child. Maternity and neonatal data included time of administration and dose of IAP, parity, gestation at birth, onset and mode of birth, birthweight, five-minute Apgar score, admission to the neonatal intensive care unit (NICU) at birth (≤6 hours after birth) and in the early postnatal period (>6 hours to 48 hours after birth). The second data set obtained from NSW Health Pathology identified all neonatal pathology. Data extraction was undertaken by the first author (KB). Data were entered into an Excel spreadsheet and subsequently, IBM Statistical Package for the Social Science (SPSS), version 25 for further analysis.

Data analysis

Descriptive analysis included frequencies, means and standard deviations (SD). Univariate analysis was conducted on covariates of interest (parity, onset of labour, mode and place of birth) to explore associations. Significant associations and a priori variables of interest were analysed further using an ordered logistic regression for the three-level outcome: (1) IAP in accord with local guidelines, (2) IAP ≥4 hours before birth but not in accord with local guidelines and (3) IAP <4hours before birth. We modelled that IAP was administered in accord with local guidelines, compared to <4hrs before birth and ≥4hrs before birth but not in accord with local guidelines. The effect size of each covariate of interest; parity, onset of labour, place and mode of birth was assessed. Adjusted estimates were expressed as odds ratios with corresponding 95% CI. A significance level of 0.05 was used in all analyses. Missing data were treated as missing observations.

Ethical Approval

The chairperson of the Hunter New England (HNE) Human Research Ethics Committee (HREC) judged that formal ethical approval was not required as our study conformed to the obligations of the provision of privacy and confidentiality of patient data and clinical information, according to the NSW Health records and Information Privacy Act 2002. University of Technology Sydney, HREC, ratified this decision (No. 2014000115). Data

were de-identified and individual consent was not required.

Results

Of 3,808 eligible women, 63% (n=2,569) were reported as screened, 96% of these (n=2,322) had a GBS result documented. Of these, 526 had a positive result recorded giving a maternal GBS colonisation rate of 23%. A sample of the 526 women positive for GBS was randomly selected resulting in a cohort of 223 women, detailed in Table 5.1.

Table 5.1 - Sample characteristics of ^eligible screened women, positive for GBS, and their babies

Women	Eligible screened women, positive for GBS	Randomly selected sample of eligible screened women positive for GBS
	N = 526	N = 223
Maternal age	Mean 29 (SD 5.54)	Mean 30 (SD 5.95)
Primiparous*	144 (26%)	79 (35.4%)
Mother Aboriginal or Torres Strait Islander	42 (8%)	22 (9.9%)
Smoking at booking	78 (14.8%)	36 (16.1%)
No alcohol in pregnancy	519 (96%)	271 (92%)
Spontaneous vaginal birth	357 (66%)	167 (74.9%)
Babies		
Gestation	Mean 39w (SD 1.63) Min 35w, Max 42.1w	Mean 40w (SD 1.33) Min 35w, Max 41.6w
Eligible term**	501 (95%)	215 (90%)
Eligible preterm***	25 (5%)	8 (9%)
Birth weight	Mean 3,491 (SD 510.32) Min 2,090, Max 4,830	Mean 3,525 (SD 528.17) Min 2,170, Max 4,430
5 min APGAR ≥ 7	26 (5%)	17 (7.6%)
No resuscitation required	434 (82.5%)	174 (78%)
Admission to NICU# (birth)##	40 (8%)	18 (8.1%)
Admission to NICU (postnatal)###	34 (6%)	13 (5.8%)

^Eligible women = women whose pregnancy reaches 35 weeks gestation, *Primiparous = first pregnancy, **Eligible term = ≥37 weeks gestation, ***Eligible preterm =≥35 weeks and <37 weeks gestation, #NICU=neonatal intensive care unit, ##Admission to NICU (birth) = ≤ 6 hours of birth, ###Admission to NICU (postnatal) = >6, up to 48 hours post birth, min = minimum, max = maximum, SD = standard deviation

The random sample of 223 included 35 (16%) women who were positive for GBS but who received no IAP, as detailed in Table 5.2. The majority of women (79%) who did receive IAP were given benzylpenicillin. The remaining 12 women received clindamycin (n=1), cephalothin (n=7), or chlorhexidine douche (n=4). As these modalities use a different timeframe for administration, these 12 women and their babies were excluded from further calculations of IAP provision. The 176 women who received benzylpenicillin for IAP were the focus of the remaining analysis.

Table 5.2 - Descriptive analysis of IAP provision and timing of IAP relative to birth

	N=223	100%	Missing data
Any IAP (Women who received benzylpenicillin)	188 (176)	84.3% (78.9%)	0
No IAP	35	15.6%	0
	N=176	100%	
IAP in accord with local guidelines	54	31.2%	3
IAP ≥ 4 hours before birth but not in accord with local guidelines	43	24.4%	2
IAP < 4 hours before birth	77	44.3%	2

IAP in accord with local guidelines=benzylpenicillin given at least 4 hours before birth and then 4-hourly until birth, when necessary, IAP= intravenous antibiotic prophylaxis

Of the 176 women who received benzylpenicillin, 64% birthed in the tertiary hospital birthing unit, 15% in an associated birth centre and 21% experienced vaginal birth in the operating theatre. Analysis of parity revealed 39% of women were primiparous and 61% multiparous. All 176 women received an initial dose of 1.2g of benzylpenicillin and 51% received repeat dose(s) of 600mgs (IV), as recommended in the GBS management guidelines of the LHD and illustrated in Figure 5.1.

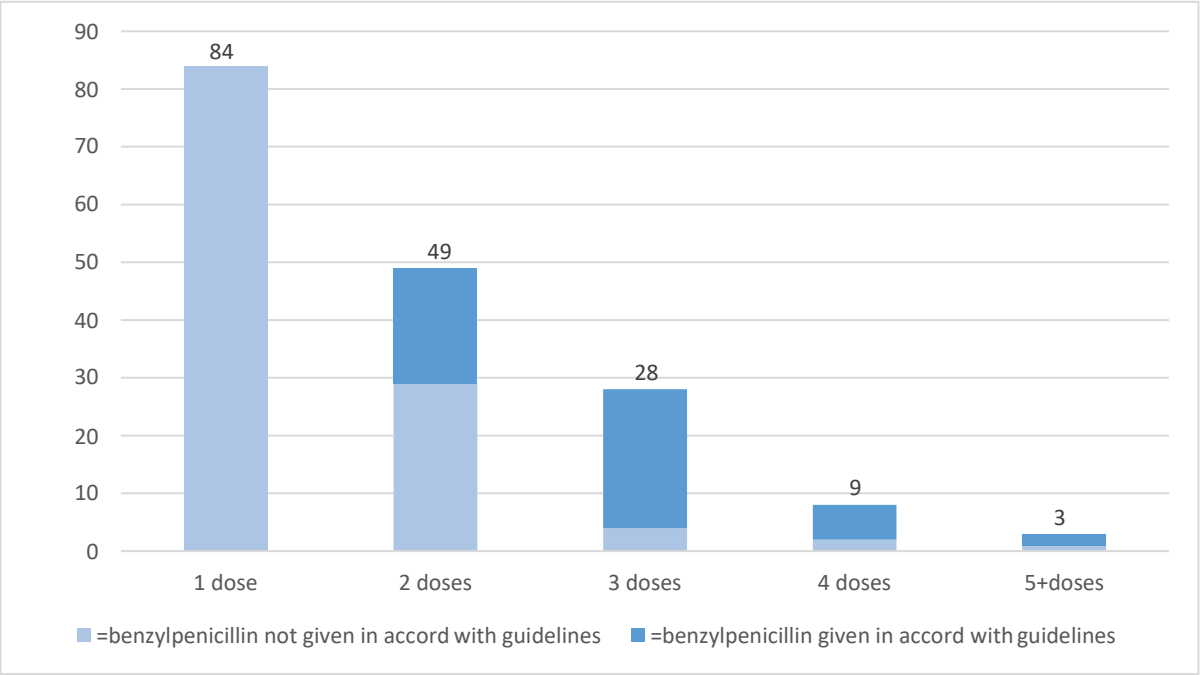


Figure 5.1 - Number of benzylpenicillin doses given in accord with guidelines

The majority of women (n=84) received one dose of IAP however none of these women received IAP in accord with guidelines as shown in Figure 5.1. The most common reason for non-compliance was a time frame of <4 hours between administration of IAP and birth (n=73/84). The remaining 11 women were still in labour at four hours after the initial dose but did not receive a repeat dose as recommended in the guidelines. Box 1 provides examples of compliance and non-compliance of IAP provision.

Guideline compliance	Guideline non-compliance
A labour where a woman had IAP and then birthed four hours later, complies with the guideline A labour where a woman had IAP, then a second dose four hours later and then birthed two hours after that, complies with guidelines	A labour where a woman had IAP and then birthed <4 hours after administration, does not comply with the guideline A labour where a woman had IAP and then a follow up dose 6 hours later, instead of 4 hours later, does not comply with guidelines

Box 5.1 - Examples of clinician's compliance or non-compliance with GBS guideline

Figure 5.1 illustrates that fewer women received IAP in accord with guidelines if they had one or two doses, but women given three or more doses were more likely to get IAP in accord with guidelines.

As indicated in Table 5.2, provision of benzylpenicillin in accord with local guidelines occurred for one third of our cohort. A further quarter received IAP ≥ 4 hours before birth, but not in accord with local guidelines and the remainder, just under half, received IAP <4 hours before the birth. Just over a quarter of the cohort (27%) received IAP, not only < 4 hours before birth but under two hours between administration and birth.

Finally, just over one third of women (35.7%) received an initial dose of IAP within one hour of admission for labour, median 1 hour, 12 minutes, standard deviation (SD) 8 hours, 20 minutes (these data are not shown separately in Table 5.2).

Table 5.3 details univariate descriptive analysis of provision of IAP in relation to variables of interest. The table shows that fewer multiparous women received IAP in accord with local guidelines compared with primiparous women although this did not reach significance (p=0.52, OR=1.9, 95% CI, 0.1, 3.7). However, significantly fewer women commencing labour spontaneously received IAP in accord with local guidelines compared with women who experienced induction of labour (p=0.007, OR= 2.5, 95% CI, 1.3, 4.8).

Table 5.3 - Variables in relation to provision of IAP in accord with local guidelines

Number of women	Parity and IAP in accord with local guidelines	Overall	Primiparous	Multiparous
173	Yes	54 (31.2%)	27 (50%)	27 (50%)
	No	119 (68.7%)	41 (34.5%)	78 (65.5%)
Number of women	Onset of labour and IAP in accord with local guidelines	Overall	Spontaneous	Induced
169	Yes	52 (30.8%)	20 (38.5%)	32 (61.5%)
	No	117 (69.2%)	71 (60.7%)	46 (39.3%)
Number of women	Place of birth and IAP in accord with local guidelines	Overall	Birth Unit	OT	Birth Centre
173	Yes	54 (31.2%)	39 (72.2%)	12 (22.2%)	3 (5.6%)
	No	119 (68.7%)	71 (59.7%)	24 (20.2%)	24 (20.2%)
Number of women	Mode of birth and IAP in accord with local guidelines	Overall	Spontaneous vaginal birth	Caesarean birth	Instrumental birth
173	Yes	54 (31.2%)	39 (72.2%)	11 (20.4%)	4 (7.4%)
	No	119 (68.7%)	88 (73.9%)	19 (16%)	12 (10.1%)

IAP= intrapartum antibiotic prophylaxis, OT= operating theatre, local guidelines=1.2g of IAP initially, followed by 600mg 4-hourly until birth, when necessary

An ordered logistic regression model showed that parity and onset of labour were highly significant. The adjusted odds of receiving IAP in accord with local guidelines was three times higher among primiparous women compared to multiparous women ($p<0.001$, OR =3.4, 95% CI, 1.7, 6.7%) and three times higher among women experiencing IOL

compared to women who commenced labour spontaneously (p<0.001, OR=3.4, 95% CI, 1.8, 6.3%).

Neonatal Outcomes

Nearly all (98%) of the babies in the total sample of 223 had an Apgar ≥7 at five minutes, 87% had an Apgar of ≥9 at five minutes. A total of 31 (14%) babies were admitted to neonatal intensive care unit/special care unit (NICU). Most (n=18) within six hours of birth and a further 13 babies > 6 and up to 48 hours post birth. No babies admitted and cared for in the NICU were diagnosed with EOGBS over the study period.

Of the total cohort of 4,200 babies born in the included birth units in 2016, there were no babies diagnosed with EOGBS although three babies, whose mothers were GBS negative, were found to have sepsis due to other organisms. Two babies diagnosed with culture proven EOS were <30 weeks gestation. One was diagnosed with *E. coli* and the other with *Haemophilus influenzae*. The third, a term baby was diagnosed with an infection due to *Enterococcus faecalis*. The mothers did not receive IAP. The three babies were discharged home; short and long-term sequelae were not sought in this study. Figure 5.2 provides an overview of the expected and actual adherence to guidelines in this cohort and provides a framework for the discussion of the findings.

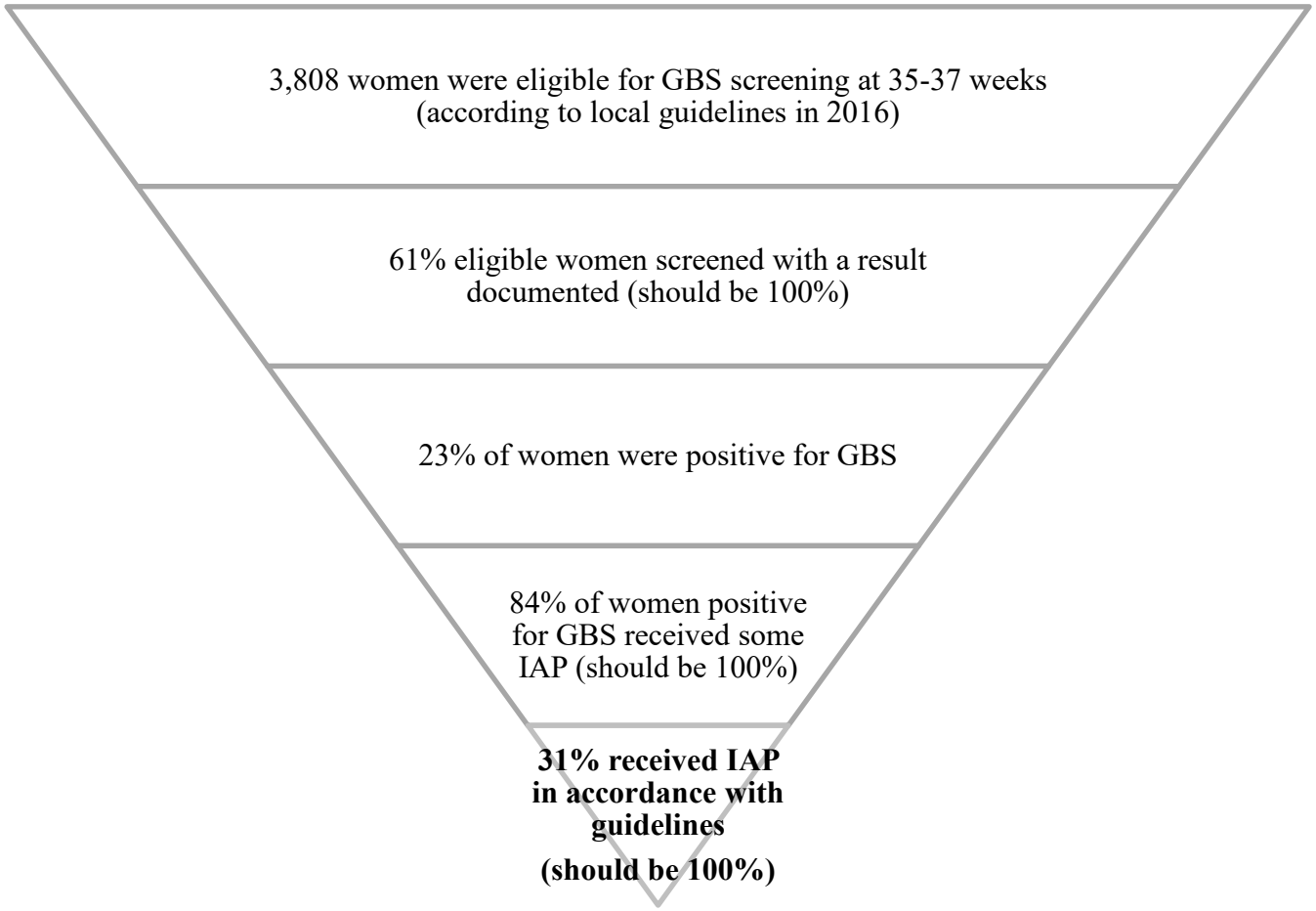


Figure 5.2 - Overview of stepwise clinician's adherence to guidelines in the study population

Discussion and conclusion

Most women in the study cohort (93%, n=3,808) were eligible for antenatal GBS screening (i.e., they had reached ≥35weeks gestation, in accord with local health service guidelines in 2016). However only 61% (n=2,322) had a result recorded. As indicated in Figure 5.2, these findings reveal a failure of adherence to the recommended guidelines since the expectation of universal screening is that 100% of eligible women will be screened. An alternative explanation for the low rate of documented screening results could be that a minority of women declined to be screened, or that screening occurred but results were not recorded in the database. Despite 39% of women not having a screening result recorded, the percentage of women positive for GBS in our total cohort (23%) is

consistent with an earlier study in our LHD (Angstetra, Ferguson & Giles 2007) and is in accord with findings from studies in similar jurisdictions internationally (CDC 2010; Kwatra et al. 2016; Seedat et al. 2016). It is reasonable to speculate therefore that the rate of GBS in the remainder of the cohort would also reach ~23%.

Since the expectation is that all women positive for GBS will receive IAP, a further failure of clinician's adherence to the guidelines was demonstrated in this cohort as only 84% of women positive for GBS received IAP, in some form. The greatest concern however, is shown in the final step of Figure 5.2. This step illustrates the expectation that 100% of women who received benzylpenicillin for IAP would be administered the drug in accord with guidelines with the expectation that therapeutic dose(s) of antibiotics would be achieved. In our cohort we found that only 31% of eligible women were provided IAP in accord with guidelines. Almost half of eligible women, positive for GBS, did not get IAP ≥ 4 hours before birth and almost two-thirds of these women had <2 hours between IAP provision and birth. Therefore, IAP was often provided in a time-frame which may have resulted in sub-therapeutic prophylaxis (Fairlie, Zell & Schrag 2013; Johnson et al. 2001). Sub-therapeutic GBS prophylaxis means that babies may not have received the benefit of the intervention but, at the same time, were exposed to the risks of antibiotics.

It is clear in our study population, clinician compliance with local guidelines was sub-optimal. However, many of these so-called "missed opportunities" were not preventable. For example, none of the 47% of women administered only one dose of benzylpenicillin, received this dose of IAP in accord with guidelines. The majority of these women (97%) birthed within four hours of receiving IAP. In our study, lack of time between admission for labour and time of birth was the most common reason for clinician's non-compliance with guidelines. This finding would particularly impact multiparous women, who tend to have shorter labours than their primiparous counterparts and are more likely to commence labour spontaneously. Our adjusted analysis reflected this as the odds of receiving IAP in accord with guidelines was three times higher for primiparous women and/or women having induction of labour.

Inability to administer repeat doses of IAP at four-hourly intervals was also a reason for non-compliance (possibly due to a high level of acuity in the birth unit). Both the issue of lack of time between admission and birth and the inability to administer repeat doses 4-

hourly are not easily resolved and, we believe, are largely a consequence of unrealistic guidelines rather than clinical error.

Findings of this study strongly suggest GBS guidelines with recommendations for optimal duration of IAP provision are not able to be met by clinicians in this setting and must be reconsidered. However, estimates of effective prophylaxis are poorly researched in clinical trials. Evidence is limited to observational studies, with researchers unable to agree on an optimal therapeutic timeframe (Braye et al. 2018; Fairlie, Zell & Schrag 2013; Illuzzi & Bracken 2006; Johnson et al. 2001; Lin et al. 2011).

Evidence for offering IOL to women with release of membranes (ROM) and positive for GBS is stronger (Oddie & Embleton 2002; Seaward et al. 1998). Therefore, the high rate of IOL (46%) in this cohort was expected since, women positive for GBS with ROM but not in labour, were offered IOL within 24 hours of confirmed ROM, in accord with the 2016 local guidelines. In comparison, the overall induction rate in HNELHD in 2016 was 34% (n=3,696) (Centre for Epidemiology and Evidence 2016).

Women positive for GBS with inadequate provision of IAP, (i.e. two-thirds of women and their babies in our sample), should have been recommended to remain in hospital for 24 hours, in accord with local guidelines so that their baby could be observed for signs of infection. It is not known how many women and babies in our study population did remain in hospital however, it is likely that the recommendation affected mostly well women who laboured quickly, birthing their second or subsequent baby and who would typically request early discharge. Since current modelling has suggested 99.8% of babies born to mothers positive for GBS will not be affected by the infection, (Seedat et al. 2019) the recommendation to remain in hospital for neonatal observation is likely to be unnecessary, stressful for families and costly for health services.

No babies in our sample and in the 4,200 births occurring in 2016 in our local hospital and freestanding birth centre, were identified as experiencing EOGBS. In fact, none of the 10 864 babies born in our LHD in 2016 had culture proven EOGBS (Centre for Epidemiology and Evidence 2016) when the global estimated average is 1 in 2,326, when a woman has been exposed to any IAP (Edmond et al. 2012). This raises a number of questions. Could the absence of EOGBS be because, notwithstanding the perceived suboptimal provision of IAP, the 84% of mothers who were provided with some IAP in

our study, actually received a therapeutic dose? Or could there be other factors contributing to our low rate of culture-confirmed EOGBS? One explanation is that the babies of the women who were positive for GBS colonisation may never have been at increased risk of EOGBS (Seedat et al. 2019). This is difficult to determine with any surety since it is also possible that a minority of babies may have presented with possible or probable GBS but were culture negative due to circulating antibiotics or sub- optimal culture sampling.

Furthermore, shifts in serotypes and/or decreased virulence of the GBS bacteria may have occurred. Population differences in exposure to GBS, a natural increase in maternal immunity, and/or a decrease in fetal/neonatal susceptibility may also play a role in low infection rates (Kwatra et al. 2016; Ribet & Cossart 2015). We suspect the low incidence of EOGBS in term babies in our LHD cannot be exclusively ascribed to the protocol of offering all pregnant women reaching 35 weeks gestation, universal GBS screening, since this does not occur. Nor can it be ascribed to around 30% of GBS colonised women being provided with appropriate IAP for GBS risk since this similarly does not occur (Braye et al. 2019b).

Intrapartum antibiotic prophylaxis carries risk for mother and baby. Risks include a rare chance of maternal anaphylaxis, increased medicalisation of labour and the neonatal period and the possibility of infection with antibiotic-resistant organisms. An important addition to the established risks of IAP management for GBS risk is the potential for adverse health outcomes for the baby due to microbial dysbiosis at birth. Contemporary studies show a correlation between dysbiosis of the baby's founding microbiome and provision of antibiotics. A 2019 systematic review found IAP was associated with profound dysbiosis of the intestinal microbiota of infants by diminishing beneficial commensals early in life (Zimmermann & Curtis 2019). Contemporary research has reported adverse health associations with IAP such as obesity, allergy, atopy and inflammatory bowel disease (Azad et al. 2015; Corvaglia et al. 2012; Le Doare et al. 2018; Mueller et al. 2015; Stearns et al. 2017) although long-term consequences of microbial dysbiosis at birth remain unclear (Koebnick et al. 2019). Further research is therefore needed into the potential adverse health effects of giving so many women and their babies, most of whom are healthy, potentially sub-optimal IAP which does not comply with guidelines, and which may not provide the alleged benefits, for an infection that is rare.

Limitations

Retrospective observational cohort studies have inherent risk of bias, as they interrogate historical data, in our case entered by clinicians at the point of care. In our study, certain data fields may have been incomplete in the ObstetriX database since midwives need to return to the GBS data field when a culture is taken and then again when a result is known. We feel there is potential to improve the completeness of GBS data by ensuring mandatory completion and update of GBS data fields after results become available. Our randomly selected sample of 223 women and babies included significantly fewer primiparous than multiparous women and there was a high rate of induction of labour. These differences may have affected clinician compliance (missed opportunities) with GBS guidelines as multiparous women tend to be more advanced in labour than primiparous women on admission to the birth unit and their labour is often shorter and of spontaneous onset (Centre for Epidemiology and Evidence 2016).

Strengths

The data underlying the results presented in this study are available from the University of Technology Sydney Institutional Data Repository. Access to these data enable researchers to undertake secondary analysis using cleaned and de-identified electronic records. This cohort study is generalisable to other jurisdictions wishing to assess their own maternity and pathology data sets. Our results will assist our LHD and others in Australia and nationally, to assess the compliance of IAP provision for maternal GBS colonisation to answer the question, are we doing more harm than good?

Recommendations

Research to establish why a small minority of babies become infected with GBS despite up to 30% of mothers being colonised, could help target GBS management.

Jurisdictions using universal screening followed by IAP for those women positive for GBS colonisation should carefully re-consider this approach, and due to the lack of evidence supporting its continued use. Guidelines should be updated to reflect findings from this study and others, e.g. Berardi et al. 2017; Bevan et al. 2019; Darlow et al. 2016; Seedat et al. 2019; Singh, Barnes & Isaacs 2019.

References

1. Angstetra, D., Ferguson, J., Giles, W., 2007. Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. Australian and New Zealand journal of Obstetrics and Gyneacology 47, 378-382.
2. Antibiotic expert groups, 2000. Therapeutic guidelines: antibiotic version 11. Therapeutic guidelines limited, Melbourne, Australia.
3. Antibiotic expert groups, 2014. Therapeutic guidelines: antibiotic version 15. Therapeutic guidelines limited, Melbourne, Australia.
4. Azad, M.B., Konya, T., Persaud, R.R., Guttman, D.S., Chari, R.S., Field, C.J., Sears, M.R., Mandhane, P.J., Turvey, S.E., Subbarao, P., Becker, A.B., Scott, J.A., Kozyrskyj, A.L., 2015. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. British journal of Obstetrics and Gyneacology 123, 983-993. 10.1111/1471-0528.13601.
5. Barber, E., Zhao, G., Buhimschi, I., Illuzzi, J., 2008. Duration of Intrapartum Prophylaxis and Concentration of Penicillin G in Fetal Serum at Delivery. Obstetrics & Gynecology 112(2), 265-270.
6. Berardi, A., Rossi, C., Bacchi Reggiani, M.L., Bastelli, A., Capretti, M.G., Chiossi, C., Fiorini, V., Gambini, L., Gavioli, S., Lanari, M., Memo, L., Papa, I., Pini, L., Rizzo, M.V., Zucchini, A., Facchinetti, F., Ferrari, F., 2017. An area- based study on intrapartum antibiotic prophylaxis for preventing group B streptococcus early-onset disease: advances and limitations. Journal of Maternal and Fetal Neonatal Medicine 30(14), 1739-1744. 10.1080/14767058.2016.1224832.
7. Bevan, D., White, A., Marshall, J., Peckham, C., 2019. Modelling the effect of the introduction of antenatal screening for group B Streptococcus (GBS) carriage in the UK. British Medical Journal Open 9(3), e024324. 10.1136/bmjopen-2018-024324.

8. Braye, K., Ferguson, J., Davis, D., Catling, C., Monk, A., Foureur, M., 2018. Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B vStreptococcal infection: An integrative review. Women Birth 31(4), 244-253. 10.1016/j.wombi.2017.10.012.
9. Braye, K., Foureur, M., de Waal, K., Jones, M., Putt, E., Ferguson, J., 2019a. Epidemiology of neonatal early-onset sepsis in one Australian health district 2006-2016. PLoS One 14(4).
10. Braye, K., Foureur, M., de Waal, K., Jones, M., Putt, E., Ferguson, J., 2019b. Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district: 2006- 2016. PLoS One 14(4), e0214295. 10.1371/journal.pone.0214295.
11. Centers for disease control and prevention, 1996. Prevention of Perinatal Group B Streptococcal Disease. Mortality and Morbidity weekly report (MMWR). Recommendations and reports 45(RR-7), 1-24.
12. Centers for disease control and prevention, 2002. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines. Mortality and Morbidity weekly report (MMWR). Recommendations and reports 51(1), 1-36.
13. Centers for disease control and prevention, 2010. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines Mortality and Morbidity weekly report (MMWR). Recommendations and reports 59(1), 1-36.
14. Centre for Epidemiology and Evidence, 2018. New South Wales Mothers and Babies report 2016. Ministry of Health, Sydney,.
15. Corvaglia, L., Legnani, E., Martini, S., Di Gioa, D., Aloisio, I., Oss, M., Biavati, B., Faldella, G., 2012. Intrapartum Antibiotic Prophylaxis in Mothers Gbs- Positive: Effects on Newborn Microbiota. Digestive and Liver Disease 44, S278, http://www.sciencedirect.com/science/article/pii/S1590865812607117.

16. Darlow, B.A., Voss, L., Lennon, D.R., Grimwood, K., 2016. Early-onset neonatal group B streptococcus sepsis following national risk-based prevention guidelines. Australian and New Zealand Journal of Obstetrics and Gynaecology 56(1), 69-74. 10.1111/ajo.12378.
17. Edmond, K., Kortsalioudaki, C., Scott, S., Schrag, S., Zaidi, A.K., Cousens, S., Heath, P.T., 2012. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis.Lancet 379(9815), 547-556. 10.1016/s0140-6736(11)61651-6.
18. Fairlie, T., Zell, E.R., Schrag, S., 2013. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. Journal of Obstetrics & Gynecology 121(3), 570-577. 10.1097/AOG.0b013e318280d4f6.
19. Foureur, M., Braye, K., Ferguson, J., deWaal, K., Putt, E., Jones, M., 2019. [Dataset] Epidemiology of neonatal early-onset sepsis, incidence and outcomes and group B streptococcal screening, intrapartum antibiotic prophylaxis provision in an Australian local health district 2006-2016. University of Technology Sydney.
20. Garland, S., Fliegner, J., 1991. Group B streptococcus (GBS) and neonatal infections: The case for intrapartum chemoprophylaxis. Australian and New Zealand Journal of Obstetrics Gynaecology 31(2), 110- 122.http://www.raosoft.com/samplesize.html, 2011. (Accessed 10/10/2018.
21. Hunter New England Local Health District, 2018. Maternity: Prevention of early-onset GBS sepsis in the newborn at term.
22. Illuzzi, J., Bracken, M., 2006. Duration of Intrapartum Prophylaxis for Neonatal Group B Streptococcal Disease: A Systematic Review. Obstetrics & Gynecology 108(5), 1254-1265.
23. Johnson, J.R., Colombo, D.F., Gardner, D., Cho, E., Fan-Havard, P., Shellhaas, C.S., 2001. Optimal dosing of penicillin G in the third trimester of pregnancy for prophylaxis against group B Streptococcus. American Journal of Obstetrics and Gynecology 185(4), 850-853. 10.1067/mob.2001.117353.

24. Koebnick, C., Tartof, S., Sidell, M., Rozema, E., Chung, J., Taylor, Z., Xiang, A., Getahun, D., 2019. Effect of In-Utero Antibiotic Exposure on Childhood Outcomes: Methods and Baseline Data of the Fetal Antibiotic EXposure (FAX) Cohort Study. Journal of Medical Internet Research. Research Protocols 8(7). DOI: 10.2196/12065.
25. Kwatra, G., Cunnington, M., Merrall, E., Adrian, P., Ip, M., Klugman, K.P., Tam, W., Madhi, S.A., 2016. Prevelance of maternal colonisation with group B streptococcus: a systematic review and meta-analysis. Lancet Infectious Diseases 16, 1076-1084.10:1016/S1473-3099(16)30055-X.
26. Le Doare, K., Heath, P.T., Plumb, J., Owen, N.A., Brocklehurst, P., Chappell, L.C., 2018. Uncertainties in screening and prevention of Group B Streptococcus disease. Clinical Infectious Diseases, https://www.ncbi.nlm.nih.gov/pubmed/30561556.
27. Le Doare, K., O'Driscoll, M., Turner, K., Seedat, F., Russell, N.J., Seale, A.C., Heath, P.T., Lawn, J.E., Baker, C.J., Bartlett, L., Cutland, C., Gravett, M.G., Ip, M., Madhi, S.A., Rubens, C.E., Saha, S.K., Schrag, S., Sobanjo-Ter Meulen, A., Vekemans, J., Kampmann, B., 2017. Intrapartum Antibiotic Chemoprophylaxis Policies for the Prevention of Group B Streptococcal Disease Worldwide: Systematic Review. Clinical Infectious Diseases 65(suppl_2), S143-S151. 10.1093/cid/cix654.
28. Lin, F., Weisman, L., Azimi, P., Young, A., Chang, K., Cielo, M., Moyer, P., Troendle, J., Schneerson, R., Robbins, J., 2011. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. Pediatric Infectious Disease Journal 30(9), 759-763.
29. McNanley, A., Glantz, J., Hardy, D., Vicino, D., 2007. The effect of Intrapartum penicillin on vaginal group B streptococcus colony counts. American Journal of Obstetrics and Gynecology 197, 583e581- 583 e584.

30. Mueller, N., Bakacs, E., Combellick, J., Grigoryan, Z., Dominguez-Bello, M., 2015. The infant microbiome development: mom matters. Trends in Molecular Medicine 21(2), 109-117. 10.1016/j.molmed.2014.12.002
31. Oddie, S., Embleton, N.D., 2002. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. British Medical Journal 325(7359), 308, https://www.ncbi.nlm.nih.gov/pubmed/12169506
32. Ribet, D., Cossart, P., 2015. How bacterial pathogens colonize their hosts and invade deeper tissues. Microbial Infections 17(3), 173-183. 10.1016/j.micinf.2015.01.004.
33. Royal College of Obstetricians and Gynaecologists, 2017. Prevention of early- onset neonatal group B streptococcal disease. Green-top guideline No. 36.
34. Schrag, S., Zell, E., Lynfield, R., Roome, A., Arnold, K., Craig, A., Harrison, L., Reingold, A., Stefonek, K., Smith, G., Gamble, M., Schuchat, A., Active Bacterial Core Surveillance Team, 2002. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. New England Journal of Medicine 347, 233-240, http://www.nejm.org/doi/pdf/10.1056/NEJMoa020205.
35. Schrag, S.J., Farley, M.M., Petit, S., Reingold, A., Weston, E.J., Pondo, T., Hudson Jain, J., Lynfield, R., 2016. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics 138(6). 10.1542/peds.2016-2013.
36. Seaward, P.G., Hannah, M.E., Myhr, T.L., Farine, D., Ohlsson, A.M., Wang, E.E., Hodnett, E.R., Haque, K.M., Weston, J.A., Ohel, G.M., 1998. International Multicenter Term PROM Study: Evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. American Journal of Obstetrics & Gynecology 179(3), 635-639, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltex t&D=ovftc&AN=00000447-199809000-00014

37. Seedat, F., Geppert, J., Stinton, C., Patterson, J., Freeman, K., Johnson, S.A., Fraser, H., Brown, C.S., Uthman, O.A., Tan, B., Robinson, E.R., McCarthy, N.D., Clarke, A., Marshall, J., Visintin, C., Mackie, A., Taylor-Phillips, S., 2019. Universal antenatal screening for group B streptococcus may cause more harm than good. British Medical Journal 364, l463. 10.1136/bmj.l463.
38. Seedat, F., Taylor-Phillips, S., Geppert, J., Stinton, C., Patterson, J., Brown, C., Tan, B., Freeman, K., Uthman, O., McCarthy, N., Robinson, E., Johnson , S., Fraser, H., Clarke, A., 2016. UK National Screening committee (UK NSC). Universal antenatal culture-based screening for maternal GBS carriage to prevent EOGBS disease. Review update.
39. Sheehy, A., Davis, D., Homer, C.S., 2013. Assisting women to make informed choices about screening for Group B Streptococcus in pregnancy: a critical review of the evidence. Women Birth 26(2), 152-157. 10.1016/j.wombi.2012.10.004.
40. Singh, T., Barnes, E.H., Isaacs, D., 2019. Early-onset neonatal infections in Australia and New Zealand, 2002-2012. Australian Study Group for Neonatal Infections. Archives of disease in childhood. Fetal and neonatal edition 104(3), F248-F252. 10.1136/archdischild-2017-314671.
41. Stearns, J.C., Simioni, J., Gunn, E., McDonald, H., Holloway, A.C., Thabane, L., Mousseau, A., Schertzer, J.D., Ratcliffe, E.M., Rossi, L., Surette, M.G., Morrison, K.M., Hutton, E.K., 2017. Intrapartum antibiotics for GBS prophylaxis alter colonization patterns in the early infant gut microbiome of low risk infants. Scientific Reports 7(1), 16527. 10.1038/s41598-017-16606-9.
42. Zimmermann, P., Curtis, N., 2019. Effect of intrapartum antibiotics on the intestinal microbiota of infants: a systematic review. Archives of disease in childhood. Fetal and neonatal edition 10.1136/archdischild-2018-316659. 10.1136/archdischild-2018-316659.

Chapter 6

Discussion

This final chapter synthesises findings from the literature review and the three epidemiological studies which constitute this thesis. The significance of the work is addressed and findings are discussed in relation to the extant literature and the broader context of maternity and neonatal care, ultimately providing insights for future research. As the work evolved, new knowledge continued to be published concerning the potential impact of antibiotics on the founding infant microbiome. These discoveries increased the impetus to discover the reported rates of culture-confirmed EOS in our region and understand whether the provision of antibiotics to ~ 30% of mainly healthy, pregnant women, and their babies, continues to be the best way to address the issue of EOS due to GBS. This concluding chapter raises more questions than answers, since the management of GBS risk in maternity and neonatal care is on one hand, an entrenched practice shrouded in assumptions and on the other, as revealed in this thesis, a poorly implemented process. I begin with my reflections on the integrative review of the literature, presented in its original form in Chapter 2.

Most published papers on the topic of GBS management that describe a standard screening and IAP administration, assert that since the introduction of this medical intervention, rates of EOGBS events have declined. The assumption therefore, is that IAP is effective at reducing, and some say preventing, risk of EOGBS (Boyer & Gotoff 1986; Matorras et al. 1991; Tuppurainen & Hallman 1989). When a systematic review and meta-analysis of these clinical trials (Ohlsson & Shah 2014) was undertaken however, it became apparent that the few RCTs focusing on this area had poor methodology resulting in a high risk of bias. This finding raised questions around the validity of these studies and whether the maternity community should continue to rely on evidence from these clinical trials to support current modalities for GBS risk management. However, any opportunity for further, more robust, clinical studies of GBS management that could

provide unbiased evidence of effectiveness, is non-existent since the intervention is now widespread and the outcome EOGBS, is rare. The review contained in this work supported the Cochrane authors' assessment of RCTs interrogated in their analysis. The integrative method utilised here to review the literature and presented in Chapter 2 of this thesis was chosen as this method of review can encompass a broad range of studies (Whittemore & Knafl 2005). Observational studies that were located and critiqued also reported a lowering of EOGBS in settings where screening and IAP were provided, but, importantly, simultaneously identified sub-optimal provision of both screening and prophylaxis. Findings from the integrative review raised questions. Were there yet untested, and even unknown, factors in the populations investigated which were also responsible for the lowering of EOGBS over four decades of universal screening and IAP provision (Braye et al. 2019a)?

With the advent of greater vigilance for potential sepsis events in maternity care and advances in blood culture systems and neonatal management, EOS including EOGBS, has become rare in term babies born in high-income jurisdictions. However, despite a more targeted treatment of potential maternal and/or neonatal sepsis, GBS in those high-income jurisdictions is reported as the most common organism affecting term babies and has resulted in much research attention and focus on continuing to reduce rates of EOS caused by GBS by using the medical intervention of screening and IAP provision.

My LHD provided an opportunity to examine EOS events and the management of GBS risk in fine detail since the district maintains a robust maternity database, managed by a skilled clinical data custodian. Ethics clearance enabled interrogation of aggregated data as well as de-identified medical records enabling detailed investigation. Study 1, an epidemiological study of EOS in our LHD, showed EOS due to GBS was, in fact, the most common cause of term EOS in our LHD although rates were extremely low.

The LHD had utilised universal screening together with IAP provision for up to 30% of the birthing population for more than a decade. The change in screening from a risk- based method to a universal screening approach followed publication of a local observational study in 2007 that claimed to have established the benefits of universal screening

(Angstetra, Ferguson & Giles 2007). These researchers calculated the number needed to treat (with IAP) to prevent one case of EOGBS was 1,191; with 5,704 women needing to undergo universal screening. These large numbers question the risk versus benefit of universal screening and GBS management with IAP to nearly a third of the birthing population, particularly in light of emerging research linking IAP with microbial dysbiosis and long-term adverse health outcomes as detailed in this work. The UK National Institute for Health Care and Excellence (NICE) in their assessment of universal screening decided that risks may outweigh benefits and did not recommend support for the process continuing to recommend a risk-based approach only (NICE, 2012). The impact of antimicrobial exposure on the microbiome of mother and child is yet to be quantified and should certainly provide further pause for thought.

Such an extensive application of intravenous antibiotics to a mostly healthy population of women, and their babies became increasingly concerning to me as a clinical midwife; particularly in the light of newly emerging evidence of the potential impact of antibiotics on the maternal microbiome and consequently the baby's founding microbiome (Azad et al. 2015), and provided impetus to study local rates of EOS and current GBS management in detail. Therefore the three studies contained in this thesis were designed to investigate different aspects of EOS and, in particular, the management of GBS colonisation in pregnant women in my local health service; and elicit benefits and risks of preventative modalities.

Although, in Study 1, GBS was identified as the most common bacteria affecting term babies (Braye et al. 2019), the rate of culture-confirmed EOGBS events in the study setting was extremely low, with reduction from 0.35/1000 live-births in 2006 to 0.10/1000 in 2016 (Braye et al. 2019b). Similar findings have been found in other jurisdictions (Russell et al. 2017; Schrag et al. 2016; Seedat et al. 2016). As well as establishing GBS as the most common bacteria affecting term babies (Braye et al. 2019a), investigating EOS events in detail highlighted the importance of using a definition of 'culture-confirmed' EOS and EOGBS in studies of this nature, reinforcing the question of the validity of previously published studies (Matorras et al. 1991) that use both 'culture-confirmed' and clinically 'possible 'or 'probable' definitions of EOS (Braye et al. 2018).

Why the EOGBS rate in our study setting was lower than that identified in jurisdictions using similar methods of GBS management, was not clear. What was clear however, was the studies that included possible or probable EOGBS diagnosis, as opposed to a culture-confirmed EOGBS, led to higher, but unreliable, rates of reported EOGBS in their study population. These studies have a higher risk of bias as discussed in the integrative literature review presented in Chapter 2 (Braye et al. 2018).

I am confident that our pathology data were reliable as these data were based on culture-confirmed results that were gathered directly from NSW Health Pathology and other accredited services. Furthermore, our analysis of blood culture utilisation in the health district, showed that the intensity of surveillance did not change over the period of the study. Having confirmed the study hypothesis that EOGBS was, in fact, the most common bacteria to affect term newborns in this setting, I then focused on an examination of maternal GBS colonisation, screening, the administration of IAP and neonatal EOGBS events in this population.

Study 2 demonstrated that screening and IAP provision was modest (Braye et al. 2019b). This companion study to Study 1 demonstrated that 1 in 4 eligible pregnancies (n=21,064) were reported as not screened (Braye et al. 2019b). In fact, whether universal screening was undertaken or not, *per se*, did not appear to influence the rate of EOGBS events. Furthermore the majority of term babies with EOGBS, (7 of 10 babies), were born to mothers who screened negative to the bacteria. Importantly, five of these seven mothers had other risk factors that should have triggered the provision of IAP if a risk-based approach to screening had been applied. In these cases a negative GBS result may have blinkered the perception of clinicians around the safety of their protocols. Study 2 raised more questions. For example, was universal screening the most effective method for identifying women positive for GBS? It appeared that an unacceptable proportion of women, eligible for GBS universal screening, and then eligible for IAP were being missed altogether. Reasons for these so-called missed opportunities were not clear in Study 2; but it did appear clear from these data that current GBS management in this setting was not meeting the expectations of guidelines.

Support and lobby groups (GBS/CIDP Foundation International 2019; Group B Strep support group) advocating universal screening for GBS risk in jurisdictions where a risk-based approach is currently offered, promote universal screening to women as coverage of all eligible consenting mothers with an implied guarantee of prevention of this serious infection. This work (Braye et al. 2019b) and others (Seedat et al. 2019; UK National Screening Committee 2012) dispute that claim for the following reasons.

Universal screening and IAP provision in our LHD was not able to prevent all EOGBS events. The results of the first two studies suggest a significant proportion of women with pregnancies eligible for GBS screening were not screened and the majority of babies with EOGBS (7 of 10) were born to mothers who were screened but had an antenatal culture result that was negative for GBS. Finally, although this is contested, it appears apparent that less women and babies would be exposed unnecessarily to intrapartum antibiotics if a more nuanced, risk-based approach was offered in place of universal screening (Seedat et al. 2016). A risk-based approach would also likely result in a reduction in women and babies recommended to remain in hospital for postnatal observation and, although individual families must experience considerable distress if their baby is affected by GBS, a risk-based approach has been found to be less complex and less expensive to administer than universal screening (Bevan et al. 2019; Seedat et al. 2016).

The final study, presented in this thesis, used a subset of data interrogated in the previous two studies. This in-depth observational study enabled close analysis of how well clinicians adhered to local GBS guidelines. The most significant finding was that therapeutic prophylaxis might not have been achieved in the majority of the sample population due to provision of IAP deemed inadequate by local guidelines. The most common reason recorded by clinicians when IAP provision was not in accord with local guidelines, or not given at all, was a lack of time available to provide IAP at least four hours before birth. More often than not in this setting, local GBS guidelines were not able to be met, however most missed opportunities for the provision of the intervention e.g. a lack of time before birth to administer an adequate dose, appeared to have been unavoidable. As in Study 2, a number of eligible pregnancies in Study 3 did not have evidence of a GBS screen documented in the maternity database. Of those that did 63%

(n=2,322) had a documented positive or negative result. Of these 2,322, 525 (23%) were documented as positive for GBS. Results were similar for Studies 2 and 3 at 69% and 63% of pregnancies with a result recorded and a rates of maternal colonisation of 21.5% and 23% respectively. These rates align with rates from other jurisdictions although it is possible that there were pregnancies positive for GBS with no record on the maternity database. Positive results would be unlikely to be missed however, as results are checked with the pathology database on admission for labour.

In the sample of 223 women positive for GBS and included in Study 3, 8 out of every 10 received some IAP but of those, 2 out of every 3 did not receive IAP in accord with guidelines. Study 3, similar to Study 2, suggested that there were other factors as well as current GBS management causing the low EOGBS rates in this setting. It could be argued, however that the antibiotics that 8 of 10 women received were enough to reduce bacterial load and prevent or mask culture-confirmed EOGBS infection, even though the dose(s) women received were deemed to be inadequate according to the guideline. The overarching question: *'Are we using the optimal strategy to reduce the risk of neonatal EOGBS?'* must surely be answered in the negative.

Significance and contribution to the wider body of knowledge

Many clinical questions, including those in this thesis, do not have single, unambiguous answers. My aim was to identify gaps in knowledge, add insights to the wider body of knowledge, and open conversation and debate rather than presenting a firm position or declaring the 'right' answers to complex questions around the optimal strategies for management of GBS risk. Indeed, important questions have arisen from the studies in this thesis: Why have rates of EOGBS reduced substantially in high-income countries since the introduction of IAP, as it is acknowledged that provision of IAP is often sub-optimal? What factors, other than IAP, have contributed to the low rates of EOGBS? Will vaccination soon become a valid option for the reduction of infant GBS infection?

Are there other reasons for low rates of EOGBS?

As this work has demonstrated, EOGBS has been declining across high-income countries, despite minor fluctuations both up and down, including in jurisdictions which predominantly follow a risk-based approach to IAP provision (Darlow et al. 2016; Seedat et al. 2016). There is scant evidence that universal GBS screening and IAP have been the predominant factor in the current low rates of EOGBS.

Neonatal EOGBS has been described for more than 50 years and there is some evidence that in the USA incidence began to increase in the 1970s (McCraken 1973). Reports from the USA in 1973 documented many cases of early and late-onset neonatal GBS infection with high mortality (Barton, Feigin & Lins 1973; Franciosi, Knostman & Zimmerman 1973; McCraken 1973).

The subtypes of GBS causing EOS and LOS in neonates are diverse with five clonal complexes, each containing multiple subtypes making the identification of isolates in different populations challenging when considering the implementation of novel therapies including vaccination (Furfaro, Chang & Payne 2018). Maternal GBS immunity may well have increased since the 1970s due to increasing maternal GBS exposure, leading to reductions in EOGBS incidence independent of interventions though I know of no published evidence to support this statement. Currently EOGBS in term babies displays very low mortality and morbidity, in contrast to the above cited reports from 1973. Although improvements to neonatal care will have had an impact, the natural waxing and waning of community infections and virulence of the infecting GBS serotypes may well have declined as well. Lastly, it is possible that over the last 50 years, improved antenatal care, better maternal nutrition and hygiene, increased use of empirical intrapartum antibiotics irrespective of screening results, and increased recourse to operative obstetric management have interacted in some way with EOS risk, perhaps by altering the maternal

microbiome and consequently the neonatal founding microbiome. The decline in EOGBS morbidity provides a further rationale for focusing on early diagnosis and management on a case by case basis rather than taking a broader, poorly focused, preventative approach. It would seem apparent that there is further scope for investigation of these many factors.

If GBS management is to continue in some form, maternal vaccination is an attractive alternative, and could target both early and late-onset GBS infection by establishing immune protection based on vaccine or natural antibodies, as discussed in detail in Study 2 (Chapter 4). To date, no studies have been sufficiently powered to provide robust evidence of vaccine efficacy. It has been estimated that a study of ~60,000+ pregnant women would be required to detect a significant reduction in all GBS related infection (Kobayashi et al. 2016). It is apparent, as discussed above and from a recent review (Furfaro, Chang & Payne 2018) that GBS epidemiology is highly complex and dynamic, and geographically specifically based. Establishing which serotypes are dominant within different populations is an important step in understanding the pathogenesis of GBS, furthering knowledge and thus enabling the success of future prevention strategies. Vaccination, like current management, will not prevent all cases of GBS infection and, also like current GBS management, will not be acceptable to all women. A proportion of women will decline any of the GBS risk interventions offered, but women's views have not been well researched. There is a gap in the literature; studies assessing the attitudes of women and their families related to a potential GBS vaccine should be undertaken and experiences of recent implementation of other vaccines taken into account.

Recommendations for future research and clinical practice arising from this work

The work presented here has highlighted serious limitations around current modalities of GBS management, in particular a universal screening approach and subsequent administration of IAP for women found to be positive for GBS.

Based on this work, together with other research, and given that it is impossible to prevent

all EOS, I recommend that policy makers: a) must decide whether current EOGBS incidence and its attendant low morbidity continues to justify a universal screening approach, especially given the doubtful evidence concerning the effectiveness of this process; b) consider a formal risk-benefit analysis, similar to that undertaken by UK National Screening Committee (UK National Screening Committee 2012); c) consider whether a purely risk-based approach to EOGBS prevention will be adequate and acceptable; and d) consider whether continued improvements in risk assessment (see description of neonatal calculator below), advanced diagnostic technology for sepsis together with excellence in maternity and neonatal care, will provide sufficient assurance for women and clinicians given our inability to prevent all cases of EOGBS using current modalities.

Women's views have not been part of the management of GBS debate with the exception of input from some individuals personally affected by EOGBS and support and lobby groups in the UK (Group B Strep support group) and USA (GBS/CIDP Foundation International 2019). Women must be included in the discussion around this vexed issue. Continuity of maternity care is a good place to start; however in reality this model is not available to most women (Sandall et al. 2015). Therefore, research must be undertaken involving women accessing all models of maternity care to determine women's views, health literacy around this topic and the acceptability of different approaches. This new knowledge can be incorporated into any GBS management of the future.

Given the degree of polarisation amongst clinicians and consumer advocacy groups around the practice of screening and IAP there is an urgent need for qualitative research that unpacks the belief systems of women, midwives, obstetricians, neonatologists and microbiologists. A comprehensive educational approach to discuss evidence (and lack of evidence) with women, clinicians and students is needed. Guideline review and development could then follow with involvement of consumer representation.

Studies examining the longer term evolutionary sero-epidemiology of human GBS infection and studies on how GBS virulence has changed, plus long-term research evaluating changes in GBS maternal immunity will inform debate. Modelling of the

potential impact of GBS vaccination and its cost effectiveness will be required in advance of implementation of any vaccine candidate (Giorgakoudi, O'Sullivan & Health 2018).

The neonatal calculator (Kaiser Permanente Division of Health 2018) has been used successfully in several jurisdictions including Australia, to assist in the reduction of neonatal antibiotic provision in the immediate post-natal period. Based on findings in this thesis, together with the results of others on this topic (Bridges et al. 2019; Goel et al. 2019; Kaiser Permanente Division of Health 2018), I recommend that policy makers and maternity clinicians consider validating the neonatal calculator tool in their own setting in conjunction with women and neonatal colleagues, to enable assessment of the estimated risk to an individual woman of having a baby with EOS.

Whilst wanting the best outcomes for women and babies, it has been argued that clinicians may provide 'too much medicine' (Glasziou et al. 2013) and 'too much, too soon' (Miller et al. 2016). The alternative to this medical paradigm is a physiological or wellness paradigm (Schneider Jamner & Stokols 2000). Women and clinicians who espouse this way of thinking, consider that generally pregnancy and childbirth is a safe and normal part of a woman's life (Buckley 2015; Dahlen et al. 2014; Fahy, Foureur & Hastie 2008; Stenglin & Foureur 2013). With this in mind, clinicians and researchers may consider a 'wellness calculator' that estimates the likelihood of infants who are likely to be born healthy, rather than, or in addition to, discussing the potential for neonatal illness rates with women. Clearly there is a need for further work. Processes of healthcare should be redesigned with consumer input at its centre, to facilitate more acceptable and consistent practice around any future strategies for the reduction of GBS risk.

Conclusion

The integrative literature review and three interrelated but distinct studies contained in this body of work have interrogated the complex and, at times controversial, issues surrounding management of GBS colonisation in pregnant women. Group B streptococcus is a commensal in most people but can present as a serious bacterial pathogen which has the potential, albeit rare, to infect neonates in the first few days of

life. Strategies to limit EOS are important and scientifically defensible, although any intervention to reduce medical risk should be derived from robust and reliable evidence. This is not the case for GBS risk intervention and management, evidence is neither robust nor reliable. Screening for GBS risk and provision of IAP has become routine in many high-income countries. Since its widespread introduction in the 1980s, adverse events have been identified as associated with antibiotic prophylaxis. Risks include the global issue of antibacterial microbial resistance, potential harmful alteration of the baby's microbiome, and the increasing medicalisation of birth, including the early postnatal period.

Individual women (and their families) are impacted by the consequences of testing positive for GBS in late pregnancy. Consequences may include being unable to birth within some models of care or exclusion from a preferred place of birth, or position for birth e.g. birth in water, and then, after the birth, a request to remain in hospital so that the baby may be monitored for signs of infection. Given the low quality of evidence supporting universal screening and the large numbers of women, estimated at over 99%, who, if screened and positive for GBS, would not be at risk of having a baby with EOGBS, it is apparent that current strategies for GBS management are unrealistic at best, and harmful to mothers and babies at worst.

Research presented in this thesis has addressed the rates of EOS and rates of EOGBS, the effectiveness of IAP, screening and provision of IAP in one Australian LHD and clinician compliance with GBS management. I foresee that dissemination of study results via publication, conference presentations and the availability of this thesis and data to other researchers via open access will enable clinicians and policy makers to consider the issues around GBS more broadly, optimising outcomes for mothers and babies, enabling women to receive the information they need to make an informed choice around this vexed and somewhat mysterious clinical issue.

Appendices

Appendix 1 Publication 1

Contents lists available at ScienceDirect

Women and Birth

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Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B *Streptococcal* infection: An integrative review

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ABSTRACT

Background: In some countries, up to 30% of women are exposed to intrapartum antibiotic prophylaxis for prevention of early-onset group B *Streptococcal* infection. Intrapartum antibiotic prophylaxis aims to reduce the risk of neonatal morbidity and mortality from this infection. The intervention may adversely affect non-pathogenic bacteria which are passed to the newborn during birth and are considered important in optimising health. Since many women are offered intrapartum antibiotic prophylaxis, effectiveness and implications of this intervention need to be established. This review considers clinical trials and observational studies analysing the effectiveness of intrapartum antibiotic prophylaxis.
Methods: An integrative literature review was conducted. One systematic review, three clinical trials and five observational studies were identified for appraisal.
Findings: Randomised controlled trials found intrapartum antibiotic prophylaxis effective but all retrieved randomised clinical trials had significant methodological flaws. High quality observational studies reported high rates of effectiveness but revealed less than optimal adherence to screening and administration of the prophylaxis. Scant consideration was given to short term risks, and long-term consequences were not addressed.
Discussion: Studies found intrapartum antibiotic prophylaxis to be effective. However, evidence was not robust and screening and prophylaxis have limitations. Emerging evidence links intrapartum antibiotic prophylaxis to adverse short and longer-term neonatal outcomes.
Conclusion: Our review found high quality evidence of the effectiveness of intrapartum antibiotic prophylaxis was limited. Lack of consideration of potential risks of the intervention was evident. Women should be enabled to make informed decisions about GBS management. More research needs to be done in this area.

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RESEARCH ARTICLE

Epidemiology of neonatal early-onset sepsis in a geographically diverse Australian health district 2006-2016

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Abstract

Aim

To describe the epidemiology of EOS including blood culture utilisation, across a large and geographically diverse Australian health district.

Background

Sepsis in the first three days of life remains a leading cause of death and morbidity. In high-income countries, group B *Streptococcus* (GBS) and *Escherichia coli (E. coli)* have dominated as causes of EOS for five decades.

Method

An 11-year retrospective cohort study to determine the epidemiology of EOS. Incidence rates were calculated per 1000 live births. Logistic regression with linear temporal trend and covariates for potential effect modifiers were employed. Blood culture utilisation was determined by examining the rate of babies undergoing blood culture within 72 hours of birth.

Results

Among 93,584 live born babies, 65 had confirmed EOS (0.69/1000 live births); 22 term, 43 preterm. **Across the 4 largest birth units, the proportion of babies having blood culture within 72 hours of birth varied from 1.9–5.1% for term and 21–35% for preterm babies.** The annual change in the EOS rate was significant, OR 0.91 (95% CI, 0.84 to 0.99, p = 0.03). Group B *Streptococcus* was the most common cause of EOS in term neonates at 0.35/1000 live births (95% CI, 0.07–0.63) in 2006 and 0.1/1000 live births (95% CI, 0–0.2) in 2016. *Escherichia coli* was the most common cause in preterm babies at 3.4/1000 (95% CI,

0.11–6.76) in 2006 reducing significantly to 1.35/1000 live births (95% CI, -0.07–2.78) by 2016.

Conclusions

Escherichia coli and GBS were the most common causes of EOS in preterm and term babies respectively. Rates of all cause term and preterm EOS declined significantly as did preterm sepsis due to *E. coli*. While rate of sepsis due to early-onset GBS declined, this did not reach significance. Given the high proportion of preterm babies undergoing blood culture, it is unlikely that any EOS events were missed.

Introduction and Background

Neonatal EOS refers to culture-proven bloodstream and/or central nervous system infection occurring in live born neonates soon after birth. It remains a significant cause of infant morbidity and mortality in both high and low-income countries [1]. Most events occur in the first 48 hours of life [2]. Based on varying definitions, recent reported estimated incidences of culture proven EOS range from 0.01 to 0.53/1000 live births in Europe [3], 0.77/1000 in the USA [4, 5] to 0.83/1000 in Australia [6]. Recorded mortality has been as high as 30% in high-income and 60% in low-income countries[3] but has reduced in high income jurisdictions in recent years to around 10% of all babies with EOS [3, 7]. Preterm babies continue to suffer a much higher mortality than term infants [8]. Neonatal EOS is almost always due to pathogenic microorganisms acquired from the mother, either during or preceding birth [2, 5]. Infection may be trans-placental (haematogenous) but is more commonly thought to occur by an ascending route from the mother's genitourinary tract [9].

Risk factors for early-onset sepsis

Perinatal maternal risk factors reported to be associated with EOS include recto-vaginal GBS colonisation, rupture of membranes (ROM) $\geq$18 hours, prematurity, and intrapartum fever [3]. Recently authors have questioned the value of including fever as a surrogate for chorioamnionitis[10]. However currently, maternal fever ($\geq$38˚) remains a risk factor for EOS in most jurisdictions [8, 11–13]. Other risk factors include bacteriuria in the index pregnancy and having a previous child diagnosed with early-onset group B streptococcal infection (EOGBS) [11].

Pathogens

Early-onset sepsis due to *E. coli* is associated with high rates of mortality and morbidity, especially in preterm newborns [5]. The rate of multiple resistant *E. coli* has been described as stable overall but increasing in very low birth weight neonates (<1.500g) [14]. In term babies, population-based neonatal infection surveillance studies demonstrate that GBS remains the pathogen most frequently associated with term EOS [6, 15–17].

Early-onset group B streptococcal sepsis

Whilst there is a decline in early-onset GBS (EOGBS) sepsis whenever any maternal intrapartum antibiotic prophylactic (IAP) is provided [18] and others have noted evidence for IAP to be strong [6, 19], the most recent Cochrane review on the effectiveness of IAP concludes that whilst IAP appeared to reduce EOGBS, this may be due to bias. The Cochrane reviewers found

a high risk of bias for one or more key domains in the methodology and execution of the studies included in their analysis [20]. Therefore, Cochrane states there is a lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBS. More recently we undertook a broader, integrative review and concluded the evidence that the incidence of EOGBS can be reduced by widespread administration of maternal IAP is not robust [20].

Aim

To describe the epidemiology of EOS including blood culture utilisation, across a large and geographically diverse Australian health district.

Materials and methods

A retrospective cohort study design was employed using data from a cohort of live born babies and their mothers birthing in the Hunter New England local health district (HNELHD) in New South Wales (NSW), Australia over the period 2006–2016.

Study setting and population

New South Wales is the largest and most populous state in Australia covering a region of 131,785 square kilometres, equivalent to the size of England. In 2008 the state was divided into 15 local health districts (LHDs). The HNELHD is geographically and socially diverse. As of 2016, the health district had 873,741 residents. Aboriginal and Torres Strait Islander people account for 4.0% (equating to 21% of NSW's Indigenous population) and 19% of residents were born overseas [21]. The health district spans 25 local government areas and is the only regional health district in NSW with a metropolitan hospital and level three neonatal intensive care unit (NICU), an along-side birth centre and a freestanding birth centre nearby. In total, these centres support around 4000 births per year. The district also includes a mix of several large regional hospitals providing care for 500 to 1500 births per year through to 11 rural units servicing a small percentage of people located in more remote settings supporting <250 births per year.

Our study population included women from the original Hunter area birthing in 2006 to 2007. From 2008 onwards when HNELHD was formed, the cohort of women increased to include the 16 units mentioned above. The study population included women and babies of all risk categories, birthing within all publicly funded maternity services in the HNELHD including hospital, birth centre and planned births at home. From 2006 onwards women in the Hunter area/HNELHD were offered universal screening for GBS risk.

In this paper the term "pregnancies" better describes the total cohort of women as one woman could have been pregnant more than once during the study period, however, the term "women" represents all women and each of her pregnancies resulting in a live birth(s) from 2006 to 2016.

Blood culture utilisation

To evaluate EOS surveillance intensity, data from 2013 to 2016 were analysed to determine the proportion of babies from whom at least one blood culture was collected during the first 72 hours of life stratified by gestation (term or preterm).

Demographics

Inclusion criteria comprised live born infants and their mothers, born in the Hunter area 2006 to 2007 and expanded to include the newly formed HNELHD between 1st January 2008 and 31st December 2016. Stillborn babies, duplicate entries and entries with inadequate data were excluded Fig 1.

Information was obtained from medical records and the maternity ObstetriX database. ObstetriX (changed to e. Maternity in 2017) is a state wide surveillance system providing point-of-care data collection across antenatal, intrapartum, and immediate postnatal periods. Clinicians contribute information soon after birth. Local health district data custodians maintain the database.

We collected demographic data for mothers and babies, antenatal and intrapartum risk factors for EOS together with the neonatal hospital course and short-term neonatal outcomes. Maternal GBS colonisation, prematurity, and rupture of membranes (ROM) ≥18 hours, plus maternal age (age is categorical including ≤20 years versus all others), were collected and used in analysis. While history of maternal GBS bacteriuria and a previous child with EOGBS are both GBS risk factors, considered in a decision to offer IAP, we were unable to obtain information on either. Data on rates of fever were poorly transcribed into the database and therefore were not included as a risk factor for sepsis in our analysis.

Microbiological cultures

Results of culture positive blood and cerebrospinal fluid (CSF) specimens were accessed from the publicly funded pathology service provider (Auslab) and three of four private pathology providers. Early-onset sepsis events were identified from laboratory data, when significant isolates (bacteria or fungi) were obtained from blood culture and/or CSF collected within the first 72 hours of life. Cultures yielding ≥3 bacterial species or a potential contaminant e.g. coagulase negative *Staphylococci*, as specified by Schrag and colleagues, 2016 were assumed to have been contaminated and were therefore excluded [5].

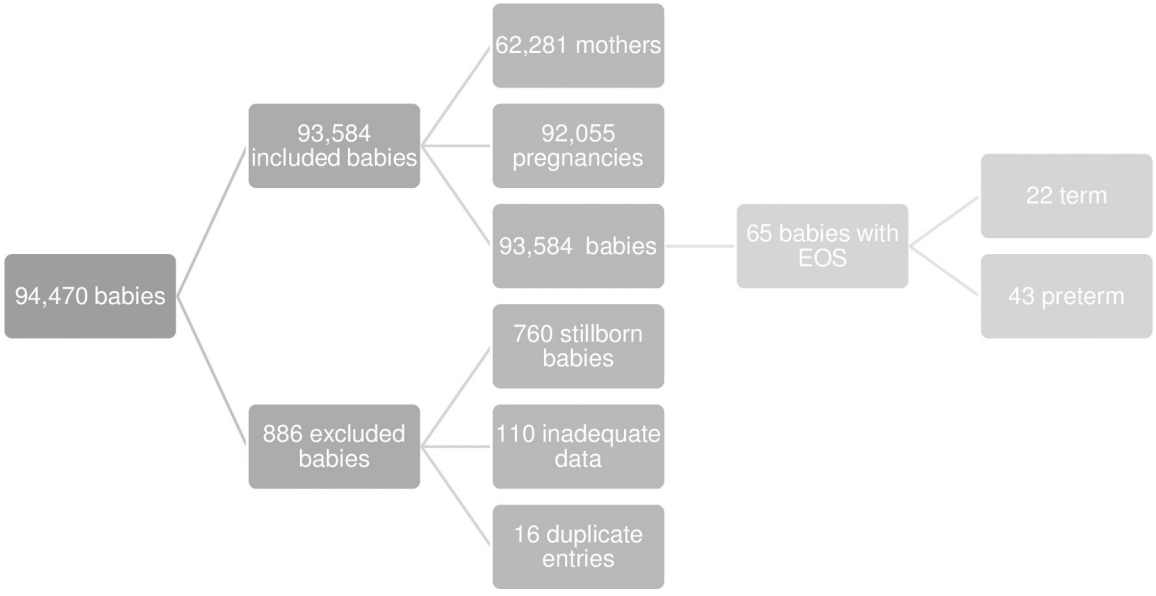

Fig 1. Inclusions and exclusions.

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Definition of early-onset sepsis

Researchers use a range of time frames to define EOS ranging from 48 hours to 7 days post birth [11]. The definition used here is neonatal sepsis arising within 72 hours of birth in accord with the definition used by the UK National institute for clinical care excellence (NICE) [3, 22].

Morbidity and mortality

Admission and short-term morbidity were reported as serious or not serious. Serious morbidity was defined as the need for significant respiratory or circulatory support requiring neonatal intensive care and/or encephalopathy or seizures. It was not possible to assess long-term morbidity. Live status of each baby with an EOS event as of December 2017 was derived from the HNELHD patient demographics system, which is linked to NSW death registration data.

Prevention of group B streptococcal sepsis

Between 2006 and 2008, starting with the metropolitan unit in HNELHD, a program of GBS screening for women reaching ≥35 weeks' gestation was commenced. Mothers with recto/vaginal GBS colonisation or certain other risk factors for EOGBS (as documented above) are offered IAP in labour, or at rupture of membranes if this occurs first in order to reduce the likelihood of EOGBS.

Ethics approval

The study was approved by the HNELHD Human research ethics committee (HREC) on 05/05/2016 with variation applied for and granted 09/03/2018 16/05/18/5/5.05 SSA. LNRSSA/16/HNE/225 and The University of Technology Sydney (HREC): No. 2014000115. This publication adheres to the provision of privacy and confidentiality of patient data and clinical information, including NSW health records and information privacy act, 2002. The purpose of our study was to describe the epidemiology of EOS rather than individual events; therefore consent from individuals was not required. All data was de-identified and password protected.

Statistical analysis

Descriptive statistics on sample characteristics are provided. Incidence rates were calculated as cases per 1000 live births per year with t-tests being used for continuous variables. Chi-squared tests were used for proportions and Wilcoxon rank sum tests for comparisons of medians. P-values >0.05 suggest a statistically detectable difference between groups, which may or may not be clinically relevant and/or meaningful. We explored temporal trends in background all-cause EOS sepsis in the individual birth data by using logistic regression with a linear temporal trend and covariates for potential effect modifiers.

Potential effect modifiers used were positive maternal GBS recto-vaginal colonisation, prematurity (<37 weeks gestation), rupture of membranes (ROM) ≥18 hours and maternal age (<20 years versus all others). We provide estimates of odds ratios, graphical visualisation, probabilities of events and the associated 95% confidence intervals and p-values. All models were checked for calibration and discrimination and we use a conventional significance level of 0.05 throughout.

Results

Study population

After exclusions, the study population included 62,281 women who had 92,055 pregnancies. These women gave birth to 93,584 babies. There was an increase in the birthing population during and after 2008 as the area restructured and HNELHD was formed. Ninety-eight per cent of live born babies (90,510) were singletons and 8,165 (8.9%) of the pregnancies were preterm resulting in 9,146 (9.8%) preterm live born babies. Eight per cent of women (9,336) identified as Aboriginal or Torres Strait Islander (ASTI).

Table 1 provides a descriptive statistical summary of the data. It reports various characteristics of our sample overall, stratified by EOS and No EOS. The p-values correspond to statistical comparisons between the No EOS and EOS strata. Table 1 suggests statistically significant differences between the No EOS and EOS groups for term versus preterm babies, type of pregnancy (singleton or other), ATSI mothers, rupture of membranes >18 hours and pregnancies with positive maternal GBS colonisation. These variables with the exception of the type of pregnancy (singleton versus other) and mothers that are ATSI are recognised risk factors for EOGBS Table 1A & 1B. These results suggest that risk factors for EOS appear in our sample.

Early-onset sepsis

In total, 65 culture-proven EOS events were identified Fig 2. Over 80% of EOS was evident within 48 hours of birth 82, and 88% for term and preterm groups respectively. Most, but not all, babies subsequently diagnosed with EOS were born at the metropolitan unit 50/65 (77%). The annual change in the background rate of all-cause EOS was significant at the 0.05 level with a multiplicative change in the odds of EOS reducing by approximately 9% per year over the study period as indicated by an odds ratio of 0.91 (95% CI, 0.84 to 0.99, p = 0.03). Six women who identified as ATSI mothers had babies with EOS Table 1A & 1B.

Term babies with early-onset sepsis. Twenty-two, (34%) of the 65 babies with EOS were term gestation. Baseline (2006) incidence of EOS in term infants was estimated with adjustment for gestation, birth weight, maternal GBS carriage, ROM ≥18 hours and maternal age to be approximately 0.5 (95% CI, 0.02 to 0.97)/1000 live births. By 2016, the rate was 0.19 (95% CI, 0 to 0.4).

Preterm babies with early-onset sepsis. Forty-three babies who developed EOS were preterm. Baseline incidence of preterm EOS was estimated with adjustment for gestation, birth weight, maternal GBS colonisation, ROM ≥18 hours and maternal age to be approximately 22/1000 live births (95% CI, 1.3 to 42.7) in babies with gestations <30 weeks and 3.4/1000 live births (95% CI, 0.1 to 6.8) in babies with gestations 30 to 36 weeks and 6 days. By 2016, the respective rates had fallen significantly to 8.8/1000 live births <30 weeks (95% CI, -0.5 to 18) and 1.4/1000 live births between 30 and 36 and 6 days (95% CI, -0.1 to 2.8) Fig 3.

EOS surveillance intensity 2013–2016

Across the 4 largest birth units, the proportion of babies having at least one blood culture within 72 hours of birth varied from 1.9 to 5.1% for term and 21 to 35% for preterm babies with large year-to-year variation. Across the smaller units that do not care for preterm babies, the proportion of babies cultured was 1.1% or less, with a mean of 0.7%.

Diagnosis

All EOS events were diagnosed by blood culture. Forty-one (63%) babies also underwent lumbar puncture; 11/41 (27%) term and 30/41 (73%) preterm. Lumbar punctures were taken

Table 1. 1a & 1b. Sample characteristics of women, their pregnancies, and babies.

Table 1a. Women	Value	Overall (%)	No EOS (%)	EOS (%)	P value
Number of pregnancies		92055	91990 (99.9)	65 (0.1)	
Type of pregnancy	Singleton	90510 (98)	90453 (98)	57 (88)	<0.001
	Multiple	1545 (2)	1537 (2)	8 (12.3)	
Term pregnancy (%)	Term	83890 (91)	83868 (91)	22 (34)	<0.001
	Preterm	8165 (9)	8122 (9)	43 (66)	
Median maternal age [IQR]		28 [24 to 32]	28 [24 to 32]	28 [24 to 32]	0.682
Aboriginal/Torres Strait Islander	Yes	9336 (10)	9330 (10)	6 (9)	<0.001
	No	82590 (90)	82533 (90)	57 (88)	
	Not stated	103 (0.1)	103 (0.1)	0 (0)	
	Missing	26 (0)	24 (0)	2 (3)	
Rupture of membranes ≥ = 18	Yes	8881 (10)	8847 (10)	34 (52)	<0.001
	No	83129 (90)	83100 (90)	29 (45)	
	Missing	45 (0)	43 (0)	2 (0)	
GBS result (total pregnancies)	Positive	13288 (14)	13278 (14)	10 (15)	0.028
	Negative	48236 (53)	48212 (52)	24 (37)	
	Unknown	30531 (33)	30500 (33)	31 (48)	
Alcohol consumption	1 to < 5	2416 (3)	2415 (3)	1 (1.5)	0.002
	1+daily	236 (0.3)	236 (0.3)	0 (0)	
	5+daily	216 (0.2)	216 (0.2)	0 (0)	
	None	88406 (96)	88344 (96)	62 (95)	
	Unknown	522 (0.6)	522 (0.6)	0 (0)	
	Missing	259 (0.3)	257 (0.3)	2 (3)	
Smoking at booking	Yes	19143 (21)	19130 (21)	13 (20)	<0.001
	No	72469 (79)	72419 (79)	50 (77)	
	Unknown	184 (0.2)	184 (0.2)	0 (0)	
	Missing	17 (0)	17 (0)	0 (0)	
Prior pregnancy	Yes	66648 (72)	66606 (72)	42 (65)	0.369
	No	25390 (28)	25367 (28)	23 (35)	
	Missing	17 (0)	17 (0)	0 (0)	
Table 1b. Babies					
All babies		93584	93519 (99.9)	65 (0.1)	
Singleton	Yes	90510 (97)	90453 (97)	57 (88)	
Term	Yes	84438 (90)	84416 (90)	22 (34)	<0.001
	No	9146 (10)	9103 (10)	43 (66)	
Mean birth weight (SD)		3360 (641)	3360 (640)	2217 (1135)	<0.001
Median gestational age [IQR])		40 [38, 41]	40 [38, 41]	33 [29, 39]	<0.001

Legend: EOS = early-onset sepsis, [IQR] = interquartile range, ASTI = Aboriginal or Torres Strait Islander
1 to <5- = one drink daily and not more than 5 at one sitting, eligible = a pregnancy ≥ 35 weeks gestation, ROM = rupture of membranes, GBS = group B streptococcus

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within two days of a positive blood culture in 31/41 (76%) cases. Of the 41 lumbar puncture tests taken, four (10%) were positive and results were in accord with the blood culture.

Gram-negative species predominated significantly in preterm EOS events, 24/43 (55%) and (4/23) 17% in term babies (p = 0.006); *E. coli* and other *Enterobacteriaceae* were the leading causes in 20/43 (45%) of the preterm cohort Table 2. The rate of EOS due to *E. coli* over the study period was 0.19/1000 live births (n = 18); 0.02/1000 live births (n = 2) in the term cohort and 1.75/1000 live births (n = 16) in the preterm cohort.

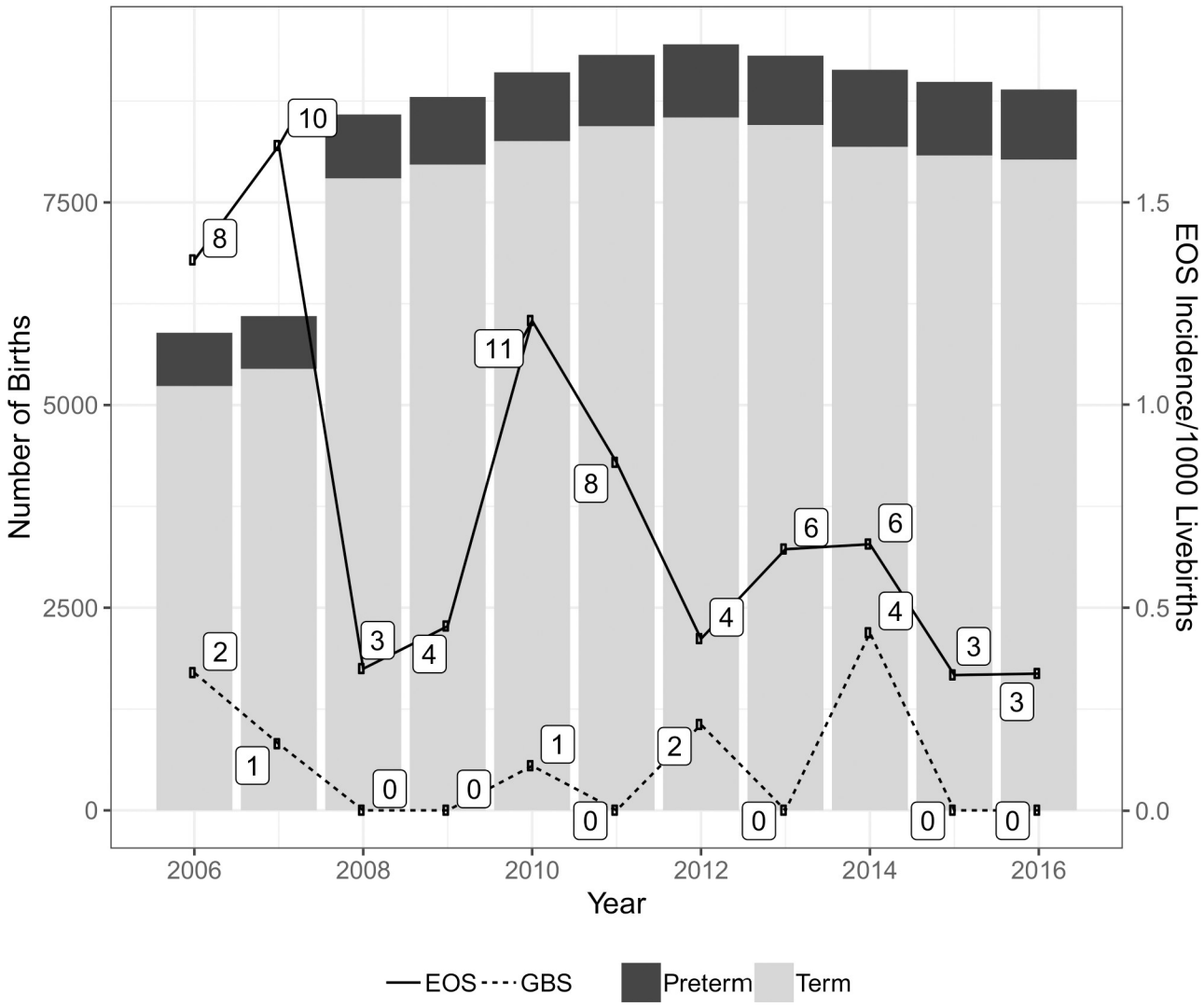

Fig 2. Early-onset sepsis events per 1000 live births.

https://doi.org/10.1371/journal.pone.0214298.g002

Gram-positive species were responsible for most EOS cases in term babies 18/22 (82%) versus 18/43 (42%) in preterm babies Table 2. Group B *Streptococcus* constituted almost half of EOS events in term babies at 10/22 (45%). The overall rate of EOGBS was 0.19/1000 (n = 18) live births.

Neonatal clinical course

Of the 14 babies born outside the metropolitan unit, the majority 11/14 (79%) remained in their regional unit of birth for on-going care. Two babies were transferred to the local metropolitan unit and one was transferred out of the LHD. We were unable to follow up babies transferred out of area, excluding mortality. Most babies with EOS are referred to one of the public facilities for management and would have been captured within our data set. Furthermore, given the high proportion of preterm babies undergoing blood culture in our district (21 to 35%), it is unlikely events were missed.

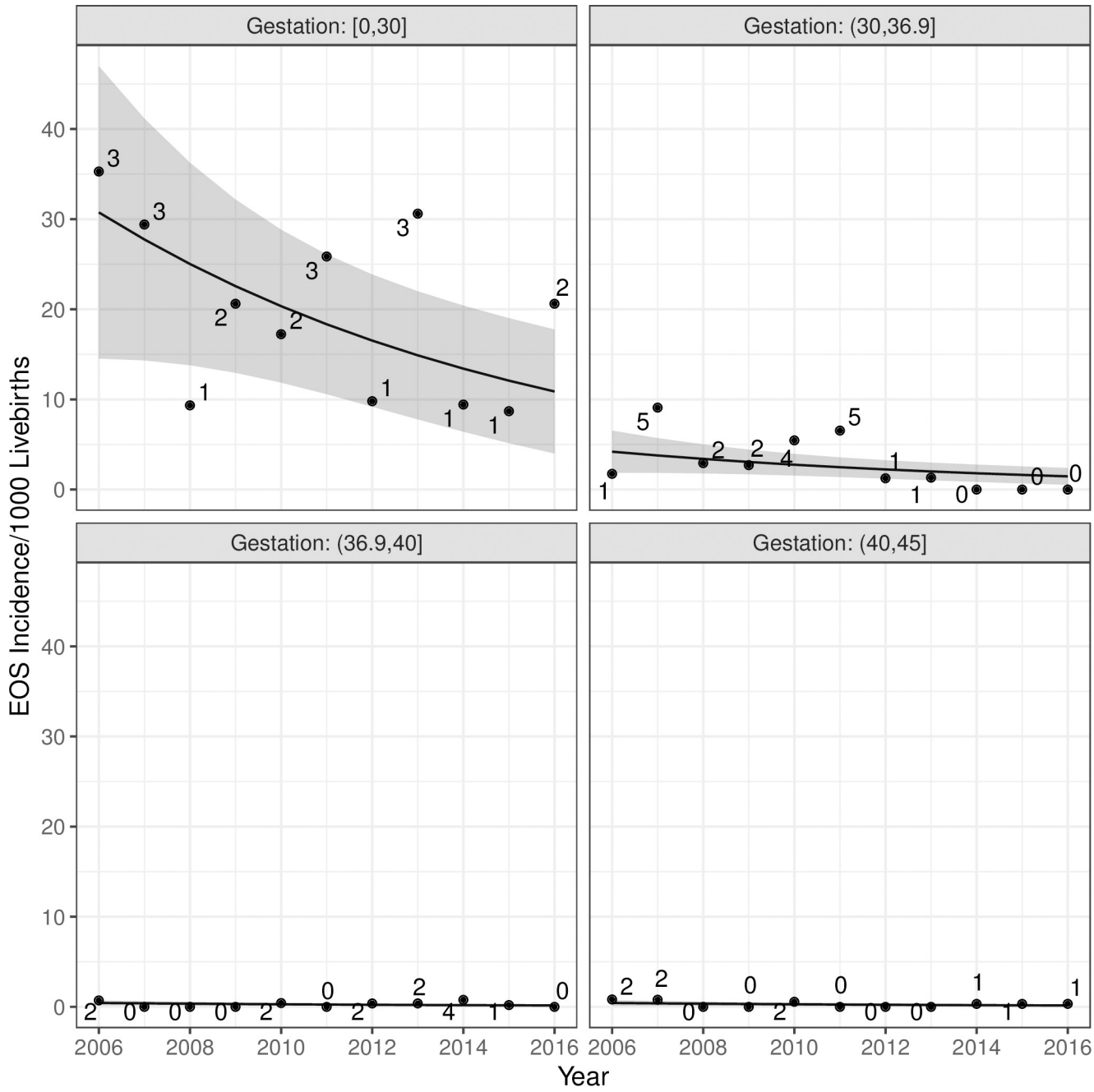

Fig 3. Early-onset sepsis events by gestation.

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All of the 65 babies were transferred to a neonatal intensive care unit/ special care unit (NICU) but only 14/65 (22%) were admitted with a primary presumptive diagnosis of sepsis. Other common reasons for admission were prematurity and/or respiratory distress.

All babies (except one unknown) subsequently diagnosed with EOS received antibiotics. Empiric treatment was reported as intravenous penicillin and gentamicin in 61/64 cases (95%). Term infants remained on antimicrobials for a median of seven days [IQR, 7.5, 5.0 to 12.5], and remained in hospital (NICU and/or ward) for a median of 7.5 days [IQR, 7.5, 3.5 to

Table 2. Term and preterm early-onset sepsis by organism.

Fungi	Term	Preterm	Total
Candida glabrata		1	**1**
Gram negative bacteria			
Acinetobacter baumannii complex	1		**1**
Escherichia coli*	**2**	**16**	**18**
Haemophilus influenzae		4	**4**
*Klebsiella pneumoniae**		1	**1**
*Morganella morganii**		1	**1**
Pseudomonas aeruginosa		1	**1**
Salmonella species*	1		**1**
*Serratia marcescens**		1	**1**
Gram positive bacteria			
Enterococcus faecalis	2		**2**
Enterococcus faecium	1		**1**
***Streptococcus agalactiae* (GBS)**	**10**	**8**	**18**
Streptococcus pneumoniae	2	4	**6**
Streptococcus species (other)	2	4	**6**
Staphylococcus aureus (methicillin-susceptible)	1	2	**3**
Total	**22**	**43**	**65**

*These species are from the *Enterobacteriaceae* family.

No events due to methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci were detected. Of the events due to *E. coli*, 67% were ampicillin resistant. No Gram-negative isolates producing extended spectrum betalactamases or carbapenemases were detected

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11.0]. Forty-one (95%) preterm babies were known to have antibiotics. Preterm babies with EOS also remained on antimicrobials for a median of seven days [IQR, 13.0, 3.3 to 16.3] and remained in hospital for a median of 19 days [IQR, 34.0, 3.8 to 37.85].

Morbidity and mortality

Thirty-three (50%) babies had serious short-term morbidity, in particular, ventilatory support requiring neonatal intensive care. Serious, short-term morbidity occurred in 8/13 (62%) term babies with non-EOGBS sepsis and 4/10 (40%) term babies with EOGBS. It was not possible to report on long-term morbidity.

Overall, 10/65 (17%) babies with EOS died; all were preterm. The rate of preterm mortality was 1.1/1000 preterm births and rate of mortality per total live births was 0.1/1000. Gestation ranged from 24 to 34 weeks and weight from 630 to 2440 grams. Six of the 10 babies that died had early-onset *E. coli* infection. Mortality occurred at a median of three days after birth [range 6 hours to 44 days]. All deaths occurred at the metropolitan hospital.

Discussion

This study provides an eleven-year, "real world" view of the epidemiology of EOS in a geographically and socially diverse setting. The EOS surveillance intensity varied with up to a two-fold difference in the proportion of term babies undergoing blood culture testing across the four largest neonatal units. Aside from the variation caused by different case mix, there are likely to be significant differences in clinician thresholds for blood culture collection, which

will impact on measured culture proven EOS rates. Blood culture utilisation should be included in future studies in accord with best epidemiological practice.

All-cause EOS events declined significantly with a multiplicative change in the odds of EOS reducing by approximately 9% per year over the study period. *Escherichia coli* (n = 18) and GBS (n = 18) were the most common bacteria causing EOS events. The very low frequency of EOS events limited what could be established statistically, however, the modelling showed a significant reduction in *E. coli* but no evidence of a significant change in EOGBS over time.

Historically, babies of ATSI mothers have been over-represented in early-onset sepsis data. In our study, there were six babies whose mothers were identified as ATSI. These babies represent 9% of all infants with EOS. This finding is similar to the proportion of ATSI women in our total cohort Table 1A & 1B and agrees with Singh et al whose work suggests the rate of EOS in babies of ATSI mothers may be decreasing [5].

The estimated incidence in 2016 of all-cause EOS in term babies was 0.19/1000 live births (95% CI, 0 to 0.4) at the overall median birth weight of 3.42 kg. After adjustment was made for gestation, birth weight, positive maternal GBS, ROM $\geq$18 hours and maternal age, this represented a non-significant decline from 0.5/1000 live births (95% CI, 0.02 to 0.97) in 2006 Fig 2. This result is consistent with other studies [5, 6].

As expected, EOS was highest in preterm infants with two-thirds of events occurring in this group. All-cause EOS events in preterm babies showed a significant decline over the years. Adjusted rates were 3.4/1000 live births in 2006 (95% CI, 0.11 to 6.76) to 1.35/1000 live births in 2016 (95% CI,-0.7 to 2.78). The most dramatic reduction occurred in babies <30 weeks gestation. After adjustment, rates in this group fell from 22/1000 live births (95% CI, 1.3 to 42.7) in 2006 to 8.8/ 1000 (95% CI, -0.5 to 18) in 2016. Preterm events that occurred from 2014–2016 were confined to babies of gestation <30 weeks Fig 2.

The decline in incidence of all preterm EOS events possibly represents the effect of local changes in the management of preterm birth which, since 2011, has included routine pre-emptive antibiotic treatment upon presentation of mothers in preterm, or suspected preterm labour (Murray, H., personal communication, 2018) and advances in neonatal intensive care provision over the study period.

A universal screening approach was recommended in our LHD across the study years, with risk factors considered if a woman was GBS unknown. The crude incidence of EOGBS across term and preterm groups in our study was low at 0.19/1000 live births and, despite minor fluctuations, did not change significantly over time. Whilst we acknowledge that EOGBS rates have increased and decreased across various jurisdictions during our study period, our results compare favourably with the contemporary incidence of EOGBS recorded by the English Neonatal Infection Surveillance unit, 0.57/1000 live births, using a risk factor approach [23]; a large, multi-centre study from the US, 0.2/1000 live births, using a universal screening approach [5] and 0.33/1000 live births in a recently published Australasian study [17]. In Australia either a universal or risk factor approach is used. New Zealand recommends a risk-based approach [24]

The use of IAP in our cohort has not been associated with a detectable increase in antimicrobial resistance or EOS due to non-GBS causes. However, increasing community colonisation with extended spectrum betalactamase-producing *E. coli* (7.5% in 2015) is documented in Australia and may, in future lead to increasing EOS events due to such strains [25] Table 2. In the tertiary facility, there have been two multi-resistant *E. coli* EOS events subsequent to this study's time period with isolates that were both resistant to gentamicin. One isolate was also resistant to ceftriaxone (*CTX-M-1* extended spectrum betalactamase gene detected).

Limitations of this study include the focus on reported culture-proven EOS events, which may have under-estimated the true burden of EOS due to false negative culture results. While

our models adjusted for relevant variables, we were unable to use all EOS risk factors, as history of GBS bacteriuria and having a previous child with EOGBS were not available from the database. Fever is currently stated as a risk factor for EOS but was poorly documented and therefore not used in our analysis.

The observational design may limit generalisability and is unable to rule out all possible biases. Our study is however, generalisable to other diverse jurisdictions that can link pathology data with a maternity outcomes database such as ObstetriX or e. Maternity.

We believe strengths of this study are the inclusion of women with low and high-risk pregnancies across a geographically and socially diverse region, over a long period of time, in a setting where maternal universal screening for GBS was in place throughout the study period. Further, unique to our study, the inclusion, and evaluation of EOS surveillance intensity by studying blood culture utilisation.

Future direction

Neonatal sepsis is an important issue in both low and high-income countries. At best, these invasive infections separate mothers and babies and strongly impact on the health care budget. At worst, invasive sepsis increases preterm birth, stillbirth, neonatal morbidity, and mortality. Although rates of GBS, the most common bacteria affecting term babies, remained low throughout our study, the potential for a vaccination to reduce risk of EOS due to GBS is attractive. In a recent multi-centre trial, GBS CPS III-TT conjugate vaccine significantly delayed maternal vaginal and rectal GBS serotype III colonisation [26].

However, a significant proportion of EOS occurs before a pregnancy is term and is due mainly to non-GBS causes. Most preterm babies do not benefit from maternal third trimester GBS screening and may not benefit from GBS vaccination. Whilst antenatal and intrapartum vigilance for signs of sepsis is crucial, a more upstream prevention such as optimisation of maternal factors that influence the neonatal and vaginal microbiome is worth consideration.

Finally, a tool that can assist clinicians in predicting the probability of EOS based on maternal risk factors as well as the baby's clinical presentation is being used in West Australia. Using this tool, the risk of EOS can be calculated in a baby born $\geq$34 weeks gestation [27]. The interactive calculator produces the probability of EOS per 1000 births. As well as reducing the proportion of newborns undergoing laboratory testing and receiving empirical antibiotic treatment [28], clinical care algorithms can assist a family's decision making around GBS screening and IAP provision, thereby possibly reducing the number of women and babies unnecessarily exposed to this intervention[29]. Such public health initiatives are best implemented, guided and audited by a multi-disciplinary maternity and neonatal care team.

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Methodology: Kathryn Braye, Maralyn Foureur, Mark Jones, John Ferguson.

Project administration: Kathryn Braye.

Supervision: Maralyn Foureur, Koert de Waal, John Ferguson.

Validation: Kathryn Braye, Maralyn Foureur, Koert de Waal, Elise Putt, John Ferguson.

Visualization: Kathryn Braye, Elise Putt.

Writing – original draft: Kathryn Braye.

Writing – review & editing: Kathryn Braye, Maralyn Foureur, Koert de Waal, Mark Jones, Elise Putt, John Ferguson.

References

1. Heron M. Deaths: leading causes for 2016. National Vital Statistics Report. US department of Health and Human Services. Center for Disease Control and Prevention; National Center for Health Statistics; 2016.
2. Tudela CM, Stewart RD, Roberts SW, Wendel GD Jr., Stafford IA, McIntire DD, et al. Intrapartum evidence of early-onset group B streptococcus. Obstet and gynecol. 2012; 119(3):626–9.
3. van Herk W, Stocker M, van Rossum A. Recognising early onset neonatal sepsis: An essential step in appropriate antimicrobial use. J Infect. 2016.
4. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr Infect Dis J. 2011; 30(11):937–41. https://doi.org/10.1097/INF.0b013e318223bad2 PMID: 21654548
5. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016; 138(6).
6. Singh T, Barnes EH, Isaacs D, Australian Study Group for Neonatal I. Early-onset neonatal infections in Australia and New Zealand, 2002–2012. Arch Dis Child Fetal Neonatal Ed 2018.
7. Royal College of Obstetricians and Gynaecologists. The Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. 2nd ed. London: Royal College of Obstetricains and Gynaecologists; 2012.
8. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines MMWR 2010; 59(1):1–36.
9. Brown RG, Marchesi JR, Lee YS, Smith A, Lehne B, Kindinger LM, et al. Vaginal dysbiosis increases risk of preterm fetal membrane rupture, neonatal sepsis and is exacerbated by erythromycin. BMC Medicine. 2018; 16(1):9. https://doi.org/10.1186/s12916-017-0999-x PMID: 29361936
10. Sung JH, Choi SJ, Oh SY, Roh CR, Kim JH. Revisiting the diagnostic criteria of clinical chorioamnionitis in preterm birth. BJOG. 2017; 124(5):775–83. https://doi.org/10.1111/1471-0528.14176 PMID: 27365145
11. UK National Screening Committee. Screening for Group B streptococcal infection in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2012.
12. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Maternal Group B Streptococcus in pregnancy: screening and management .C-Obs 19. 2016.
13. Heath P, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol. 2007; 21:411–24. https://doi.org/10.1016/j.bpobgyn.2007.01.003 PMID: 17336588
14. Mendoza-Palomar N, Balasch-Carulla M, Gonzalez-Di Lauro S, Cespedes MC, Andreu A, Frick MA, et al. Escherichia coli early-onset sepsis: trends over two decades. Eur J Pediatr. 2017; 176(9):1227–34. https://doi.org/10.1007/s00431-017-2975-z PMID: 28770413
15. Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland M. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed. 2011; 96(1): F4. https://doi.org/10.1136/adc.2009.178483 PMID: 20584804
16. Klinger G, Levy I, Sirota L, Boyko V, Reichman B, Lerner-Geva L, et al. Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants. Am J Obstet Gynecol. 2009; 201(1):38 e1-6. https://doi.org/10.1016/j.ajog.2009.03.006 PMID: 19380122
17. Chen JC, Jenkins-Marsh S, Flenady V, Ireland S, May M, Grimwood K, et al. Early-onset group B streptococcal disease in a risk factor-based prevention setting: A 15-year population-based study. Aust N Z J Obstet Gynaecol. 2018:1–8.
18. Edmond K, Kortsalioudaki C, Scott S, Schrag S, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet. 2012; 379 (9815):547–56. https://doi.org/10.1016/S0140-6736(11)61651-6 PMID: 22226047
19. Isaacs D. Evidence-based neonatal infections. United Kingdom: John Wiley & Sons Ltd; 2014.

20. Ohlsson A, Shah V. Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review). Cochrane Database Syst Rev. 2014; 6:CD007467.
21. Australian Bureau of Statistics. Hunter New England Local Area Health District: Healthstats: NSW Health; 2016 [updated 2016. cited 2019 Jan 16]. Available from http://www.healthstats.nsw.gov.au
22. National Institute for Health and Clinical Excellence. Antibiotics for early-onset neonatal infection. NICE clinical guideline No149. London. 2012.
23. Seedat F, Taylor-Phillips S, Geppert J, Stinton C, Patterson J, Brown C, et al. UK National Screening committee (UK NSC). Universal antenatal culture-based screening for maternal GBS carriage to prevent EOGBS disease. Review update. 2016.
24. NZ consensus guideline. The prevention of early-onset neonatal group B streptococcus infection. 2014.
25. Antimicrobial use and resistence in Australia: AURA report 2017 [cited 2018 Aug 8. Available from https://www.safetyandquality.gov.au/our-work/national-standards-and-accreditation.
26. Hillier SL, Ferrieri P, Edwards MS, Ewell M, Ferris D, Fine P, et al. A Phase II Randomized, Control Trial of Group B Streptococcus (GBS) Type III Capsular Polysaccharide -Tetanus Toxoid (GBS III-TT) Vaccine to Prevent Vaginal Colonization with GBS III. Clin Infect Dis. 2018.
27. Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis. JAMA Pediatr. 2017; 171 (4):365–71. https://doi.org/10.1001/jamapediatrics.2016.4678 PMID: 28241253
28. Lebedevs T, Sajogo M. Effect of the neonatal early onset sepsis calculator on pharmacy-prepared empirical antibiotics. J Pharm Pract Res. 2018; 48(5): 450–453
29. Kaiser Permanente Division of Health. Neonatal early-onset sepsis calculator. [cited 2019 Jan 08]. Available form https://neonatalsepsiscalculator.kaiserpermanente.org/2018

PLOS ONE

RESEARCH ARTICLE

Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-onset infection rates in an Australian local health district: 2006-2016

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Abstract

Background

Intrapartum antibiotic prophylaxis (IAP) to reduce the likelihood of neonatal early-onset group B streptococcal infection (EOGBS) has coincided with major reductions in incidence. While the decline has been largely ascribed to IAP following either universal screening or a risk-based approach to identify mothers whose babies may most benefit from IAP, there is lack of high quality evidence to support this view.

Aims

To describe management of maternal GBS colonisation in one local health district using universal screening and assess rates of EOGBS over time.

Methods

A retrospective cohort study was undertaken to describe compliance with GBS management, to determine the incidence of EOGBS and association between rates and maternal screening. Linking routinely collected maternity and pathology data, we explored temporal trends using logistic regression and covariates for potential effect modifiers.

Results

Our cohort included 62,281 women who had 92,055 pregnancies resulting in 93,584 live born babies. Screening occurred in 76% of pregnancies; 69% had a result recorded, 21.5% of those were positive for GBS. Prophylaxis was used by 79% of this group. Eighteen babies

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developed EOGBS, estimated incidence/1000 live births in 2006 and 2016 was 0.35 (95% CI, 0.07 to 0.63) and 0.1 (95% CI, 0 to 0.2) respectively. Seven of 10 term babies with EOGBS were born to mothers who screened negative. Data were unable to provide evidence of difference in rates of EOGBS between screened and unscreened pregnancies. We estimated the difference in EOGBS incidence from crude and weighted models to be 0 (95% CI, -0. 2 to 0.17) and -0.01 (95% CI, -0.13 to 0.10) /1000 live births respectively.

Conclusion

No change was detected in rates of EOGBS over time and no difference in EOGBS in babies of screened and unscreened populations. Screening and prophylaxis rates were modest. Limitations of universal screening suggest alternatives be considered.

Introduction

Early-onset group B streptococcal infection (EOGBS) is a high impact event that, despite its low frequency, remains a significant cause of early infant morbidity and mortality [1]. To reduce the likelihood of EOGBS, intrapartum antibiotic prophylaxis (IAP) was introduced in the 1980s and offered to women whose babies were thought to be most at risk. In the United States of America (USA), widespread use of IAP coincided with a decline in reported EOGBS rates; from 0.7/1000 live births in 1997 [2] to 0.22/ 1000 in 2016 [3]. However, since the pre-prevention era, the proportion of women and babies exposed to IAP has more than doubled (from 12% to 30%) in the USA and other high-income countries [4].

Antibiotics have saved millions of lives, but they are not without risk. Most recently concerns have been raised about the possible link between IAP exposure and dysbiosis of the infant's founding microbiome, which may lead to adverse health effects in later life [5–9]. Research which highlights benefits, risks and limitations of GBS screening and IAP provision is therefore warranted.

Background

Neonatal group B streptococcal colonisation and infection. Prior to the implementation of screening and IAP provision, it was believed that up to 50% of babies born vaginally to mothers with GBS colonisation would be colonised by the bacterium as part of their founding microbiome. Most of these babies were not compromised by GBS colonisation and remained well [10, 11]. In the absence of IAP, it is reported that 1–3% of babies colonised with GBS will develop EOGBS [12]; however, this proportion is difficult to quantify in the era of widespread IAP. In a global systematic review and meta-analysis, the incidence of EOGBS was 0·43/ 1000 live births (95% CI, 0·37–0·49) and global case fatality 12·1%, (6·2–18·3) [1].

Screening approaches. In 1996 the centers for disease control and prevention (CDC) published guidelines recommending that clinicians select women whose babies may benefit from IAP and offer prophylaxis to reduce the likelihood of EOGBS. The selection criteria were based on certain risk factors including maternal recto-vaginal GBS colonisation, rupture of membranes (ROM) $\geq$18 hours, intrapartum fever and prematurity [12–14]. History of bacteriuria in the index pregnancy and having a sibling diagnosed with EOGBS are also risk factors [12, 13].

In 2002, based on a large retrospective study in the USA [15], the CDC recommended universal screening for vaginal and rectal GBS colonisation of all pregnant women at 35–37 weeks' gestation as the best method for GBS management [16]. When GBS status was unknown, a risk-based based approach for IAP was recommended. In 2010 the CDC continued to recommend universal screening [12] although globally, countries remain divided regarding optimal GBS management.

In Australia the evolution of GBS management strategies began in the late 1970s, based on the observation of an unexpectedly large number of EOGBS reported in one city. As a consequence of a review into local EOGBS rates in a large metropolitan Melbourne hospital, policy recommended a universal GBS screen for pregnant women and provision of IAP to those at risk [17]. This review influenced GBS management throughout the country. However Australia has never had a national GBS policy and Australian states and territories recommend different approaches for selecting women for IAP. Queensland, for example, recommends a risk-based approach [18] and NSW recommends either universal screening or a risk-based approach [19]. The latest guidelines from the Royal Australian and New Zealand college of Obstetricians and Gynaecologists (RANZCOG) [13] also recommend either approach. Conversely, New Zealand has undertaken local research [20–22] and continues to offer a risk-based approach to manage GBS risk. A recent Australian systematic review concluded that the odds of EOGBS in infants of any gestation were significantly lower with universal screening compared with risk-based screening (OR 0.45, 95% CI, 0.37–0.53). However the authors noted the quality of the studies critiqued was low [23].

Incidence of early-onset group B streptococcal infection. Reported rates of neonatal EOGBS vary markedly, particularly in areas with limited access to laboratory diagnosis. Variation in rates may reflect changes in reporting of cases and/or natural fluctuation, a true increase or decrease in incidence, or less than optimal implementation of prevention strategies. Rates of EOGBS are often reported on a voluntary basis and therefore may not represent all confirmed cases. Our data include live births only. Although it is probable that GBS was a contributing factor in a proportion of stillborn babies in our district [24], it was not possible to obtain data on these babies.

Reported live birth rates of EOGBS in the USA, and other high-income countries including Australia, have remained stable for nearly two decades, at below 0.5/1000 live births [12, 25, 26]. Exceptions include New Zealand where researchers compared 1998–99 EOGBS rates which were estimated at 0.5/1000 live births (95% CI, 0.38, 0.65) [22] to rates five years later after instituting a national consensus risk-based approach. In 2009–11 EOGBS rates had halved to 0.26/1000 live births (95% CI, 0.18–0.37) [21]. Other countries have reported an increase in rates. The UK from 0.48/1,000 live births (95% CI, 0.43 to 0.53) in 2000–2001 to 0.57/1,000 live births in 2014/2015 (95% CI, 0.52–0.62) and [14] the Netherlands 0·11/1000 live births to 0·19/1000 live births ($p<0·0001$.)[16].

Local practice. In 2005, our local health district, now called Hunter New England Local Health District (HNELHD), changed GBS management from identification of risk factors to universal culture based screening and provision of IAP in line with the CDC guidelines of the time [16]. A local study, reported a dramatic decline in EOGBS (84%) when universal screening was employed to select candidates for IAP. The study reported that to prevent one case of the infection 5,704 women needed to be screened and 1,911 women with a positive GBS result would be required to have IAP [27].

The regime for IAP was set locally at 1.2-grams of penicillin followed by 600mg four hourly until birth [28] and, due to our very low EOGBS rates, this regime has not changed despite the Australian therapeutic guidelines [29] and CDC [30] recommendations of 3-grams of penicillin followed by 1.5–1.8 grams four hourly until birth. Over a decade has passed since this local

study and the change from a risk-based approach to universal screening. We were interested to assess compliance with universal GBS screening and IAP protocols and EOGBS rates in this population.

Aims

To describe compliance with GBS management in an era of universal screening and to assess rates of neonatal EOGBS over time in a diverse Australian local health district.

Methods

Study setting and population

A retrospective cohort study was employed using data from pregnancies that resulted in live born babies in the Hunter New England local health district, New South Wales (NSW) Australia, over the period 2006–2016.

The study population included women whose pregnancies resulted in live born babies birthing in all publicly funded maternity services within HNELHD and their babies. The term "pregnancies" or "women whose pregnancies" is used in this paper as around one third of women had more than one pregnancy during the study period. Included births occurred in hospitals, alongside and freestanding birth centres and at home, between 1st January 2006 and 31st December 2016 Table 1.

Information concerning babies and their mothers was obtained from the maternity ObstetriX database and the NSW Health Pathology database (Auslab). ObstetriX (now e. Maternity) is a state wide surveillance system providing point-of-care data collection across antenatal, intrapartum and immediate postnatal periods. Clinicians contribute information soon after birth. The database is maintained by local health district (LHD) data custodians. The medical records of babies affected by EOGBS and their mothers were also scrutinised. Provision of IAP was documented in the medical record with two clinicians signing for receipt and timing of the medication.

Table 1. Pregnancies resulting in live born babies per unit 2006–2016.

Birthing unit	Pregnancies	Babies
John Hunter Hospital	41946	42964
Maitland	17285	17472
Tamworth	8058	8194
Manning	6379	6459
Armidale	3849	3913
Inverell	2283	2314
Muswellbrook	2180	2184
Belmont Midwifery Group Practice	1996	1996
Singleton	1795	1795
Moree	1708	1714
Gunnedah	1628	1628
Narrabri	1234	1235
Scone	880	882
Glen Innes	662	662
Gloucester	121	121
Manilla	51	51
TOTALS	92,055	93,584

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We collected data on maternal antenatal and intrapartum risk factors, together with neonatal outcomes for the 18 babies with confirmed EOGBS. Maternal GBS colonisation, prematurity, ROM≥18 hours and maternal age were collected and used in analysis. While intrapartum fever, history of maternal GBS bacteriuria and history of a previous child with EOGBS are risk factors, and therefore considered in a decision to offer IAP, we were unable to obtain information on these variables at a population level.

Microbiological cultures

Neonatal EOGBS can be defined as culture proven GBS bacteria found in a normally sterile site; either blood, causing sepsis or cerebrospinal fluid (CSF) causing meningitis, or both [31]. Researchers use a range of time frames to define early-onset; from 48 hours to 7 days post birth. We applied the definition used by the National Institute for Health Care and Excellence (NICE) guidelines. This guideline defines EOS as sepsis occurring ≤72 hours after birth [31].

Neonatal cultures positive for GBS were accessed from the NSW health pathology database used for most public health pathology across HNELHD. Blood and CSF culture data were also accessed from 3 of 4 private providers who service small facilities in the north-western region of HNELHD.

Gestation and eligibility for group B streptococcal screening

Term gestation was defined as ≥37 weeks gestation, preterm <37 weeks gestation. Eligibility for GBS screening applied to all women whose pregnancies were ≥35 weeks gestation, which includes a small number of women whose pregnancies were preterm. Pregnancies that reached ≥35 weeks but <37 weeks gestation were classified as "eligible preterm pregnancies". Screening should occur within five weeks of birth to maximise accuracy [26].

Definition of screened and not screened

Identification of women whose pregnancies were screened or not screened required the combination of several fields within the obstetric database. Eligible pregnancies were regarded as "screened" if they met either of two categories: "screened with a result" available intrapartum or at ROM (n = 60,674 69%) or "Screened with no result" where screening results were not available or pending at the time of birth or ROM. Women whose pregnancies were regarded as "not screened" occurred if there was no entry in the ObstetriX database or a text entry that stated either "screening declined" or "not screened".

Definition of adequate intrapartum antibiotic prophylaxis

Intrapartum antibiotic prophylaxis was defined as adequate when the initial dose of IAP was given at least four hours prior to birth in line with current CDC and RANZCOG guidelines [12, 13].

Mortality and morbidity

Live status (as of December 2017) for each baby who had experienced an EOGBS event was derived from the HNELHD patient demographics system linked to NSW death registration data. Admission and short-term morbidity were reported as serious or not serious. Serious morbidity was defined as the need for significant respiratory support requiring neonatal intensive care; or circulatory support and/or encephalopathy or seizures. It was not possible to assess long-term morbidity in our study.

Ethics approval

The study was deemed by the chair of Hunter New England (HNE) human research ethics committee (HREC) not to require formal approval by the ethics committee. The study conforms to the obligations of the provision of privacy and confidentiality of patient data and clinical information, including NSW Health records and Information Privacy Act 2002 as requested in our letter of approval from HNE research Ethics and Governance unit. University of Technology Sydney, HREC, ratified this decision. No. 2014000115. Data were de-identified for the purposes of this study. Individual consent was not required.

Statistical analysis

Descriptive statistics for women, their pregnancies, and live born babies are provided Table 1. Early-onset GBS incidence rates were calculated as events/1000 live births per year. We explored EOGBS in the babies of all women whose pregnancies reached ≥35 weeks gestation and were therefore eligible for GBS screening. Given the low number of EOGBS events we report both crude and inverse probability weighting to balance groups. The inverse probability weights were estimated using a separate logistic regression model with screening status as the outcome regressed on variables plausibly related to EOGBS and/or screening including gestation, birth weight, positive maternal GBS screening, ROM ≥18 hours and maternal age at each pregnancy (categorical indicating <20 years or all others). We also used logistic regression to model trends in EOGBS incidence over time. All models were checked for calibration and discrimination and we used a conventional significance level of 0.05 throughout.

Results

Study population

Sixteen publicly funded birthing units were included Table 1 ranging from one metropolitan facility with an alongside birth centre and an associated freestanding birth centre nearby (in total around 4000 births per year), several regional units (700 to 1500 births per year) through to small rural units (<250 births per year).

After exclusions, (babies who were stillborn and entries with inadequate or duplicate data) the study population included 62,281 women who had 92,055 pregnancies over the study period resulting in 93,584 live born babies. Ninety-eight per cent of babies (90,510) were singletons and 9.7% (9,146) of babies were preterm. Sixty-five babies had confirmed EOS. We found 18 babies with EOGBS, 10 term and eight preterm (0.19/1000 live births) Fig 1. Half of the term babies with EOGBS were born in the metropolitan unit and half in regional units. One was transferred from a regional unit to a higher level of care. All preterm babies with EOGBS were born at the metropolitan unit.

Maternal GBS screening, colonisation and antibiotic prophylaxis

Nearly all women (96%) in our study had pregnancies ≥ 35 weeks and therefore were eligible for GBS screening. Seventy-six per cent of those eligible were reported to have a GBS screen. Of those, 69% had a result recorded in the database and 21.5% of those pregnancies were positive for GBS Table 2. Antibiotic prophylaxis was received by 79% of these women. Rates of positive maternal GBS colonisation in the cohort neither changed significantly from year to year nor materially between 2006 and 2016 Fig 2. Twelve per cent of women whose pregnancies were reported as GBS negative also received IAP Table 2. Reasons for administration of IAP to these women were not collected. Whether adequate IAP was given (≥4 hours before birth) could not be determined at a population level but was identified in individual cases.

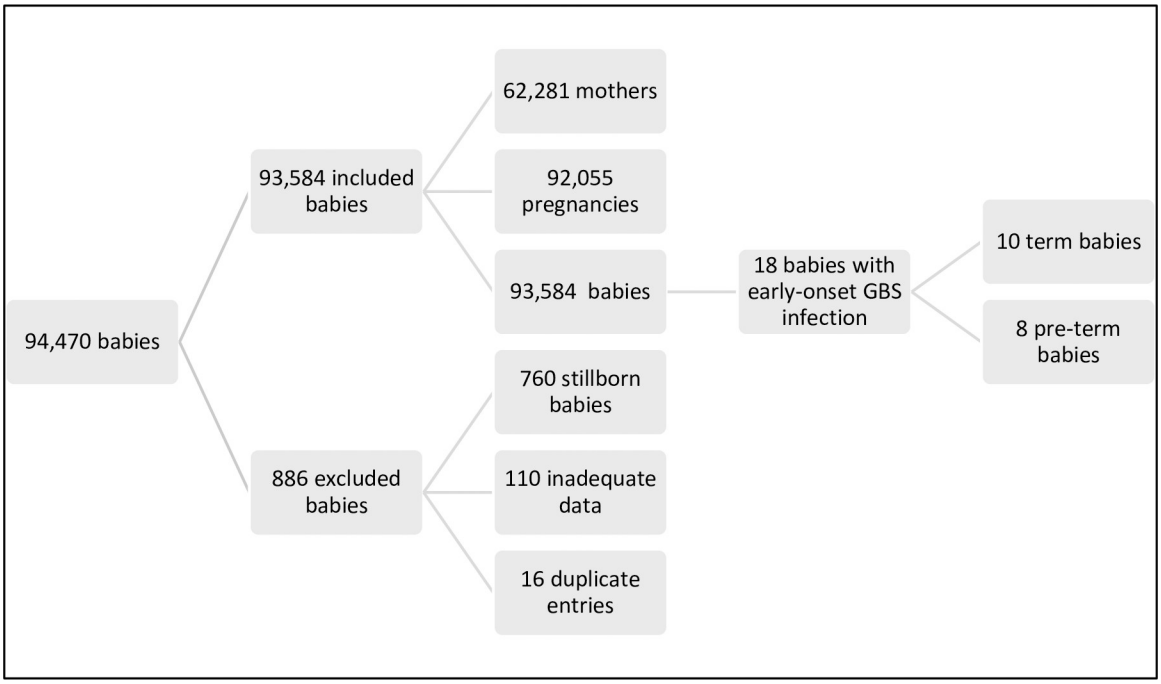

Fig 1. Inclusions and exclusions. EOGBS = early-onset group B streptococcal infection.

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Early-onset group B streptococcal infection over time

The odds ratio for the annual temporal trend of EOGBS obtained from the exponentiated parameter estimates was 0.88 (95% CI, 0.75 to 1.03, p = 0.11). Model estimates for incidence per /1000 live births in 2006 and 2016 were 0.35 (95% CI, 0.07 to 0.63) and 0.1 (95% CI, 0 to 0.2) respectively Fig 4. A bootstrapped estimate for the difference between the 2006 and 2016 incidence of EOGBS was -0.28 (95% CI, -0.04 to 0.74) suggesting negligible support for a change even over the 10-year interval.

Eligible babies with early-onset group B streptococcal infection

Ten term (therefore eligible) babies had EOGBS, a crude rate of 0.12/1000 term live births. All of these babies had mothers who were screened for GBS. These babies either had an eligible mother with a negative antenatal GBS screen (n = 7) or a mother with a positive GBS result that was unknown in labour and thus was unable to trigger IAP (n = 3). Six of the seven negative cultures were taken within five weeks of birth.

A further preterm baby, whose mother was eligible for GBS screening ($\geq$ 35 weeks gestation) and had a positive result known in labour and was subsequently diagnosed with EOGBS.

Six of these 11 babies had additional risk factors documented (prematurity and/or maternal GBS colonisation, ROM $\geq$ 18 hours, fever), which would qualify for IAP using a risk-factor only approach.

Two mothers in the eligible group received some IAP, however neither of these women received a dose $\geq$4 hours before birth.

Preterm babies with early-onset group B streptococcal infection

Eight babies with EOGBS were preterm (0.87/1000 preterm live births). Gestations ranged from 24 to 36 weeks. Two mothers in the preterm group received IAP (including the mother

Table 2. Eligible pregnancies, maternal GBS screening and colonisation rates, and IAP provision.

Birthing unit	Eligible pregnancies	Eligible pregnancies Screened (%)	Result recorded Pos/Neg (%)	GBS pos (%)	IAP given for GBS pos pregnancies (%)	IAP given for eligible not screened pregnancies (%)
John Hunter Hospital	38,885	32,011 (82)	29,529 (76)	7,089 (24)	5,600 (79)	825 (12)
Maitland	17,051	11,494 (67)	10,954 (64)	2,407 (22)	1,918 (80)	527 (9)
Tamworth	7,873	5,178 (66)	4,764 (61)	827 (17)	695 (84)	390 (14)
Manning	6,235	4,615 (74)	3,453 (55)	632 (18)	501 (79)	156 (10)
Armidale	3,781	2,411 (64)	2,148 (57)	401 (19)	359 (90)	202 (15)
Inverell	2,257	1,918 (85)	1,584 (70)	272 (17)	227 (83)	67 (20)
Muswellbrook	2,167	1,885 (87)	1,856 (86)	353 (19)	280 (79)	35 (12)
Belmont Midwifery Group Practice	1,996	1,479 (74)	1,417 (71)	297 (21)	24 (8)	4 (1)
Singleton	1,785	1,403 (79)	1,222 (68)	216 (18)	193 (89)	45 (12)
Moree	1,684	1,318 (78)	1,036 (62)	95 (9)	88 (93)	111 (30)
Gunnedah	1,621	1,432 (88)	996 (61)	164 (16)	148 (90)	66 (35)
Narrabri	1,223	816 (67)	583 (48)	64 (11)	44 (69)	71 (17)
Scone	876	673 (77)	646 (74)	140 (22)	127 (91)	27 (13)
Glen Innes	660	436 (66)	366 (55)	82 (22)	78 (95)	49 (22)
Gloucester	121	100 (83)	91 (75)	15 (16)	13 (87)	7 (33)
Manilla	51	33 (65)	29 (57)	4 (14)	3 (75)	0 (0)
TOTALS	88,266	67,202 (76)	60,674 (69)	13,058 (22)	10,298 (79)	2,582 (12)

Eligible pregnancy≥35 weeks gestation, Pos = positive, Neg = negative, IAP = intrapartum antibiotics prophylaxis

None of our models gave evidence that the screened and unscreened cohorts had differing rates of EOGBS Fig 3. We estimated the difference in EOGBS incidence across reported screening status from the crude and weighted models to be 0 (-0.2 to 0.17) /1000 live births and -0.01 (95% CI, -0.13 to 0.10) /1000 live births respectively. Adjusting for a temporal trend did not materially impact the estimates.

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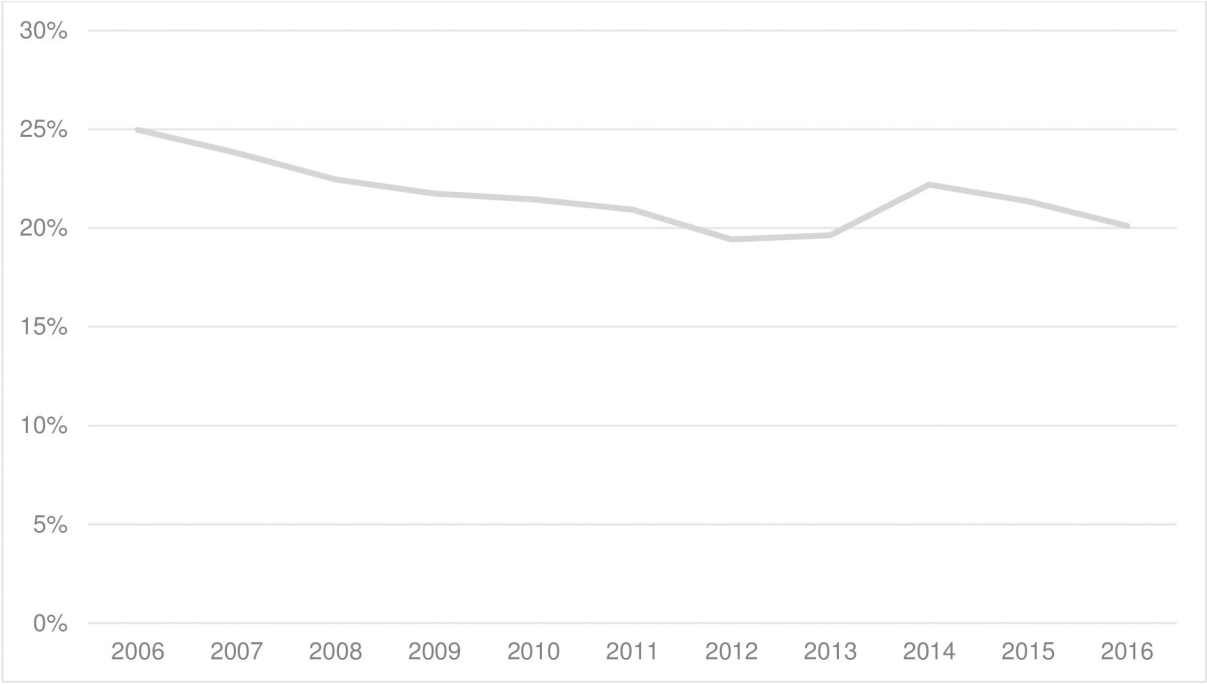

Fig 2. Maternal GBS colonisation.

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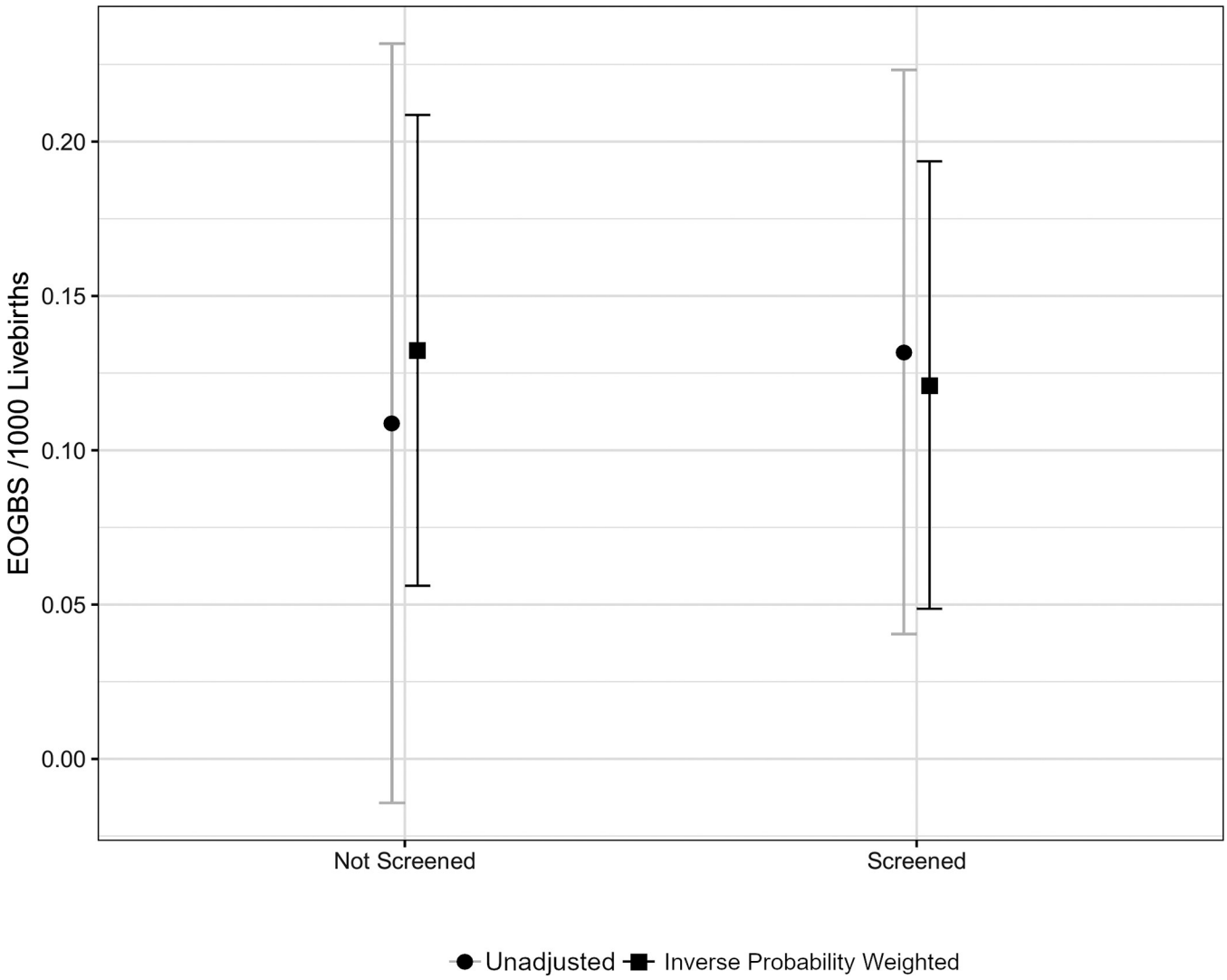

Fig 3. Screened versus unscreened pregnancies and rates of EOGBS. EOGBS = early-onset group B streptococcal infection.

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who was 36 weeks gestation and therefore eligible preterm), but neither dose was provided ≥ four hours before birth.

Morbidity and mortality

Four of 10 term babies with EOGBS had serious short-term morbidity. All required neonatal intensive care and significant continuous positive airways pressure therapy, one baby had seizure activity. All four were discharged home in a well state and were recorded as living as of December 2017, as were the other six. One preterm baby born <32 weeks gestation died (0.11/1000 live born preterm births) a combined term and preterm crude fatality rate of 0.01/1000 live births.

Discussion

This cohort study describes the management of GBS risk in our LHD in an era of universal screening and describes analysis of the rates and trends of EOGBS in an 11-year period in a diverse range of birth settings.

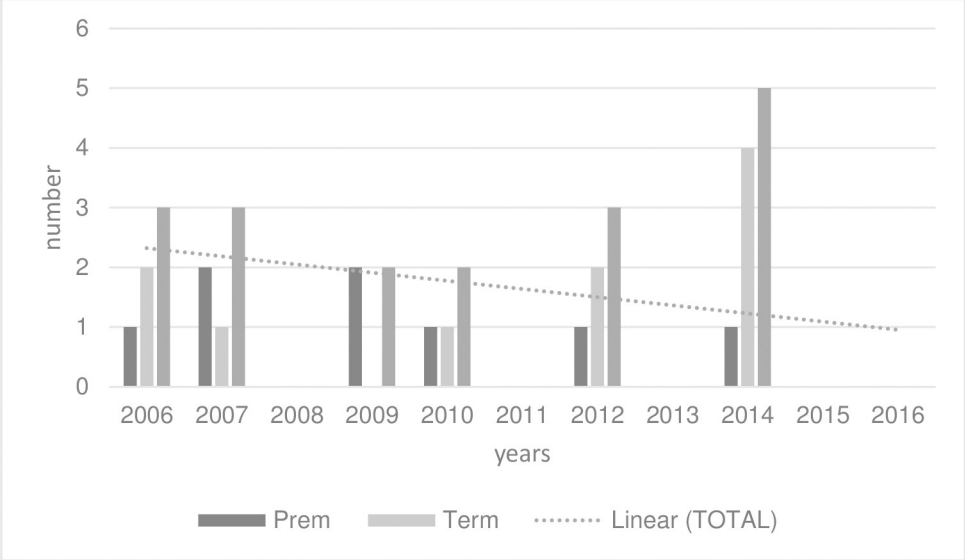

Fig 4. Incidence of term and preterm EOGBS 2006–2016.

https://doi.org/10.1371/journal.pone.0214295.g004

We found no evidence to conclude a difference in rates of EOGBS between women reported as screened or not screened for GBS. Our findings, along with others [32–34], highlight the logistical difficulty of mounting a sustained, consistent screening program across a large LHD. Furthermore, 12% of women who were not screened received IAP Table 2. The reasons for this were not analysed in this study.

Incidence of EOGBS in this population was low, at 0.19/1000 live births. The low frequency of EOGBS events limited our ability to explore time trends in incidence rates however our model did not provide evidence of a change in incidence over time. Our data align with the contemporary incidence rates recorded by a large, multi-centre study from the US, (0.2/1000 live births) [35].

It is possible and widely reported, that the rates of EOGBS may have remained low since the early 2000s because of screening and IAP provision [1, 34–36]. We found 21.5% of the 69% of pregnancies who were screened and had a result documented in the database, were positive for GBS. A modest 79% of women, who were positive for GBS at the end of their pregnancy, received some IAP Table 2. This finding is similar to the results found in a recent Australian integrative review [37]. The review found that although screening and IAP appeared to be very effective in reducing rates of EOGBS, the rate of IAP provision in the clinical setting was not optimal suggesting there may be other reasons for very low EOGBS rates. The database in our study did not specify the dose or frequency of IAP provision, so we could not establish if the IAP provided was assessed as adequate at a population level. At an individual level, to explore the experience of babies who had EOGBS, we examined individual medical records to obtain data not entered onto the ObstetriX database. None of the babies with EOGBS had mothers who were provided with adequate IAP.

In this era of universal screening and IAP provision there is no way of knowing what the rates of EOGBS in high income countries would be in babies whose mothers had GBS risk factors but no exposure to IAP. When data are compared from jurisdictions that use universal screening and IAP, versus a method based on risk factors, reported EOGBS rates are mixed, with either no change [25] increases in some jurisdictions [26,38] and decreases in others [21]. It should be noted, however, that some clinicians use a combination of the two standard

methods of selecting women most at risk of having a baby affected by this infection [39] so comparison between countries, and even areas within countries, is problematic.

Seven out of the ten term babies with EOGBS had mothers who were screened negative for GBS. These data concur with others reporting on EOGBS in the era of widespread IAP provision, finding rates of infection occurring among babies born to women with pregnancies negative for GBS were higher than previously reported [35, 40]. There are several reasons why this may be the case. These false negative results may be due to the modest predictive values of current screening protocols; which are influenced by intermittent maternal GBS colonisation [26]. Further, in some jurisdictions, swabs may be incorrectly taken and /or transported, or incorrectly processed [14].

Five of the seven term women whose pregnancies screened negative for GBS had another risk factor for infection (ROM $\geq$18 hours) warranting consideration for IAP using a risk-based approach. Even though the most common risk factor for EOGBS in our study and others [41, 42] was ROM $\geq$18 hours, numbers were too small (5/7 term women) to draw any conclusion. IAP was not administered to the five women with ROM $\geq$18 hours and a negative GBS result, in accord with local guideline recommendations at the time. Early-onset infection due to GBS occurring in babies born to women whose pregnancies have screened negative for GBS, further reflects the limitations of current methods of assessing GBS risk in our area.

As well as the protocol of screening and IAP provision that was offered to most, but not all, women with pregnancies that had a GBS positive result, it is likely that the low rates of EOGBS in our cohort maybe related to other factors. It is true that the crude rates of maternal GBS colonisation in the cohort neither changed significantly from year to year nor materially between 2006 and 2016. However, shifts in GBS serotypes and/or virulence of the bacteria may have occurred. Furthermore, population differences in exposure to GBS, maternal immunity, and foetal/neonatal susceptibility may also play a role in the reduction of infection rates [43]. Our low incidence of EOGBS in term babies cannot be exclusively ascribed to the protocol of offering women universal GBS screening and IAP.

Term babies in our study, diagnosed with EOGBS, were promptly treated and all survived. Case fatality in preterm babies with EOGBS was 0.01/1000 preterm live births.

Reduction in mortality since the 1970s, which was then as high as half of both term and preterm babies with EOGBS, is thought to be largely due to advances in maternity and neonatal care [14].

Limitations

Like many before, this study underestimates the true burden of EOGBS because it focuses on live born babies with culture-proven events, missing stillbirths and cases of clinical infection. Due to the rarity of EOGBS small case numbers prevented a more in-depth analysis; particularly of screened versus non-screened pregnancies.

We were unable to accurately record incidences of intrapartum fever and some other risk factors; a previous baby with EOGBS or bacteriuria in the index pregnancy and we were unable to access information for babies who were term and otherwise well but may have received antibiotics because of deemed inadequate chemoprophylaxis.

Our study uses a retrospective ascertainment of screening results, which may suffer from reporting bias. The high rate of undocumented GBS results in the database is a limitation and may be due, in part, to substandard data entry.

Strengths

This retrospective study covering 11 years includes regional, rural and some remote birthing populations using a range of birthing options; from a metropolitan unit, to smaller regional

units, birth centres and planned homebirth. Our study is generalisable to other jurisdictions with similar demographics and can be replicated in areas where researchers are able to collect pathology data and link these with a maternity and neonatal database such as ObstetriX or e. Maternity.

Future direction

Three decades ago, IAP was introduced as a safe but interim solution to manage GBS risk [35]. Mortality rates since the 1970s have dropped markedly and EOGBS is now a rare and treatable infection, even in babies who are not exposed to IAP as this study and others report [35]. Since the introduction of universal screening and IAP, the number of women and babies exposed to prophylactic antibiotics in labour for GBS risk has more than doubled (12% to 30%) in some jurisdictions. Most term babies exposed to IAP have negligible risk of succumbing to the infection and are therefore, arguably, exposed to IAP unnecessarily. Intrapartum antibiotic provision is not without its own set of risks. There is emerging speculative data associating intrapartum antibiotics with adverse health issues later in life [5–9]. Interventions of any kind are likely to have wider effects than acknowledged by evaluators. For ethical and methodological reasons, it is imperative that any harmful effects of interventions as well as their short-term benefits, are considered, analysed and, if relevant, alleviated. Furthermore, if universal screening continues to be recommended and used widely, high quality research to assess the relative benefits and risks of a universal screening protocol versus a risk-based approach is warranted. This will provide clinicians, women, and their families' access to high-quality evidence to enable them to discuss and make decisions about the risks they are prepared to embrace.

The potential for a maternal GBS vaccination to reduce the risk of EOGBS in term babies is supported by studies, which demonstrate that higher maternal serotype-specific antibody concentrations are associated with a lower risk of EOGBS. However, performing field trials on protein-conjugated GBS vaccines during pregnancy is not without its challenges, with large efficacy trials versus limited immunogenic studies being considered once a correlate of protection is universally identified and accepted [44].

Apart from vaccination, there may be other methods of reducing missed opportunities to provide IAP to those who would most benefit while reducing the number of mothers and babies unnecessarily exposed to IAP. Accurate and rapid methods of intrapartum GBS testing, aimed at a specific cohort of women who experience ROM without timely onset of labour, may assist in the identification of GBS status and assist women and clinicians in subsequent GBS risk management. To ensure optimum equity in maternity care, such a test should ideally be available to women accessing a variety of birth settings. In our LHD this proposal would require a point-of-care molecular test. Logistical and expense considerations may be challenging due to the wide variety of birth settings in our region. Point-of-care testing, however, has been offered for some time at a large metropolitan hospital in an adjoining LHD and may reduce the number of women and babies at term gestation unnecessarily exposed to intrapartum antibiotics.

Following presentation of this study, decision makers in our LHD have resolved not to increase the dose of prophylactic antibiotics for maternal GBS colonisation due to our very low and stable term EOGBS rates. This HNELHD will therefore not be in line with the current Australian therapeutic guidelines and the CDC recommendations for prophylaxis, which we believe, warrant review.

Based on the results of this study we, along with others [45], strongly recommend that primary attention to risk factors for EOGBS infection and timely prophylaxis or antibiotic treatment as indicated would be a more effective strategy for reduction of EOGBS in both preterm

and term groups rather than the universal screening approach which failed to identify all infants at risk.

Author Contributions

Conceptualization: Kathryn Braye, Maralyn Foureur.

Data curation: Kathryn Braye, Mark Jones, Elise Putt, John Ferguson.

Formal analysis: Kathryn Braye, Mark Jones.

Investigation: Kathryn Braye, Elise Putt, John Ferguson.

Methodology: Kathryn Braye, Maralyn Foureur, Mark Jones, John Ferguson.

Project administration: Kathryn Braye.

Supervision: Maralyn Foureur, Koert de Waal, John Ferguson.

Validation: Maralyn Foureur, Koert de Waal, Mark Jones, Elise Putt, John Ferguson.

Visualization: Elise Putt.

Writing – original draft: Kathryn Braye.

Writing – review & editing: Kathryn Braye, Maralyn Foureur, Koert de Waal, Mark Jones, Elise Putt, John Ferguson.

References

1. Edmond K, Kortsalioudaki C, Scott S, Schrag S, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet. 2012; 379 (9815):547–56. https://doi.org/10.1016/S0140-6736(11)61651-6 PMID: 22226047
2. Centers for Disease Control and Prevention. Emerging Infections Program Network. Group B Streptococcus. Active Bacterial Core Surveillance Report. 1997.
3. Centers for Disease Control and Prevention. Emerging Infections Program Network. Group B Streptococcus. Active Bacterial Core Surveillance Report. 2016.
4. Van Dyke M, Phares C, Lynfield R, Thomas A, Arnold K, Craig A. Evaluation of universal antenatal screening for group B streptococcus. New Eng J Med. 2009; 360:2626–36. https://doi.org/10.1056/NEJMoa0806820 PMID: 19535801
5. Butel MJ, Waligora-Dupriet AJ, Wydau-Dematteis S. The developing gut microbiota and its consequences for health. J Dev Orig Health Dis. 2018:1–8.
6. Azad MB, Konya T, Persaud RR, Guttman DS, Chari RS, Field CJ, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. BJOG. 2015; 123:983–93. https://doi.org/10.1111/1471-0528.13601 PMID: 26412384
7. Neuman H, Forsythe P, Uzan A, Avni O, Koren O. Antibiotics in early life: dysbiosis and the damage done. FEMS Microbiol Rev. 2018; 42(4):489–99. https://doi.org/10.1093/femsre/fuy018 PMID: 29945240
8. Örtqvist A, Lundholm C, Halfvarson C, Ludvigsson J. Fetal and early life antibiotics exposure and very early onset inflammatory bowel disease: a population-based study. Gut. 2019;68(2).
9. Miller JE, Wu C, Pedersen LH, de Klerk N, Olsen J, Burgner DP. Maternal antibiotic exposure during pregnancy and hospitalization with infection in offspring: a population-based cohort study. Int J Epidemiol. 2018; 47(2):561–71. https://doi.org/10.1093/ije/dyx272 PMID: 29415232
10. Gilbert G, Hewitt M, Turner C, Leeder S. Epidemiology and predictive values of risk factors for neonatal group B streptococcal sepsis. Aust N J Z Obstet Gynaecol. 2002; 45(5):497–503.
11. Heath P, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol. 2007; 21:411–24. https://doi.org/10.1016/j.bpobgyn.2007.01.003 PMID: 17336588
12. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines MMWR 2010; 59(1):1–36.
13. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Maternal Group B Streptococcus in pregnancy: screening and management .C-Obs 19. 2016.

14. UK National Screening Committee. Screening for Group B streptococcal infection in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2012.
15. Schrag S, Zell E, Lynfield R, Roome A, Arnold K, Craig A, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. New Eng J Med. 2002; 347:233–40. https://doi.org/10.1056/NEJMoa020205 PMID: 12140298
16. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines. MMWR Recomm Rep 2010; 59:1–36. 2002;51(1):1–36.
17. Garland S, Fliegner J. Group B streptococcus (GBS) and neonatal infections: The case for intrapartum chemoprophylaxis. Aust N J Z Obstet Gynaecol. 1991; 31(2):110–22.
18. Queensland Government department of health. Queensland clinical guidelines. Early onset group B streptococcus disease. 2015.
19. Maternal Group B Streptococcus (GBS) and minimisation of neonatal early-onset GBS sepsis. Minstry of Health. NSW government. 2016.
20. Darlow B. Early-onset neonatal Group B Streptococcal (GBS) disease in New Zealand: results of a two year surveillance study. Paediatr Child Health. 2013; 24(49).
21. Darlow BA, Voss L, Lennon DR, Grimwood K. Early-onset neonatal group B streptococcus sepsis following national risk-based prevention guidelines. Aust N Z J Obstet Gynaecol. 2016; 56(1):69–74. https://doi.org/10.1111/ajo.12378 PMID: 26172580
22. Grimwood K, Darlow BA, Gosling IA, Green R, Lennon DR, Martin DR, et al. Early-onset neonatal group B streptococcal infections in New Zealand 1998–1999. Paediatr Child Health. 2002; 38(3):272–7.
23. Kurz E, Davis D. Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review. JBI Database System Rev Implement Rep. 2015; 13(3):206–46. https://doi.org/10.11124/jbisrir-2015-1876 PMID: 26447057
24. Seale AC, Blencowe H, Bianchi-Jassir F, Embleton N, Bassat Q, Ordi J, et al. Stillbirth With Group B Streptococcus Disease Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017; 65 (suppl_2):S125–S32. https://doi.org/10.1093/cid/cix585 PMID: 29117322
25. Chen JC, Jenkins-Marsh S, Flenady V, Ireland S, May M, Grimwood K, et al. Early-onset group B streptococcal disease in a risk factor-based prevention setting: A 15-year population-based study. Aust N Z J Obstet Gynaecol. 2018:1–8.
26. Seedat F, Taylor-Phillips S, Geppert J, Stinton C, Patterson J, Brown C, et al. UK National Screening committee (UK NSC). Universal antenatal culture-based screening for maternal GBS carriage to prevent EOGBS disease. Review update. 2016.
27. Angstetra D, Ferguson J, Giles W. Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. A N Z J Obstet Gynaecol. 2007; 47:378–82.
28. Antibiotic expert groups. Therapeutic guidelines: antibiotic version 13. Melbourne: Therapeutic guidelines limited; 2006.
29. Antibiotic expert groups. Therapeutic guidelines: antibiotic version 14. Melbourne: Therapeutic guidelines limited; 2010.
30. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococal Disease. MMWR 1996; 45(RR-7):1–24.
31. National Institute for Health and Care Excellence. Recognising risk factors for infection during pregnancy, labour and birth. 2014.
32. Lin F, Weisman L, Azimi P, Young A, Chang K, Cielo M, et al. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. Pediatr Infect Dis J. 2011; 30 (9):759–63. https://doi.org/10.1097/INF.0b013e31821dc76f PMID: 21540758
33. Berardi A, Lugli L, Rossi C, China M, Chiossi C, Gambini L, et al. Intrapartum antibiotic prophylaxis failure and group-B streptococcus early-onset disease. J Matern Fetal Neonatal Med. 2011; 24(10):1221–4. https://doi.org/10.3109/14767058.2011.552652 PMID: 21714691
34. Fairlie T, Zell ER, Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. J Obstet Gynecol 2013; 121(3):570–7.
35. Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016; 138(6).
36. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr Infect Dis J. 2011; 30(11):937–41. https://doi.org/10.1097/INF.0b013e318223bad2 PMID: 21654548

37. Braye K, Ferguson J, Davis D, Catling C, Monk A, Foureur M. Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B Streptococcal infection: An integrative review. Women Birth. 2018; 31(4):244–53. https://doi.org/10.1016/j.wombi.2017.10.012 PMID: 29129472

38. Bekker V, Bijlsma MW, van de Beek D, Kuijpers TW, van der Ende A. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. Lancet Infect Dis. 2014; 14(11):1083–9. https://doi.org/10.1016/S1473-3099(14)70919-3 PMID: 25444407

39. Sheehy A, Davis D, Homer CS. Assisting women to make informed choices about screening for Group B Streptococcus in pregnancy: a critical review of the evidence. Women Birth. 2013; 26(2):152–7. https://doi.org/10.1016/j.wombi.2012.10.004 PMID: 23182754

40. Verani J, Spina N, Lynfield R, Schaffner W, Harrison L, Holst A, et al. Early-onset Group B Streptococcal disease in the United States: potential for further reduction. Obstet and gynecol. 2014; 123(4):828–37.

41. Berardi A, Rossi C, Bacchi Reggiani ML, Bastelli A, Capretti MG, Chiossi C, et al. An area-based study on intrapartum antibiotic prophylaxis for preventing group B streptococcus early-onset disease: advances and limitations. J Matern Fetal Neonatal Med. 2017; 30(14):1739–44. https://doi.org/10.1080/14767058.2016.1224832 PMID: 27593156

42. Vergnano S, Embleton N, Collinson A, Menson E, Bedford Russell A, Heath P. Missed opportunities for preventing group B streptococcus infection. Arch Dis Child Fetal Neonatal Ed. 2010; 96:F72–3.

43. Kwatra G, Cunnington M, Merrall E, Adrian P, Ip M, Klugman KP, et al. Prevelance of maternal colonisation with group B streptococcus: a systematic review and meta-analysis. Lancet Infect Dis. 2016; 16:1076–84. https://doi.org/10.1016/S1473-3099(16)30055-X PMID: 27236858

44. Russell NJ, Seale AC, O'Driscoll M, O'Sullivan C, Bianchi-Jassir F, Gonzalez-Guarin J, et al. Maternal Colonization With Group B Streptococcus and Serotype Distribution Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017; 65(suppl_2):S100–S11. https://doi.org/10.1093/cid/cix658 PMID: 29117327

45. Seedat F, Geppert J, Stinton C, Patterson J, Freeman K, Johnson SA, et al. Universal antenatal screening for group B streptococcus may cause more harm than good. BMJ. 2019; 364:l463. https://doi.org/10.1136/bmj.l463 PMID: 30787018

Appendix 4 Ethics approval from HNEHREC

29 May 2014

Ms K. Braye
Delivery Suite
John Hunter Hospital

Dear Ms Braye

Re: A study of the management of group B streptococcal colonisation in pregnant women: Benefits and risks of preventative modalities

Thank you for your enquiry regarding the proposed audit **A study of the management of group B streptococcal colonisation in pregnant women: Benefits and risks of preventative modalities** to be conducted in the division of Maternity and Gynaecology in the Hunter New England Local Health District. This audit does not need the approval of the Hunter New England Human Research Ethics Committee.

Please note that any publications resulting from this audit should adhere to the provision of privacy and confidentiality of patient data and clinical information, including the *NSW Health Records and Information Privacy Act 2002.*

Yours sincerely

Production Note:

Signature removed prior
to publication.

For: Professor M Parsons
Chair
Hunter New England Human Research Ethics Committee

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)
(New Lambton NSW 2305)
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Appendix 5 Ethics approval from UTS

Subject: UTS HREC Approval

Research Ethics <research.ethics@uts.edu.au> Wed, 2 Jul 2014, 16:24
to Kate Braye, Maralyn Foureur, Research Ethics

Dear Applicant

The UTS Human Research Ethics Committee reviewed your application titled, "A study of the management of group B streptococcal colonisation in pregnant women: Benefits and risks of preventative modalities", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). I am pleased to inform you that ethics approval is now granted.

Your approval number is UTS HREC REF NO. 2014000115
Your approval is valid five years from the date of this email.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually from the date of approval, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: http://rmprod.itd.uts.edu.au/RMENet/HOM001N.aspx
* if accessing outside of UTS network: https://remote.uts.edu.au , and click on "RMENet - ResearchMaster Enterprise" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

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Thesis References

Aagaard, K., Ma, J., Antony, K.M., Ganu, R., Petrosino, J. & Versalovic, J. 2014, 'The placenta harbors a unique microbiome', *Science Translational Medicine*, vol. 6, no. 237.

American College of Obstetricians and Gynecologists (ACOG) 2019, *Prevention of Group B Streptococcal Early-Onset Disease in Newborns-committee opinion*.

Angstetra, D., Ferguson, J. & Giles, W. 2007, 'Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit', *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 47, pp. 378-82.

Antibiotic expert group 2000, *Therapeutic guidelines: antibiotic version 11*, Therapeutic guidelines limited, Melbourne.

Antibiotic expert group 2006, *Therapeutic guidelines: antibiotic version 13*, Therapeutic guidelines limited, Melbourne.

Antibiotic expert group 2010, *Therapeutic guidelines: antibiotic version 14*, Therapeutic guidelines limited, Melbourne.

Antibiotic expert group 2014, *Therapeutic guidelines: antibiotic version 15*, Therapeutic guidelines limited, Melbourne.

Australian Bureau of Statistics 2016, *Hunter New England Local Area Health District (HNELHD): Healthstats*, internet, NSW Health, viewed 16 January 2019.

Azad, M.B., Bridgman, S.L., Becker, A.B. & Kozyrskyj, A.L. 2014, 'Infant antibiotic exposure and the development of childhood overweight and central adiposity', *International Journal of Obesity*, vol. 38, no. 10, pp. 1290-8.

Azad, M.B., Konya, T., Persaud, R.R., Guttman, D.S., Chari, R.S., Field, C.J., Sears, M.R., Mandhane, P.J., Turvey, S.E., Subbarao, P., Becker, A.B., Scott, J.A. & Kozyrskyj, A.L. 2015, 'Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study', *British Journal of Obstetrics and Gynaecology*, vol. 123, pp. 983-93.

Baker, C. 1997, 'Group B streptococcal infections', *Clinics in Perinatology*, vol. 28, pp. 59-70.

Baker, C. & Edwards, M. 1988, 'Group B Streptococcal Infections Perinatal Impact and Prevention Methods', *Annals of the New York Academy of Sciences*, pp. 193-201.

Barber, E., Zhao, G., Buhimschi, I. & Illuzzi, J. 2008, 'Duration of Intrapartum Prophylaxis and Concentration of Penicillin G in Fetal Serum at Delivery', *Obstetrics and Gynecology*, vol. 112, no. 2, pp. 265-70.

Barcaite, E., Bartusevicius, A., Tameliene, R., Kliucinskas, M., Maleckiene, L. & Nadisauskiene, R. 2008, 'Prevalence of maternal group B streptococcal colonisation in European countries', *Acta Obstetricia et Gynecologica Scandinavica*, vol. 87, pp. 260-71.

Barton, L.L., Feigin, R.D. & Lins, R. 1973, 'Group B beta hemolytic streptococcal meningitis in infants', *Journal of Pediatrics*, vol. 82, p. 719.

Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K.F., Simel, D. & Stroup, D.F. 1996, 'Improving the quality of

reporting of randomized controlled trials. The CONSORT statement', *Journal of the American Medical Association*, vol. 276, no. 8, pp. 637-9.
Bekker, V., Bijlsma, M.W., van de Beek, D., Kuijpers, T.W. & van der Ende, A. 2014, 'Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study', *Lancet Infectious Diseases*, vol. 14, no. 11, pp. 1083-9.
Berardi, A., Lugli, L., Rossi, C., China, M., Chiossi, C., Gambini, L., Guidi, B., Pedna, M., Piepoli, M., Simoni, A. & Ferrari, F. 2011, 'Intrapartum antibiotic prophylaxis failure and group-B streptococcus early-onset disease', *Journal of Maternal-Fetal & Neonatal Medicine*, vol. 24, no. 10, pp. 1221-4.
Berardi, A., Rossi, C., Bacchi Reggiani, M.L., Bastelli, A., Capretti, M.G., Chiossi, C., Fiorini, V., Gambini, L., Gavioli, S., Lanari, M., Memo, L., Papa, I., Pini, L., Rizzo, M.V., Zucchini, A., Facchinetti, F. & Ferrari, F. 2017, 'An area-based study on intrapartum antibiotic prophylaxis for preventing group B streptococcus early-onset disease: advances and limitations', *Journal of Maternal and Fetal Neonatal Medicine*, vol. 30, no. 14, pp. 1739-44.
Bergman, N.J. 2019, 'Birth practices: Maternal-neonate separation as a source of toxic stress', *Birth Defects Research*, vol. 111, no. 15, pp. 1087-109.
Bevan, D., White, A., Marshall, J. & Peckham, C. 2019, 'Modelling the effect of the introduction of antenatal screening for group B Streptococcus (GBS) carriage in the UK', *British Medical Journal Open*, vol. 9, no. 3, p. e024324.
Bienenfeld, S., Rodriguez-Riesco, L.G. & Heyborne, K.D. 2016, 'Avoiding Inadequate Intrapartum Antibiotic Prophylaxis for Group B Streptococci', *Obstetrics and Gynecology*, vol. 128, no. 3, pp. 598-603.
Blaser, M. 2011, 'Antibiotic overuse: Stop the killing of beneficial bacteria', *Nature*, vol. 476, no. 7361, pp. 393-4.
Blaser, M.J. 2010, 'Harnessing the power of the human microbiome', *Proceedings of the National Academy of Sciences*, vol. 107, no. 14, pp. 6125-6.
Blaser, M.J. & Dominguez-Bello, M.G. 2016, 'The Human Microbiome before Birth', *Cell Host & Microbe*, vol. 20, no. 5, pp. 558-60.
Bokulich, N.A., Chung, J., Battaglia, T., Henderson, N., Jay, M., Li, H., A, D.L., Wu, F., Perez-Perez, G.I., Chen, Y., Schweizer, W., Zheng, X., Contreras, M., Dominguez-Bello, M.G. & Blaser, M.J. 2016, 'Antibiotics, birth mode, and diet shape microbiome maturation during early life', *Science Translational Medicine*, vol. 8, no. 343.
Boyer, K. & Gotoff, S. 1986, 'Prevention of group B streptococcal disease with selective chemoprophylaxis', *The New England Journal of Medicine*, vol. 314, no. 26, pp. 1665-9.
Braye, K., Ferguson, J., Davis, D., Catling, C., Monk, A. & Foureur, M. 2018, 'Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B Streptococcal infection: An integrative review', *Women and Birth*, vol. 31, no. 4, pp. 244-53.
Braye, K., Foureur, M., de Waal, K., Jones, M., Putt, E. & Ferguson, J. 2019, 'Epidemiology of neonatal early-onset sepsis in one Australian health district 2006-2016', *PloS One*, vol. 14, no. 4, pp. 1-14.
Braye, K., Foureur, M., de Waal, K., Jones, M., Putt, E. & Ferguson, J. 2019, 'Group B streptococcal screening, intrapartum antibiotic prophylaxis, and neonatal early-

onset infection rates in an Australian local health district: 2006-2016', *PloS One*, vol. 14, no. 4, pp. 1-15.
Bridges, M., Pesek, E., McRae, M. & Chabra, S. 2019, 'Use of an Early Onset-Sepsis Calculator to Decrease Unnecessary NICU Admissions and Increase Exclusive Breastfeeding', *Journal of Obstetric and Gynecological Neonatal Nursing*, vol. 48, no. 3, pp. 372-82.
Brown, R.G., Marchesi, J.R., Lee, Y.S., Smith, A., Lehne, B., Kindinger, L.M., Terzidou, V., Holmes, E., Nicholson, J.K., Bennett, P.R. & MacIntyre, D.A. 2018, 'Vaginal dysbiosis increases risk of preterm fetal membrane rupture, neonatal sepsis and is exacerbated by erythromycin', *BMC Medicine*, vol. 16, no. 1, p. 9.
Buckley, S. 2015, *Hormonal Physiology of childbearing: evidence and implications for women, babies and maternity care*, Childbirth connection: a program of national partnership for women and families, Washington DC.
Butel, M.J., Waligora-Dupriet, A.J. & Wydau-Dematteis, S. 2018, 'The developing gut microbiota and its consequences for health', *Journal of Developmental Origins of Health and Disease*, vol. 9, no. 6, pp. 590-7.
Centers for Disease Control and Prevention 1996, 'Prevention of Perinatal Group B Streptococcal Disease', *Mortality and Morbidity weekly report (MMWR). Recommendations and reports*, vol. 45, no. RR-7, pp. 1-24.
Centers for Disease Control and Prevention 1997, *Emerging Infections Program Network. Group B Streptococcus. Active Bacterial Core Surveillance Report*.
Centers for Disease Control and Prevention 2002, 'Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines', *Mortality and Morbidity weekly report (MMWR). Recommendations and reports*, vol. 51, no. 1, pp. 1-36.
Centers for Disease Control and Prevention 2010, 'Prevention of Perinatal Group B Streptococcal Disease: Revised guidelines ', *Mortality and Morbidity weekly report (MMWR). Recommendations and reports*, vol. 59, no. 1, pp. 1-36.
Centers for Disease Control and Prevention 2016, 'Emerging Infections Program Network. Group B Streptococcus. Active Bacterial Core Surveillance Report'.
Centre for Epidemiology and Evidence 2016, *New South Wales Mothers and Babies report 2016*, Ministry of Health Sydney.
Chan, W.S.W., Chua, S.C., Gidding, H.F., Ramjan, D., Wong, M.Y.W., Olma, T., Thomas, L. & Gilbert, G.L. 2014, 'Rapid identification of group B streptococcus carriage by PCR to assist in the management of women with prelabour rupture of membranes in term pregnancy', *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 54, no. 2, pp. 138-45.
Chen, J.C., Jenkins-Marsh, S., Flenady, V., Ireland, S., May, M., Grimwood, K. & Liley, H.G. 2018, 'Early-onset group B streptococcal disease in a risk factor-based prevention setting: A 15-year population-based study', *Australian and New Zealand Journal of Obstetrics and Gynaecology*, pp. 1-8.
Chu, D., Antony, K., Ma, J., Prince, A., Showalter, L., Moller, M. & Aagaard, K. 2016, 'The early infant gut microbiome varies in association with a maternal high-fat diet', *Genome Medicine*, vol. 8, no. 1, p. 77.
Chu, D.M., Ma, J., Prince, A.L., Antony, K.M., Seferovic, M.D. & Aagaard, K.M. 2017, 'Maturation of the infant microbiome community structure and function

across multiple body sites and in relation to mode of delivery', *Nature Medicine*, vol. 23, no. 3, pp. 314-26.
Colbourn, T. & Gilbert, R. 2007, 'An overview of the natural history of early onset group B streptococcal disease in the UK', *Early Human Development*, vol. 83, no. 3, pp. 149-56.
Collado, M.C., Cernada, M., Bauerl, C., Vento, M. & Perez-Martinez, G. 2012, 'Microbial ecology and host-microbiota interactions during early life stages', *Gut Microbes*, vol. 3, no. 4, pp. 352-65.
Colombo, D., Lew, J., Pedersen, C., Johnson, J. & Fan-Havard, P. 2006, 'Optimal timing of ampicillin administration to pregnant women for establishing bactericidal levels in the prophylaxis of group B streptococcus', *American Journal of Obstetrics and Gynecology*, vol. 194, pp. 466-70.
Cong, X., Xu, W., Romisher, R., Poveda, S., Forte, S., Starkweather, A. & Henderson, W. 2016, 'Gut Microbiome and Infant Health: Brain-Gut-Microbiota Axis and Host Genetic Factors', *Yale Journal of Biology and Medicine*, vol. 89, pp. 299-306.
Corvaglia, L., Legnani, E., Martini, S., Di Gioa, D., Aloisio, I., Oss, M., Biavati, B. & Faldella, G. 2012, 'Intrapartum Antibiotic Prophylaxis in Mothers GBS-Positive: Effects on Newborn Microbiota', *Digestive and Liver Disease*, vol. 44, p. S278.
Critical Appraisal Skills Programme (CASP) 2014, *CASP checklists*, Oxford Centre for Triple Value Healthcare, Oxford, viewed 27 May 2015, <http://www.casp-uk.net/>.
Dahlen, H.G., Kennedy, H.P., Anderson, C.M., Bell, A.F., Clark, A., Foureur, M., Ohm, J.E., Shearman, A.M., Taylor, J.Y., Wright, M.L. & Downe, S. 2013, 'The EPIIC hypothesis: intrapartum effects on the neonatal epigenome and consequent health outcomes', *Medical Hypotheses*, vol. 80, no. 5, pp. 656-62.
Dahlen, H.G., Tracy, S., Tracy, M., Bisits, A., Brown, C. & Thornton, C. 2012, 'Rates of obstetric intervention among low-risk women giving birth in private and public hospitals in NSW: a population-based descriptive study', *British Medical Journal*, vol. 2, no. 5.
Dangor, Z., Kwatra, G., Izu, A., Adrian, P., Cutland, C.L., Velaphi, S., Ballot, D., Reubenson, G., Zell, E.R., Lala, S.G. & Madhi, S.A. 2015, 'Correlates of protection of serotype-specific capsular antibody and invasive Group B Streptococcus disease in South African infants', *Vaccine*, vol. 33, no. 48, pp. 6793-9.
Darbyshire, P., Collins, C., McDonald, H.M. & Hiller, J.E. 2003, 'Taking antenatal group B Streptococcus seriously: women's experiences of screening and perceptions of risk', *Birth*, vol. 30, no. 2, pp. 116-23.
Darlow, B., Campbell, N., Austin, N., Chin, A., Grigg, C., Skidmore, C., Voss, L., Walls, T., Wise, M. & Werno, A. 2015, 'The prevention of early-onset neonatal group B streptococcus infection: New Zealand Consensus Guidelines 2014', *New Zealand Medical Journal*, vol. 128, no. 1425, pp. 69-76.
Darlow, B.A. 2013, ' Early-onset neonatal Group B Streptococcal (GBS) disease in New Zealand: results of a two year surveillance study', *Paediatric Child Health*, vol. 24, no. 49.
Darlow, B.A., Voss, L., Lennon, D.R. & Grimwood, K. 2016, 'Early-onset neonatal group B streptococcus sepsis following national risk-based prevention

guidelines', *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 56, no. 1, pp. 69-74.
Di Renzo, G., Melin, P., Berardi, A., Blennow, M., Carbonell-Estrany, X., Donzelli, G., Hakansson, S., Hod, M., Hughes, R., Kurtzer, M., Poyart, C., E , Shinwell, C., Stray-Pedersen, B., Wielgos, M. & El Helali, N. 2014, 'Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference', *Journal of Maternal-Fetal and Neonatal Medicine*, pp. 1-17.
Dominguez-Bello, M.G., Godoy-Vitorino, F., Knight, R. & Blaser, M.J. 2019, 'Role of the microbiome in human development', *Gut*, vol. 68, no. 6, pp. 1108-14.
Edmond, K., Kortsalioudaki, C., Scott, S., Schrag, S., Zaidi, A.K., Cousens, S. & Heath, P.T. 2012, 'Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis', *Lancet*, vol. 379, no. 9815, pp. 547-56.
Edwards, R., Clark, P., Sistrom, C. & Duff, P. 2002, 'Intrapartum antibiotic prophylaxis: relative effects of recommended antibiotics on Gram-negative pathogens', *American Journal of Obstetrics and Gynecology*, vol. 100, pp. 534-9.
Evans, D. 2003, 'Hierarchy of Evidence: a framework for ranking evidence evaluating healthcare interventions', *Journal of Clinical Nursing*, vol. 12, pp. 77-84.
Faa, G., Gerosa, C., Fanni, D., Nemolato, S., van Eyken, P. & Fanos, V. 2013, 'Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy', *Journal of Maternal-Fetal & Neonatal Medicine*, vol. 26 Suppl 2, pp. 35-43.
Fabbrini, M., Rigat, F., Rinaudo, C.D., Passalaqua, I., Khacheh, S., Creti, R., Baldassarri, L., Carboni, F., Anderloni, G., Rosini, R., Maione, D., Grandi, G., Telford, J.L. & Margarit, I. 2016, 'The Protective Value of Maternal Group B Streptococcus Antibodies: Quantitative and Functional Analysis of Naturally Acquired Responses to Capsular Polysaccharides and Pilus Proteins in European Maternal Sera', *Clinical Infectious Diseases*, vol. 63, no. 6, pp. 746-53.
Fahy, K., Foureur, M. & Hastie, C. (eds) 2008, *Birth Territory and Midwifery Guardianship*, Elsevier, Philadelphia.
Fairlie, T., Zell, E.R. & Schrag, S. 2013, 'Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease', *Obstetrics and Gynecology*, vol. 121, no. 3, pp. 570-7.
Finfgeld, D.L. 2001, 'New directions for feminist therapy based on social constructionism', *Archives of Psychiatric Nursing*, vol. 15, no. 3, pp. 148-54.
Foureur, M., Braye, K., Ferguson, J., deWaal, K., Putt, E. & Jones, M. 2019, '[Dataset] Epidemiology of neonatal early-onset sepsis, incidence and outcomes and group B streptococcal screening, intrapartum antibiotic prophylaxis provision in an Australian local health district 2006-2016.', University of Technology Sydney.
Franciosi, R.A., Knostman, J.D. & Zimmerman, R.A. 1973, 'Group B streptococcal neonatal and infant infections', *Journal of Pediatrics*, vol. 82, p. 707.
Fujimura, K. & Lynch, S. 2015, 'Microbiota in allergy and asthma and the emerging relationship with the gut microbiome', *Cell Host & Microbe*, vol. 17, no. 5, pp. 592-602.
Furfaro, L.L., Chang, B.J. & Payne, M.S. 2018, 'Perinatal Streptococcus agalactiae Epidemiology and Surveillance Targets', *Clinical Microbiology Reviews*, vol. 31, no. 4, pp. 49-18.

Garland, S. & Fliegner, J. 1991, 'Group B streptococcus (GBS) and neonatal infections: The case for intrapartum chemoprophylaxis', *Australian and New Zealand Journal of Obstetrics Gynaecology*, vol. 31, no. 2, pp. 110-22.

GBS/CIDP Foundation International 2019, USA, viewed 26/10/2019.

Gilbert, G., Hewitt, M., Turner, C. & Leeder, S. 2002, 'Epidemiology and predictive values of risk factors for neonatal group B streptococcal sepsis', *Australian of New Zealand Journal of Obstetrics and Gynaecology*, vol. 45, no. 5, pp. 497-503.

Giorgakoudi, K., O'Sullivan, C. & Health, P. 2018, 'Cost-effectiveness analysis of maternal immunisation against group B streptococcus (GBS) disease: a modelling study', *Vaccine*, vol. 36, no. 46, pp. 7033-42.

Glasziou, P., Moynihan, R., Richards, T. & Godlee, F. 2013, 'Too much medicine; too little care', *British Medical Journal*, vol. 347, pp. 42-7.

Goel, N., Shrestha, S., Smith, R., Mehta, A., Ketty, M., Muxworthy, H., Abelian, A., Kirupaalar, V., Saeed, S., Jain, S., Asokkumar, A., Natti, M., Barnard, I., Pitchaikani, P.K. & Banerjee, S. 2019, 'Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population', *Archives of Disease in Childhood: Fetal and Neonatal Edition*.

Grimwood, K., Darlow, B.A., Gosling, I.A., Green, R., Lennon, D.R., Martin, D.R. & Stone, P.R. 2002, 'Early-onset neonatal group B streptococcal infections in New Zealand 1998-1999', *Paediatric Child Health*, vol. 38, no. 3, pp. 272-7.

Group B Strep support group, Sussex, UK, viewed 15 August 2019, <https://gbss.org.uk/>.

Hannah, M., Ohlsson, A., Wang, E., Matlow, A., Foster, G., Willan, A., Hodnett, E., Weston, J., Farine, D., Gareth, P. & Seaward, R. 1997, 'Maternal colonisation with group B streptococcus and pre-labour rupture of the membranes at term: the role of induction of labor', *American Journal of Obstetrics and Gynecology*, vol. 177, no. 4, pp. 780-5.

Healy, S., Humphreys, E. & Kennedy, C. 2016, 'Midwives' and obstetricians' perceptions of risk and its impact on clinical practice and decision-making in labour: An integrative review', *Women and Birth*, vol. 29, no. 2, pp. 107-16.

Heath, P.T. & Schuchat, A. 2007, 'Perinatal group B streptococcal disease', *Best Practice & Research: Clinical Obstetrics & Gynaecology*, vol. 21, no. 3, pp. 411-24.

Heron, M. 2016, *Deaths: leading causes for 2016. National Vital Statistics Report. US department of Health and Human Services*, vol. 67, Centers for Disease Control and Prevention; National Center for Health Statistics.

Hill, A.M. & Butler, H.M. 1940, 'Haemolytic streptococci following childbirth and abortion; clinical features with special reference to groups other than A', *Medical Journal of Australia*, vol. 1, pp. 293-9.

Hillier, S.L., Ferrieri, P., Edwards, M.S., Ewell, M., Ferris, D., Fine, P., Carey, V., Meyn, L., Hoagland, D., Kasper, D.L., Paoletti, L.C., Hill, H. & Baker, C.J. 2018, 'A Phase II Randomized, Control Trial of Group B Streptococcus (GBS) Type III Capsular Polysaccharide -Tetanus Toxoid (GBS III-TT) Vaccine to Prevent Vaginal Colonization with GBS III', *Clinical Infectious Diseases*.

Hoffmann, T.C. & Del Mar, C. 2015, 'Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review', *Journal of the American Medical Association Internal Medicine*, vol. 175, no. 2, pp. 274-86.
Hoffmann, T.C. & Del Mar, C. 2017, 'Clinicians' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review', *Journal of the American Medical Association Internal Medicine*, vol. 177, no. 3, pp. 407-19.
Homer, C.S.E., Scarf, V., Catling, C. & Davis, D. 2014, 'Culture-based versus risk-based screening for the prevention of group B streptococcal disease in newborns: A review of national guidelines', *Women and Birth*, vol. 27, no. 1, pp. 46-51.
Hood, M., Janney, A. & Dameron, G. 1961, 'Beta hemolytic streptococcus group B associated with problems of the perinatal period', *American Journal of Obstetrics and Gynecology*, pp. 809-18.
Hunter New England Local Health District 2018, 'Maternity: Prevention of early-onset GBS sepsis in the newborn at term'.
Illuzzi, J.L. & Bracken, M.B. 2006, 'Duration of intrapartum prophylaxis for neonatal group B streptococcal disease: a systematic review', *Obstetrics and Gynecology*, vol. 108, no. 5, pp. 1254-65.
Isaacs, D. 2014, *Evidence-based neonatal infections*, John Wiley & Sons Ltd, United Kingdom.
Jeffery, H. & McIntosh, E. 1994, 'Antepartum screening and non-selective intrapartum chemoprophylaxis for group B streptococcus', *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 34, no. 1, pp. 14-9.
Johnson, J.R., Colombo, D.F., Gardner, D., Cho, E., Fan-Havard, P. & Shellhaas, C.S. 2001, 'Optimal dosing of penicillin G in the third trimester of pregnancy for prophylaxis against group B Streptococcus', *American Journal of Obstetrics and Gynecology*, vol. 185, no. 4, pp. 850-3.
Kaiser Permanente Division of Health 2018, *Neonatal early-onset sepsis calculator* https://neonatalsepsiscalculator.kaiserpermanente.org/, viewed 2 November 2018.
Klinger, G., Levy, I., Sirota, L., Boyko, V., Reichman, B., Lerner-Geva, L. & Israel Neonatal, N. 2009, 'Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants', *American Journal of Obstetrics and Gynecology*, vol. 201, no. 1, pp. 38 e1-6.
Knight, M., Callaghan, W.M., Berg, C., Alexander, S., Bouvier-Colle, M.H., Ford, J.B., Joseph, K.S., Lewis, G., Liston, R.M., Roberts, C.L., Oats, J. & Walker, J. 2009, 'Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group', *BMC Pregnancy and Childbirth*, vol. 9, no. 55.
Kobayashi, M., Vekemans, J., Baker, C., Ratner, A., Le Doare, K. & Schrag, S. 2016, 'Group B Streptococcus vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries', *F1000 Research*, vol. 5, p. 2355.
Koebnick, C., Tartof, S., Sidell, M., Rozema, E., Chung, J., Taylor, Z., Xiang, A. & Getahun, D. 2019, 'Effect of In-Utero Antibiotic Exposure on Childhood Outcomes: Methods and Baseline Data of the Fetal Antibiotic Exposure (FAX)

Cohort Study', *Journal of Medical Internet Research. Research Protocols* vol. 8, no. 7.
Kurz, E. & Davis, D. 2014, 'Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review protocol', *Joanna Briggs Institute Database System of Reviews and Implementation Reports*, vol. 12, no. 7, pp. 62-71.
Kurz, E. & Davis, D. 2015, 'Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review', *Joanna Briggs Institute Database System of Reviews and Implementation Reports*, vol. 13, no. 3, pp. 206-46.
Kuzniewicz, M.W., Puopolo, K.M., Fischer, A., Walsh, E.M., Li, S., Newman, T.B., Kipnis, P. & Escobar, G.J. 2017, 'A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis', *Journal of the American Medical Association Pediatric*, vol. 171, no. 4, pp. 365-71.
Kwatra, G., Cunnington, M., Merrall, E., Adrian, P., Ip, M., Klugman, K.P., Tam, W. & Madhi, S.A. 2016, 'Prevalence of maternal colonisation with group B streptococcus: a systematic review and meta-analysis', *Lancet Infectious Diseases*, vol. 16, pp. 1076-84.
Lancefield, R. & Hare, R. 1935, 'The serological differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women.', *Journal of Experimental Medicine*, no. 61, pp. 335-49.
Lauder, A.P., Roche, A.M., Sherrill-Mix, S., Bailey, A., Laughlin, A.L., Bittinger, K., Leite, R., Elovitz, M.A., Parry, S. & Bushman, F.D. 2016, 'Comparison of placenta samples with contamination controls does not provide evidence for a distinct placenta microbiota', *Microbiome*, vol. 4, p. 29.
Le Doare, K. & Heath, P.T. 2013, 'An overview of global GBS epidemiology', *Vaccine*, vol. 31 Suppl 4, pp. 7-12.
Le Doare, K., Heath, P.T., Plumb, J., Owen, N.A., Brocklehurst, P. & Chappell, L.C. 2018, 'Uncertainties in screening and prevention of Group B Streptococcus disease', *Clinical Infectious Diseases*, vol. 4, pp. 720-5.
Le Doare, K., Kampmann, B., Vekemans, J., Heath, P.T., Goldblatt, D., Nahm, M.H., Baker, C., Edwards, M.S., Kwatra, G., Andrews, N., Madhi, S.A., Meulen, A.S., Anderson, A.S., Corsaro, B., Fischer, P. & Gorringe, A. 2019, 'Serocorrelates of protection against infant group B streptococcus disease', *Lancet Infectious Diseases*, vol. 19, no. 5, pp. 162-71.
Le Doare, K., O'Driscoll, M., Turner, K., Seedat, F., Russell, N.J., Seale, A.C., Heath, P.T., Lawn, J.E., Baker, C.J., Bartlett, L., Cutland, C., Gravett, M.G., Ip, M., Madhi, S.A., Rubens, C.E., Saha, S.K., Schrag, S., Sobanjo-Ter Meulen, A., Vekemans, J. & Kampmann, B. 2017, 'Intrapartum Antibiotic Chemoprophylaxis Policies for the Prevention of Group B Streptococcal Disease Worldwide: Systematic Review', *Clinical Infectious Diseases*, vol. 65, no. suppl_2, pp. S143-S51.
Le Doare, K.L. 2016, 'Global maternal group B streptococcus colonisation', *Lancet Infectious Diseases*, vol. 16, no. 9, pp. 992-3.
Lebedevs, T. & Sajogo, M. 2018, 'Effect of the neonatal early onset sepsis calculator on pharmacy-prepared empirical antibiotics', *Journal of Pharmacy Practice and Research*, vol. 48, no. 5, pp. 450-3.

Lin, F., Weisman, L., Azimi, P., Young, A., Chang, K., Cielo, M., Moyer, P., Troendle, J., Schneerson, R. & Robbins, J. 2011, 'Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease', *Pediatric Infectious Disease Journal*, vol. 30, no. 9, pp. 759-63.

Lin, F.Y., Brenner, R.A., Johnson, Y.R., Azimi, P.H., Philips, J.B., 3rd, Regan, J.A., Clark, P., Weisman, L.E., Rhoads, G.G., Kong, F. & Clemens, J.D. 2001, 'The effectiveness of risk-based intrapartum chemoprophylaxis for the prevention of early-onset neonatal group B streptococcal disease', *American Journal of Obstetrics and Gynecology*, vol. 184, no. 6, pp. 1204-10.

MacDonald, C., McLachlan, R., Handorf, S. & Green, J. 2010, 'Group B streptococcus: The impact of risk and prophylaxis on midwives and women in the childbirth experience', *Birthspirit midwifery journal*, vol. 6, pp. 47-54.

Madhi, S.A., Cutland, C.L., Jose, L., Koen, N.G., F Wittke, M Olugbosi, A Meulen, S Baker, S , Dull, P., Vas, N. & Slobod, K. 2016, 'Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial', *Lancet Infectious Diseases*, vol. 16, pp. 923-34.

Madhi, S.A., Dangor, Z., Heath, P.T., Schrag, S., Izu, A., Sobanjo-Ter Meulen, A. & Dull, P.M. 2013, 'Considerations for a phase-III trial to evaluate a group B Streptococcus polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young infants', *Vaccine*, vol. 31 Suppl 4, pp. D52-7.

Marziali, G., Foschi, C., Parolin, C., Vitali, B. & Marangoni, A. 2019, 'In-vitro effect of vaginal lactobacilli against group B Streptococcus', *Microbial Pathogenesis*, vol. 136, p. 103692.

Matorras, R., Garcia-Perea, A., Omenaca, F., Diez-Enciso, M., Madero, R. & Usandizaya, J. 1991, 'Intrapartum chemoprophylaxis of early-onset group B streptococcal disease', *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 40, no. 1, pp. 57-62.

McCraken, G.H. 1973, 'Group B streptococci in neonatal infections', *Journal of Pediatrics*, vol. 82, no. 4, pp. 703-6.

McDonald, K., Amir, L.H. & Davey, M.-A. 2011, 'Maternal bodies and medicines: a commentary on risk and decision-making of pregnant and breastfeeding women and health professionals', *BMC Public Health*, vol. 11.

McNanley, A.R., Glantz, J.C., Hardy, D.J. & Vicino, D. 2007, 'The effect of intrapartum penicillin on vaginal group B streptococcus colony counts', *American Journal of Obstetrics and Gynecology*, vol. 197, no. 6, pp. 583 e1-4.

Mendoza-Palomar, N., Balasch-Carulla, M., Gonzalez-Di Lauro, S., Cespedes, M.C., Andreu, A., Frick, M.A., Linde, M.A. & Soler-Palacin, P. 2017, 'Escherichia coli early-onset sepsis: trends over two decades', *European Journal of Pediatrics*, vol. 176, no. 9, pp. 1227-34.

Miller, J.E., Wu, C., Pedersen, L.H., de Klerk, N., Olsen, J. & Burgner, D.P. 2018, 'Maternal antibiotic exposure during pregnancy and hospitalization with infection in offspring: a population-based cohort study', *International Journal of Epidemiology*, vol. 47, no. 2, pp. 561-71.

Miller, S., Abalos, E., Chamillard, M., Ciapponi, A., Colaci, D., Comande, D., Diaz, V., Geller, S., Hanson, C., Langer, A., Manuelli, V., Millar, K., Morhason-Bello, I.,

Castro, C.P., Pileggi, V.N., Robinson, N., Skaer, M., Souza, J.P., Vogel, J.P. & Althabe, F. 2016, 'Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide', *Lancet*, vol. 388, no. 10056, pp. 2176-92.

Money, D. & Allen, V. 2013, 'The prevention of early onset neonatal group B streptococcal disease', *Journal of Obstetrics and Gynaecologists of Canada*, vol. 35, no. 10, pp. 939-51.

Moroi, H., Kimura, K., Kotani, T., Tsuda, H., Banno, H., Jin, W., Wachino, J.I., Yamada, K., Mitsui, T., Yamashita, M., Kikkawa, F. & Arakawa, Y. 2019, 'Isolation of group B Streptococcus with reduced beta-lactam susceptibility from pregnant women', *Emerging Microbes and Infections*, vol. 8, no. 1, pp. 2-7.

Mueller, N.T., Bakacs, E., Combellick, J., Grigoryan, Z. & Dominguez-Bello, M.G. 2015, 'The infant microbiome development: mom matters', *Trends in Molecular Medicine*, vol. 21, no. 2, pp. 109-17.

Muller-Pebody, B., Johnson, A.P., Heath, P.T., Gilbert, R.E., Henderson, K.L. & Sharland, M. 2011, 'Empirical treatment of neonatal sepsis: are the current guidelines adequate?', *Archives of Disease and Childhood Neonatal Fetal Edition.*, vol. 96, no. 1, p. F4.

Nabhan, A.F., Elhelaly, A. & Elkadi, M. 2014, 'Antibiotic prophylaxis in prelabor spontaneous rupture of fetal membranes at or beyond 36 weeks of pregnancy', *International Journal of Gynecology and Obstetrics*, vol. 124, no. 1, pp. 59-62.

National association of testing authorities Australia, viewed 18 August 2019, <https://www.nata.com.au/>.

National Institute for Health and Care Excellence (NICE) 2012, *Neonatal infection (early onset): antibiotics for prevention and treatment.*, viewed 20 November 2016, <https://nice.org.uk/guidance/cg149>.

National Institute for Health and Care Excellence (NICE) 2014, *Recognising and assessing early-onset neonatal infection after the birth*, viewed 5 June 2015, <http://pathways.nice.org.uk/pathways/antibiotics-for-early-onsetneonatal-infection>.

National Institute for Health and Care Excellence (NICE) 2015, *Preterm labour and birth*, viewed 28 December 2019, <https://www.nice.org.uk/guidance/ng25>.

Neuman, H., Forsythe, P., Uzan, A., Avni, O. & Koren, O. 2018, 'Antibiotics in early life: dysbiosis and the damage done', *Federation of European Microbiological Societies Biology Reviews*, vol. 42, no. 4, pp. 489-99.

New South Wales Ministry of Health 2016, *Maternal Group B Streptococcus (GBS) and Minimisation of Neonatal Early-Onset GBS Sepsis*, New South Wales Ministry of Health, Sydney, Australia.

Oddie, S. & Embleton, N.D. 2002, 'Risk factors for early onset neonatal group B streptococcal sepsis: case-control study', *British Medical Journal*, vol. 325, no. 7359, p. 308.

Odent, M. 2015, 'Group B Streptococcal Infection: Beyond the Mysteries', *Midwifery Today*, no. 113.

Ohlsson, A. & Shah, V. 2009, 'Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review)', *Cochrane Database of Systematic Reviews*, p. CD007467.

Ohlsson, A. & Shah, V. 2013, 'Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review)', *Cochrane Database of Systematic Reviews*, p. CD007467.
Ohlsson, A. & Shah, V. 2014, 'Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review)', *Cochrane Database of Systematic Reviews*, vol. 6, p. CD007467.
Örtqvist, A., Lundholm, C., Halfvarson, C. & Ludvigsson, J. 2019, 'Fetal and early life antibiotics exposure and very early onset inflammatory bowel disease: a population-based study', *Gut*, vol. 68, no. 2.
O'Sullivan, C.P., Lamagni, T., Patel, D., Efstratiou, A., Cunney, R., Meehan, M., Ladhani, S., Reynolds, A.J., Campbell, R., Doherty, L., Boyle, M., Kapatai, G., Chalker, V., Lindsay, D., Smith, A., Davies, E., Jones, C.E. & Heath, P.T. 2019, 'Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014–15: a prospective surveillance study', *Lancet Infectious Diseases*, vol. 19, no. 1, pp. 83-90.
Palmeira, P., Quinello, C., Silveira-Lessa, A., Zago, C. & Carneiro-Sampaio, M. 2012, 'IgG Placental Transfer in Healthy and Pathological Pregnancies', *Clinical and Developmental Immunology*, vol. 2012, p. 13.
Penders, J., Thijs, C., Vink, C., Stelma, F.F., Snijders, B., Kummeling, I., van den Brandt, P.A. & Stobberingh, E.E. 2006, 'Factors influencing the composition of the intestinal microbiota in early infancy', *Pediatrics*, vol. 118, no. 2, pp. 511-21.
Pinto, N.M., Soskolne, E.I., Pearlman, M.D. & Faix, R. 2003, 'Neonatal Early-onset Group B Streptococcal Disease in the Era of Intrapartum Chemoprophylaxis: Residual Problems', *Journal of Perinatology*, vol. 23, pp. 265-71.
PLoS ONE 2018, *PLoS ONE author guidelines*, viewed 12 July 2019, <https://journals.plos.org/plosone/s/authorship>.
Polit, D. & Beck, C. 2014, *Essentials of nursing research*, 8 edn, Wolters Kluwer, Philadelphia.
Queensland Government Department of Health 2015, *Queensland clinical guidelines. Early onset group B streptococcus disease*.
Rautava, S., Collado, M.C., Salminen, S. & Isolauri, E. 2012, 'Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial', *Neonatology.*, vol. 102.
Ravel, J., Brotman, R.M., Gajer, P., Ma, B., Nandy, M., Fadrosh, D.W., Sakamoto, J., Koenig, S.S., Fu, L., Zhou, X., Hickey, R.J., Schwebke, J.R. & Forney, L.J. 2013, 'Daily temporal dynamics of vaginal microbiota before, during and after episodes of bacterial vaginosis', *Microbiome*, vol. 1, no. 1, p. 29.
Ribet, D. & Cossart, P. 2015, 'How bacterial pathogens colonize their hosts and invade deeper tissues', *Microbial Infections*, vol. 17, no. 3, pp. 173-83.
Romero, R., Hasson, S., Gaier, P., Tarka, A., Fadrosh, D., Nikita, L., Galluppi, M., Lamont, R.F., Chaemsaithong, P., Miranda, J., Chaiworapongsa, T. & Ravel, J. 2014, 'The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women', *Microbiome*, vol. 2, no. 4.
Rosen, G.H., Randis, T.M., Desai, P.V., Sapra, K.J., Ma, B., Gajer, P., Humphrys, M.S., Ravel, J., Gelber, S.E. & Ratner, A.J. 2017, 'Group B Streptococcus and the Vaginal Microbiota', *Journal of Infectious Diseases*, vol. 216, no. 6, pp. 744-51.

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2016, *Maternal Group B Streptococcus in pregnancy: screening and management .C-Obs 19*, viewed 21 August 2018, <https://ranzcog.edu.au/statements-guidelines>.

Royal College of Obstetricians and Gynaecologists (RCOG) 2012, *The Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36*, 2nd edn, Royal College of Obstetricians and Gynaecologists, London.

Royal College of Obstetricians and Gynaecologists (RCOG) 2013, *Group B streptococcus (GBS) infection in newborn babies*.

Russell, N.J., Seale, A.C., O'Sullivan, C., Le Doare, K., Heath, P.T., Lawn, J.E., Bartlett, L., Cutland, C., Gravett, M., Ip, M., Madhi, S.A., Rubens, C.E., Saha, S.K., Schrag, S., Sobanjo-Ter Meulen, A., Vekemans, J. & Baker, C.J. 2017, 'Risk of Early-Onset Neonatal Group B Streptococcal Disease With Maternal Colonization Worldwide: Systematic Review and Meta-analyses', *Clinical Infectious Diseases*, vol. 65, no. suppl_2, pp. S152-S9.

Russell, S.L., Gold, M.J., Willing, B.P., Thorson, L., McNagny, K.M. & Finlay, B.B. 2013, 'Perinatal antibiotic treatment affects murine microbiota, immune responses and allergic asthma', *Gut Microbes*, vol. 4, no. 2, pp. 158-64.

Sackett, D. 1996, 'Evidence Based Medicine: what is and what it isn't', *British Medical Journal*, vol. 312.

Sandall, J., Soltani, H., Gates, S., Shennan, A. & Devane, D. 2015, 'Midwife-led continuity models versus other models of care for childbearing women (Review)', *Cochrane Database of Systematic Reviews*.

Schneider Jamner, M. & Stokols, D. (eds) 2000, *Promoting Human Wellness: New Frontiers for Research, Practice and Policy*, University of California Press, California.

Schrag, S., Zell, E., Lynfield, R., Roome, A., Arnold, K., Craig, A., Harrison, L., Reingold, A., Stefonek, K., Smith, G., Gamble, M. & Schuchat, A. 2002, 'A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates', *New England Journal of Medicine*, vol. 347, pp. 233-40.

Schrag, S.J., Farley, M.M., Petit, S., Reingold, A., Weston, E.J., Pondo, T., Hudson Jain, J. & Lynfield, R. 2016, 'Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014', *Pediatrics*, vol. 138, no. 6.

Schrag, S.J. & Verani, J.R. 2013, 'Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine', *Vaccine*, vol. 31, pp. 20-6.

Seale, A.C., Bianchi-Jassir, F., Russell, N.J., Kohli-Lynch, M., Tann, C.J., Hall, J., Madrid, L., Blencowe, H., Cousens, S., Baker, C.J., Bartlett, L., Cutland, C., Gravett, M.G., Heath, P.T., Ip, M., Le Doare, K., Madhi, S.A., Rubens, C.E., Saha, S.K., Schrag, S.J., Sobanjo-Ter Meulen, A., Vekemans, J. & Lawn, J.E. 2017, 'Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children', *Clinical Infectious Diseases*, vol. 65, no. suppl_2, pp. S200-S19.

Seale, A.C., Blencowe, H., Bianchi-Jassir, F., Embleton, N., Bassat, Q., Ordi, J., Menéndez, C., Cutland, C., Briner, C., Berkley, J.A., Lawn, J.E., Baker, C.J.,

Bartlett, L., Gravett, M.G., Heath, P.T., Ip, M., Le Doare, K., Rubens, C.E., Saha, S.K., Schrag, S., Meulen, A.S.-t., Vekemans, J. & Madhi, S.A. 2017, 'Stillbirth With Group B Streptococcus Disease Worldwide: Systematic Review and Meta-analyses', *Clinical Infectious Diseases*, vol. 65, no. suppl_2, pp. S125-S32.

Seaward, P., Hanna, T., Farine, D., Ohlsson, A. & Wang, E. 1998, 'International multicenter term PROM study: evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. Premature Rupture of the Membranes', *American Journal of Obstetrics and Gynecology*, vol. 179, pp. 635-9.

Seedat, F., Geppert, J., Stinton, C., Patterson, J., Freeman, K., Johnson, S.A., Fraser, H., Brown, C.S., Uthman, O.A., Tan, B., Robinson, E.R., McCarthy, N.D., Clarke, A., Marshall, J., Visintin, C., Mackie, A. & Taylor-Phillips, S. 2019, 'Universal antenatal screening for group B streptococcus may cause more harm than good', *British Medical Journal*, vol. 364, p. l463.

Seedat, F., Taylor-Phillips, S., Geppert, J., Stinton, C., Patterson, J., Brown, C., Tan, B., Freeman, K., Uthman, O., McCarthy, N., Robinson, E., Johnson , S., Fraser, H. & Clarke, A. 2016, *UK National Screening committee (UK NSC). Universal antenatal culture-based screening for maternal GBS carriage to prevent EOGBS disease*, viewed 10 February 2019, <https://www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc>.

Sheehy, A., Davis, D. & Homer, C.S. 2013, 'Assisting women to make informed choices about screening for Group B Streptococcus in pregnancy: a critical review of the evidence', *Women and Birth*, vol. 26, no. 2, pp. 152-7.

Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G.R., Chiche, J.D., Coopersmith, C.M., Hotchkiss, R.S., Levy, M.M., Marshall, J.C., Martin, G.S., Opal, S.M., Rubenfeld, G.D., van der Poll, T., Vincent, J.L. & Angus, D.C. 2016, 'The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)', *Journal of the American Medical Association*, vol. 315, no. 8, pp. 801-10.

Singh, T., Barnes, E.H. & Isaacs, D. 2019, 'Early-onset neonatal infections in Australia and New Zealand, 2002-2012. Australian Study Group for Neonatal Infections', *Archives of Disease in Childhood Fetal and Neonatal Edition*, vol. 104, no. 3, pp. F248-F52.

Spurbeck, R.R. & Arvidson, C.G. 2011, 'Lactobacilli at the front line of defence against vaginally acquired infections', *Future Microbiology*, vol. 6, no. 5, pp. 567-82.

Stapleton, S.R. 2011, 'Validation of an online data registry for midwifery practices: a pilot project', *Journal of Midwifery and Womens Health*, vol. 56, no. 5, pp. 452-60.

Stearns, J.C., Simioni, J., Gunn, E., McDonald, H., Holloway, A.C., Thabane, L., Mousseau, A., Schertzer, J.D., Ratcliffe, E.M., Rossi, L., Surette, M.G., Morrison, K.M. & Hutton, E.K. 2017, 'Intrapartum antibiotics for GBS prophylaxis alter colonization patterns in the early infant gut microbiome of low risk infants', *Scientific Reports*, vol. 7, no. 1, p. 16527.

Stenglin, M. & Foureur, M. 2013, 'Designing out the Fear Cascade to increase the likelihood of normal birth', *Midwifery*, vol. 29, pp. 819-25.

Stinson, L.F., Boyce, M.C., Payne, M.S. & Keelan, J.A. 2019, 'The Not-so-Sterile Womb: Evidence That the Human Fetus Is Exposed to Bacteria Prior to Birth', *Frontiers in Microbiology*, vol. 10.

Sung, J.H., Choi, S.J., Oh, S.Y., Roh, C.R. & Kim, J.H. 2017, 'Revisiting the diagnostic criteria of clinical chorioamnionitis in preterm birth', *British Journal of Obstetrics and Gynaecology*, vol. 124, no. 5, pp. 775-83.

Tapiainen, T., Koivusaari, P., Brinkac, L., Lorenzi, H.A., Salo, J., Renko, M., Pruikkonen, H., Pokka, T., Li, W., Nelson, K., Pirttilä, A.M. & Tejesvi, M.V. 2019, 'Impact of intrapartum and postnatal antibiotics on the gut microbiome and emergence of antimicrobial resistance in infants', *Scientific Reports*, vol. 9, no. 1, p. 10635.

The Australian Commission on Quality and Safety in Health Care 2017, *Antimicrobial use and resistance in Australia (AURA)*, viewed 3 March 2018, <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/aura-2017-second-australian-report-antimicrobial-use-and-resistance-human-health>.

Tudela, C.M., Stewart, R.D., Roberts, S.W., Wendel, G.D., Jr., Stafford, I.A., McIntire, D.D. & Sheffield, J.S. 2012, 'Intrapartum evidence of early-onset group B streptococcus', *Journal of Obstetrics and Gynecology*, vol. 119, no. 3, pp. 626-9.

Tuppurainen, N. & Hallman, M. 1989, 'Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients', *Journal of Obstetrics & Gynecology*, vol. 73, no. 4, pp. 583-7.

UK National Screening Committee 2012, *Screening for Group B streptococcal infection in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)*, viewed 1 August 2016, <http://www.screening.nhs.uk/policies>.

Valkenburg-van den Berg, A.W., Houtman-Roelofsen, R.L., Oostvogel, P.M., Dekker, F.W., Dorr, P.J. & Sprij, A.J. 2010, 'Timing of group B streptococcus screening in pregnancy: a systematic review', *Gynecologic and Obstetric Investigation*, vol. 69, no. 3, pp. 174-83.

Van Dyke, M., Phares, C., Lynfield, R., Thomas, A., Arnold, K. & Craig, A. 2009, 'Evaluation of universal antenatal screening for group B streptococcus', *New England Journal of Medicine*, vol. 360, pp. 2626-36.

van Herk, W., Stocker, M. & van Rossum, A.M. 2016, 'Recognising early onset neonatal sepsis: an essential step in appropriate antimicrobial use', *Journal of Infection*, vol. 72 Suppl, pp. S77-82.

Verani, J., Spina, N., Lynfield, R., Schaffner, W., Harrison, L., Holst, A., Thomas, S., Garcia, J., Scherzinger, K., Aragon , D., Petit, S., Thompson, S., Pasutti, L., Carey, R., McGee, L., Weston, E.J. & Schrag, S. 2014, 'Early-onset Group B Streptococcal disease in the United States: potential for further reduction', *Journal of Obstetrics and Gynecology*, vol. 123, no. 4, pp. 828-37.

Vergnano, S., Embleton, N., Collinson, A., Menson, E., Bedford Russell, A. & Heath, P. 2010, 'Missed opportunities for preventing group B streptococcus infection', *Archives of Disease in Childhood Fetal and Neonatal Edition*, vol. 96, pp. 72-3.

Weston, E.J., Pondo, T., Lewis, M.M., Martell-Cleary, P., Morin, C., Jewell, B., Daily, P., Apostol, M., Petit, S., Farley, M., Lynfield, R., Reingold, A., Hansen, N.I., Stoll, B.J., Shane, A.L., Zell, E. & Schrag, S.J. 2011, 'The burden of invasive

early-onset neonatal sepsis in the United States, 2005-2008', *Pediatric Infectious Diseases Journal*, vol. 30, no. 11, pp. 937-41.
Whittemore, R. & Knafl, K. 2005, 'The integrative review: updated methodology', *Journal of Advanced Nursing*, vol. 52, no. 5, pp. 546-53.
Wyllie, D., Paul, J. & Crook, D. 2011, 'Waves of trouble: MRSA strain dynamics and assessment of the impact of infection control', *Journal of Antimicrobial Chemotherapy*, vol. 66, no. 12, pp. 2685-8.
Yang, I., Corwin, E.J., Brennan, P.A., Jordan, S., Murphy, J.R. & Dunlop, A. 2016, 'The Infant Microbiome: Implications for Infant Health and Neurocognitive Development', *Nursing Research*, vol. 65, no. 1, pp. 76-88.
Zhong, H., Penders, J., Shi, Z., Ren, H., Cai, K., Fang, C., Ding, Q., Thijs, C., Blaak, E.E., Stehouwer, C.D.A., Xu, X., Yang, H., Wang, J., Wang, J., Jonkers, D.M.A.E., Masclee, A.A.M., Brix, S., Li, J., Arts, I.C.W. & Kristiansen, K. 2019, 'Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children', *Microbiome*, vol. 7, no. 1, p. 2.
Zimmermann, P. & Curtis, N. 2019, 'Effect of intrapartum antibiotics on the intestinal microbiota of infants: a systematic review', *Archive of Diseases in Childhood Fetal and Neonatal Edition*.