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Antimicrobial Stewardship in the Management of Sepsis in Maternity Hospitals – a Mixed Methodology Study

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Declaration

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date:

“One who treads a path in search of knowledge has his path to Paradise made easy by God”

Prophet Muhammad (peace be upon him)

- Riyadh us-Saleheen, 245

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Abstract

Background: Sepsis is one of the leading causes of maternal mortality and morbidity. The absence of a clear diagnostic marker challenges the process of starting antibiotic therapy. Early identification and management of sepsis is essential. Thus, the sepsis six care bundle (SSCB) was introduced in the UK to improve the care of sepsis patients.

Aim: To evaluate assessment of sepsis and subsequent management including the antibiotic therapy prescribed, and to use this data as a basis of antimicrobial stewardship programme (AMSP) and quality improvement plan within maternity units.

Methods: This study was conducted within three maternity units of NHS Greater Glasgow & Clyde using a mixed methodological approach of an initial quantitative study supplemented by a qualitative study, followed by a quality improvement for further service improvement.

Results: Sepsis was diagnosed in 3% (n=89/2690) of women. There was an inconsistent clinical application of SIRS criteria to inform diagnosis. No causative pathogen was isolated from 60% of clinical specimens. Antibiotic therapy was justified in only 31 women with positive culture results. There was a limited application of AMSPs in the maternity units and midwives did not make a positive contribution, and had a low clinical threshold for initiating therapy. Only 37.1% of the 89 women diagnosed with sepsis had the identifiable SSCB sticker prominently displayed on their medical notes. Interview findings indicate that this resulted from the absence of implementation strategies, the challenge of diagnosing sepsis and sub-optimal evaluation and review of patients post-diagnosis.

Conclusion: A specialized SSCB specifically for the obstetric population with the full contribution of the multidisciplinary team needs to be developed. Given midwives' central involvement in initial diagnosis, ongoing patient monitoring and antibiotic administration, a more midwife-centred approach to reviewing treatment is a promising way to develop AMSPs in maternity wards.

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Glossary

A&E	Accident and emergency
ACCP	American College of Chest Physicians
AGREE	Appraisal Guidelines for Research and Evaluation
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AMSP	Antimicrobial stewardship program
AUC	Area under the curve
BC	Blood culture
BCI	Behaviour change intervention
BCW	Behaviour change wheel
BD	bis die (twice daily)
BMI	Body mass index
CDC	Centres for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CEMACH	Confidential Enquiry into Maternal and Child Health
CHI	Community health index
CI	Confidence interval
CM	Clinical microbiology
Coag	Coagulase
CPG	Clinical practice guideline

CPOE	Computerised physician order entry
CRP	C-reactive protein
E.coli	*Escherichia coli*
ED	Emergency department
EGDT	Early Goal-Directed Therapy
EMR	Electronic medical record
EONS	Early onset neonatal sepsis
ESPAUR	Establishment of English surveillance programme for antimicrobial use and resistance
FBC	Full blood count
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
G+S	Group and save
GAS	Group A *Streptococcus*
GBS	Group B *Streptococcus*
GPs	General practitioners
GT	Grounded theory
HDU	High dependency unit
HPScot	Health Protection Scotland
HR	Heart rate
IBM	International Business Machines

ICD	International Classification of Diseases
ICU	Intensive care unit
ID	Infectious disease
IDL	Immediate discharge letter
IL-1	Interleukin-1
IL-6	Interleukin-6
IMEWS	Irish maternity early warning score
IPA	Intrapartum antibiotic
IQR	Interquartile range
ISD	Information Services Division
ITU	Intensive therapy unit
IV	Intravenous
K.pneumoniae	*Klebsiella pneumoniae*
LC	Lactate clearance
MAP	Mean arterial pressure
MDT	Multidisciplinary team
MEOWS	Modified early obstetric warning score
MEWS	Maternity early warning score/system
MRSA	Methicillin-resistant *Staphylococcus aureus*
NEWS	National early warning score
NHS	National Health Service

NHSGGC	National Health Service in Greater Glasgow & Clyde
NICE	National Institute for Health and Care Excellence
NPV	Negative predicated value
OD	Omni die (every day)
OR	Odds ratio
P&T	Pharmacy and therapeutics
PBPs	Penicillin binding proteins
PCT	Procalcitonin
PDSA	Plan-Do-Study-Act
PHE	Public Health England
PLLR	Pregnancy and Lactation Labelling Rule
PO	Per oral
PPH	Post-partum haemorrhage
PPI	Proton pump inhibitor
PPROM	Premature pre-labour rapture of membrane
PPV	Positive predicted value
PR	Per rectal
PRM	Princess Royal Maternity
PROM	Pre-labour rapture of membrane
QDS	Quater die sumendum (to be taken four times daily)
qSOFA	Quick sepsis- related organ failure assessment

R&D	Research and development
RCOG	Royal College of Obstetricians and Gynaecologists
ROC	Receiver operating characteristic
RR	Respiratory rate
S.aureus	*Staphylococcus aureus*
S1P	Phosphosphingolipid sphingosine-1-phosphate
SAPG	Scottish Antimicrobial Prescribing Group
SBAR	Situation-Background-Assessment-Recommendation
SBP	Systolic blood pressure
$ScvO_2$	Central venous oxygen saturation
SD	Standard deviation
SIPBS	Strathclyde Institute of Pharmacy and Biomedical Science
SIRS	Systemic inflammatory response syndrome
SN	Serial number
SOFA	Sepsis- related organ failure assessment
SOS	Sepsis in Obstetrics Score
SPSS	Statistical package for the social sciences
SSC	Surviving Sepsis Campaign
SSCB	Sepsis Six care bundle
SSI	Surgical site infection
SU	Standard unit

SVD	Spontaneous vaginal delivery
TDF	Theoretical domains framework
TDS	Ter die sumendum (to be taken three times daily)
Temp	Temperature
TNF-α	Tumour necrosis factor-α
U+E	Urea and electrolytes
UTI	Urinary tract infection
WCC	White cell count
WHO	World Health Organisation

1 Chapter 1: General Introduction

1.1 Antimicrobial therapy in the management of sepsis

The term 'antimicrobial therapy' refers to antibiotic or anti-infective treatment and has a wide scope, including antibacterial, antifungal, antiviral and antiparasitic therapies (Leekha *et al*., 2011). The first antimicrobial therapy was developed in 1929 by Alexander Fleming, followed by further discoveries of different antimicrobial treatments (Bockstael and Aerschot, 2009). These antimicrobial agents are used in response to a confirmed or suspected infection. The timely initiation of antimicrobial treatment is critical, particularly in severe or life-threatening infections, and initial treatment is usually empiric antibiotic therapy using broad spectrum antibiotics (Leekha *et al*., 2011). Mortality rates in severe or life-threatening infections are increased by delays in the administration of empiric antibiotic treatment and it is recommended that antibiotics be administered during the first hour of suspected sepsis. Even with this timely intervention, a survival rate of only 79.9% has been calculated from hospital discharge records (Liang and Kumar, 2015). The UK Sepsis Trust estimates 260,000 cases of sepsis each year, including about 44,000 reported mortalities of adults and children in the UK (UK Sepsis Trust and York Health Economics Consortium, 2017). For every one-hour delay in treatment initiation, there is a further 7.6% reduction in survival rate, with 42% survivorship following a six-hour delay in antibiotic initiation. Thus, having a one-hour window for antibiotic therapy to be initiated is a key factor in minimizing patient mortality (Liang and Kumar, 2015). In septic shock cases, time is even more critical and the recommendation is for antibiotic therapy to be administered within 30 minutes of diagnosis (Liang and Kumar, 2015). In more stable situations where infection is not life threatening, antimicrobial therapy should be withheld until microbiology advice may become available on the pathogen(s) isolated from the patient and their sensitivities to specific therapies are known (Leekha *et al*., 2011). The use of antibiotics is not limited to the active treatment of identified infections, but includes prophylactic treatment to prevent infections from

developing. It enhances clinical outcomes by reducing complications for post chemotherapy and surgery, including transplantation (Davies and Gibbens, 2013). Antibiotic prophylaxis also has been proven to reduce the risk of endometritis and surgical site infection (SSI) in women undergoing a caesarean section delivery (Weinstein and Boyer, 2016) and to lessen the likelihood of early onset neonatal sepsis when an intrapartum antibiotic is administered to the mother (National Institute for Health and Care Excellence [NICE], 2014).

Where antimicrobial therapy has been initiated, patients may nonetheless sometimes respond incompletely to therapy; it is therefore important to undertake appropriate follow-up investigations to ensure that the pathogen has been correctly identified, that the appropriate antimicrobial therapy has been prescribed and that any potential non-infectious causes have been excluded (Leekha *et al*., 2011). It is also important that empiric antibiotic therapy initiated in critically ill patients be appropriately de-escalated to a narrower spectrum antibiotic at a suitable time, i.e. once any microbiology reporting becomes available that identifies the pathogen and specifies its antimicrobial susceptibility and resistance patterns, thus aiding the choice of treatment (Leekha *et al*., 2011). Studies have shown that only 30-60% of sepsis cases are found to have a positive blood culture, for several reasons including pathogen type, load and growth capacity (Morgenthaler and Kostrzewa, 2015). One explanatory factor is that some pathogens grow more slowly than others; those which grow rapidly will appear sooner in blood cultures, while the slow growth of other pathogens may lead to false negative results if samples are collected and cultured early in the progress of the disease (Ruiz-Giardín *et al*., 2015). A second factor is the non-uniform distribution of pathogens within the body, making it difficult to determine pathogen load in organs, tissues or cells. As it is challenging to sample these sites themselves, blood, urine or sputum samples are taken instead, on the assumption that they will reflect pathogen load in the individual (Cunnington, 2015). Appreciating these factors could improve the interpretation of blood culture results.

Managing a patient's condition with antimicrobial therapy is critical, as morbidity from infection is still reported to be a leading cause of death (Bockstael and Aerschot, 2009), while the future of antimicrobial therapy is further challenged by the failure of the efforts of scientists and pharmaceutical companies to develop new antimicrobial agents in response to the evolution of pathogens' mechanisms of resistance (Tenover, 2006).

1.2 Antimicrobial resistance

The development of antimicrobial resistance (AMR) is known to be linked to the use of antibiotics; the risk of resistance to a specific antibiotic can extend to include resistance to a whole class of related antibiotics and can spread rapidly to other individuals within the same geographic region (World Health Organisation [WHO], 2015). Although the effects of resistance may vary geographically, infections have the ability to travel great distances within and between regions. It has been reported that in the 1990s a resistance pattern against *Pneumococcus* species which arose in Spain then spread across the globe to many countries including the United States of America (USA), Brazil, China, South Africa and Malaysia (Smith and Coast, 2002). Resistance can spread through food, water and other environmental chains and can be transmitted through human or animal transfer between and within countries and regions (WHO, 2015). When pathogens associated with an infectious disease develop a pattern of resistance to antimicrobial therapy this increases patient mortality and morbidity. Cases of AMR have been reported worldwide and its prevalence is increasing, placing many lives at risk (WHO, 2015). The burden of AMR threatens a return to the conditions of the pre-antimicrobial era; for example, if antibiotics could no longer be used in hip replacement surgery, it has been estimated that there would be a 30% increase in mortality rate and a 49% increase in infection rate, leading to treatment failure and increased morbidity rates in these populations (Smith and Coast, 2013; Smith and Coast, 2012). The US Centers for Disease Control and Prevention (CDC) estimates that AMR may affect up to two million people in the USA alone (Goff *et al*., 2017). The Review of AMR published in 2016 suggested

there are globally 700,000 deaths from AMR annually but this may be an under estimate as there are an estimated 200,000 deaths annually from multidrug-resistant and extremely drug-resistant tuberculosis (TB) alone, while data from India highlighted death from AMR in 60,000 cases of neonatal infection (O'Neill, 2016).

Furthermore, patients' normal flora will always be affected by exposure to antimicrobials, so it is vital to control the unnecessary use of antimicrobial therapy (Davey *et al*., 2010). Finally, the use of antibiotics is not limited to humans but there is a significant volume of antibiotic use in agricultural and veterinary medicine. This is an important contributory factor in the development of AMR, which may have long-term detrimental consequences for human therapies (Davies and Gibbens, 2013).

The WHO reports that half of antimicrobial treatments are subject to inappropriate use, that 85% of all treatments are for nonhuman use and that 75% have no therapeutic use, being used as growth-promoting agents in animal husbandry. Taking AMR into consideration, these data appear to indicate a very severe threat of increased morbidity and mortality, as continued overuse could lead to multidrug resistance and ultimately to untreatable pathogens (Nathwani and Sneddon, 2015). These risks, together with the chronic lack of newly developed antimicrobial agents, make an imminent crisis almost inevitable (Davies and Gibbens, 2013).

1.2.1 Global problem of antimicrobial resistance

Between the years 2000 and 2010 the use of antibiotic therapy increased globally by more than 30%, with annual use in 71 countries rising from 50 billion standard units (SU) to 70 billion SU. In 2010, penicillin and cephalosporin antibiotics were reported to have accounted for 60% of all antibiotic use in humans (Gelband *et al*., 2015). Estimated data on global antimicrobial resistance have raised concerns over *Escherichia coli* (*E.coli)*, *Klebsiella pneumoniae* (*K.pneumoniae*) and *Staphylococcus aureus (S.aureus)* infections, due to their association with many community and hospital infections. Fifty percent of all *E. coli* isolates

were reported to have developed resistance against fluoroquinolones and third-generation cephalosporin antibiotics, while rates of resistance to these antibiotics were reported to be 30% to 60% in *K.pneumoniae*. The proportion of *Staphylococcus aureus* isolates that were methicillin resistant was reported to be above 20% in all countries and as high as 80% in some countries (Gelband *et al*., 2015). Increased financial costs of delivering healthcare are associated with high antibiotic resistance. In Europe, the burden of direct and indirect costs was estimated at €1.5 billion per year in 2009, while in the USA, annual costs reached $20 billion and $35 billion for the healthcare system and lost productivity respectively (Gelband *et al*., 2015). Antimicrobial resistance is reported to cause 23,000 deaths in the USA each year, while the equivalent annual mortality rate in Europe was 25,000 (Gelband *et al*., 2015).

The failure of treatment due to AMR has financial consequences not only for individual patients but also for the wider communities of hospitals and families (Davies and Gibbens, 2013). The economic burden of AMR is not limited to the treatment provided or the involvement of healthcare staff, but includes the further assessments required from laboratory and radiation units, the side effects of treatment and management, the costs of longer hospital stays, the loss of patients' earnings and related reductions in the quality of life. Finally, death from a hospital-acquired infection is one possible outcome of AMR and is associated with a heavy financial burden on the patients' family and the community (Smith and Coast, 2013; Smith and Coast, 2012). It is expected that AMR will cause ten million deaths by 2050, with a consequent economic burden estimated at 100 trillion US dollars (Founou *et al*., 2017). A recent systematic review and meta-analysis of 40 studies indicates that the estimated overall healthcare cost of individual cases of AMR versus non-AMR were $8,107 and $5,469 respectively (Founou *et al*., 2017). A majority of these studies found that the greatest impact on cost was that of the so-called ESKAPE pathogens (*Enterococcus faecium*, *S.aureus*, *K.pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species), while other studies reported that the main economic burden was

associated with length of stay in hospital (Founou *et al*., 2017). The difference in cost between AMR and non-AMR patients was estimated by a study conducted in Christian Medical College & Hospital, Vellore in India to comprise an additional $141 on antibiotic therapy, $386 on pharmacy and $63 on laboratory investigations (Chandy *et al*., 2014).A recent report by the UK Sepsis Trust estimates a cost of £15.6 billion annually to treat sepsis, while the estimated economic cost of the misrecognition of sepsis in 2013 was £4,000 per patient (Frontier Economics, 2014; UK Sepsis Trust and York Health Economics Consortium, 2017). A retrospective cost analysis found that better detection and management of sepsis could reduce the length of hospital stay and would could save the National Health Service (NHS) of the UK an estimated £196 million per year (Frontier Economics, 2014).

The WHO global action plan on AMR has a fivefold set of goals, namely to take action "to improve awareness and understanding of antimicrobial resistance, to strengthen knowledge through surveillance and research, to reduce the incidence of infection, to optimize the use of antimicrobial agents, and to ensure sustainable investment in countering antimicrobial resistance" (WHO, 2015). O'Neill details seven interventions recommended to eliminate the unnecessary use of antimicrobial therapy: conducting a global public awareness campaign, enhancing hygiene to eliminate the transmission of infection, reducing unnecessary antimicrobial use in agriculture, improving global surveillance data on antimicrobial resistance and antimicrobial use in both humans and animals, developing new and rapid diagnostics to reduce unnecessary antimicrobial use, promoting the development and use of vaccines and finally, enhancing the numbers and pay of people working in infectious disease control (O'Neill, 2016).

1.2.2 Factors influencing antimicrobial resistance

1.2.2.1 Antimicrobial misuse

AMR is a global problem that is influenced by many factors, including over-the-counter sales of antibiotics in some countries and unsatisfactory manufacturing processes that produce

antimicrobial agents of low potency. These reduce the effective use of antibiotic therapies and can lead to antibiotic misuse (Smith and Coast, 2002). Such misuse takes a number of forms, including the premature discontinuation of courses of treatment, the reuse of leftover pills when needed and the skipping of antibiotic doses (Kardas *et al*., 2005).

A systematic review and meta-analysis of 46 studies with 29,291 participants in community settings found that 28.6% of antibiotic misuse resulted from leftover pills, with only 62% compliance with antibiotic prescriptions, 72.6% of which were for respiratory tract infections (Kardas *et al*., 2005). Another study evaluated self-medication with antimicrobials in 19 European countries by 15,548 participants and found that penicillins were the type most frequently misused in this way, by 54% of participants. Indications for antibiotic self-medication were mainly symptoms of the upper and lower respiratory tract, teeth and gums (Grigoryan *et al*., 2006). The antimicrobials were mainly sourced from either leftover medications or a pharmacy without prescription in countries where this is allowed (Grigoryan *et al*., 2006; Napolitano *et al*., 2013).

Patients' misuse of antibiotics is associated not only with AMR and failure to eradicate the infection but also with increased hospital costs (Kardas *et al*., 2005). The heavy consumption of antimicrobial therapies in community settings makes it necessary to reduce the misuse of antimicrobial agents by understanding population behaviours and assessing knowledge and attitudes, in order to deliver appropriate interventions (Napolitano *et al*., 2013). An Italian study found that only 9.8% of the 419 community participants understood the term 'antimicrobial resistance' and that only half of them believed that the efficacy of antibiotic therapy was reduced when therapy was discontinued prematurely. Employment of a family member within the healthcare sector was shown to contribute positively to the understanding of AMR (Napolitano *et al*., 2013). On the other hand, community physicians believed in the existence of AMR, but only in hospital settings and not within the community. They also identified diagnosis in the absence of accurate measurement as a challenge and

believed that it might lead to unjustified decisions based on no evidence (Vazquez-Lago *et al*., 2011).

Antibiotic use in hospital settings also has its challenges. For example, there is a reported failure to diagnose specific urinary tract infections at the point when antibiotics are prescribed, particularly in pregnant women. A review of culture results shows that only 4% of a sample of 578 women treated with antibiotics had a confirmed positive culture result (Sekikubo *et al*., 2017). It was also found that despite believing that antibiotic therapy is inappropriate in patients suffering from viral infections, physicians prescribed antibiotics in order to avoid the chance of infections (Vazquez-Lago *et al*., 2011).

1.2.2.2 Prescribing behaviours

Physicians' antibiotic prescribing behaviour has been evaluated qualitatively and the findings indicate that patients' comorbidity seems to make physicians more cautious, leading them to prescribe antibiotics in response to their fear of potentially fatal unexpected complications (Vazquez-Lago *et al*., 2011; Rodrigues *et al*., 2013). The selection of a particular antimicrobial therapy among the different types available for prescription is influenced by factors including the patient's comorbidity, pregnancy, age, anxiety, education level and allergy status (Rodrigues *et al*., 2013). There is also pressure from pharmaceutical companies to select certain antibiotics and a physician may prescribe a lower cost treatment either because of the patient's socioeconomic status or to save money for the healthcare system (Rodrigues *et al*., 2013). Pressure from patients has been found to influence the prescribing behaviours of physicians, who will often prescribe unnecessary antibiotic therapy if patients urge them to do so (Md Rezal *et al*., 2015).

Awareness of AMR is generally high among physicians, but many have a limited knowledge of the local extent of resistance. Data show that infectious disease physicians have better awareness of AMR rates and patterns when compared to other physicians (Md Rezal *et al*., 2015).

1.2.2.3 Selection pressure

Antimicrobial resistance could emerge from antibiotic selection pressure in veterinary medicine, agriculture and human use (Holmes *et al*., 2016). Pathogens which develop antimicrobial resistance may suffer a reduction in fitness, i.e. the ability to cause infection, as a result of reduced selection pressure, thus weakening antimicrobial resistance (Holmes *et al*., 2016). Antibiotic resistance is not associated only with pathogens detected in culture results, as there are uncultured bacteria present in the community which form a reservoir of antibiotic resistance genes (Li *et al*., 2011). The selection pressure of antibiotic therapy is thus not limited to what has been identified in cultured pathogens, but extends to uncultured pathogens in the community (Li *et al*., 2011).

There is a clear association between antibiotic use and resistance in hospital settings, while in the community the reduced use of antibiotics has led to a reduction in resistance (Hawkey, 2008). The increased use and misuse of antibiotic therapy over the last seven decades has applied selection pressure. Reducing antibiotic use is not an option where sick patients require antimicrobial therapy, but there are many forms of antimicrobial stewardship that help to ensure the sufficient use of therapy and contribute to reducing antimicrobial resistance. An example is antibiotic restriction, which can reduce antibiotic selection pressure (Hawkey, 2008; Hughes, 2014).

The impact of selection pressure on antibiotic resistance is demonstrated by a study of the outpatient use of antibiotics in 26 European countries, which found that there was greater antibiotic resistance in those countries where antibiotic consumption was higher (Goossens *et al*., 2005). Selection pressure has also been reported in a case control study of diarrhoea patients who had been exposed to antibiotic therapy before the onset of diarrhoea, which found that antibiotic resistance in *E.coli* was related to prior exposure (Zhang *et al*., 2015).

1.2.3 Antimicrobial resistance mechanisms

Resistance to an antimicrobial may develop during treatment with that agent against certain pathogens; alternatively, cumulative exposure to antimicrobials can prompt the development of AMR (Lipsitch and Samore, 2002). Pathogens have an adaptation mechanism to overcome hostile environmental conditions, allowing them to develop resistance that can be intrinsic or acquired (Bockstael and Aerschot, 2009).

Intrinsic resistance is the ability of a pathogen to resist the action of a particular antibiotic as a consequence of an inherent function or structure, one example being the absence of a susceptible target (Blair *et al*., 2015). Thus, *Pseudomonas aeruginosa* has an innate resistance to some antimicrobial therapies due to its low membrane permeability (Bockstael and Aerschot, 2009). In Gram-negative bacteria, this mechanism allows the pathogen to resist therapy by preventing the antimicrobial agent from crossing the outer membrane. There are many genes responsible for intrinsic resistance to antimicrobial therapy including treatment with aminoglycosides, fluoroquinolones and β-lactams (Blair *et al*., 2015).

Acquired resistance is the main mechanism by which a bacterium develops resistance to a single antibiotic or class, resulting from changes to the bacterial genome, acquired through mutation, which allows resistance to be transmitted to daughter cells (Bockstael and Aerschot, 2009). There are three main mechanisms within this type of resistance. The first involves alterations to the pathogen cell wall that prevent binding of the antimicrobial, reducing its penetration and thereby limiting the intracellular concentration of the antibiotic (Blair *et al*., 2015; Tenover, 2006). The second mechanism is where the mutated genes encode enzymes, such as β-lactamase, destroy the antimicrobial agent before it can exerts any antimicrobial effect. Lastly, the operation of efflux pumps can result in the removal of an antimicrobial before it reaches its target. This can occur when a gene mutation alters the antimicrobial target (Blair *et al*., 2015; Tenover, 2006). It is also known that the active efflux limits intracellular concentration and reduces the minimum inhibitory concentration leading

to an ineffective antibiotic therapy (Sun *et al*., 2014). Penicillin binding proteins (PBPs) are the main binding sites within the bacterial cell wall for β-lactam antibiotics. Resistance to β-lactams usually arises from alterations to the PBPs that reduce treatment affinity (Frère and Page, 2014; Haenni *et al*., 2010). The development of β-lactamase occurred in the 1940's, when first-generation β-lactams were still effective. This was followed by the emergence of extended-spectrum-β-lactamases, which began to be carried by many bacteria. The clinical response to this new resistance was a shift in use to carbapenem antibiotics, resulting in turn in the development of β-lactamases with carbapenem-hydrolysing activity (Blair *et al*., 2015).

Carbapenem-resistant Enterobacteriaceae (CRE) have been reported globally and fall into three main classes according to their production of Ambler class A, B and D β-lactamases. Class A carbapenemases can effectively hydrolyse carbapenems, are partially inhibited by clavulanic acid and can be either chromosome encoded or plasmid encoded, e.g. *Klebsiella pneumoniae* carbapenemases (KPCs). KPCs were first identified in 1996 and spread globally within a few years from the eastern United States to countries including Puerto Rico, Colombia, Israel, Greece and China (Nordmann *et al*., 2011). Class B metallo-β-lactamases can effectively hydrolyse all β-lactams but not aztreonam; their activity can be inhibited by EDTA. This class consists mostly of Verona integrin-encoded metallo-β-lactamase and recently of New-Delhi metallo-β-lactamase. A *K. pneumoniae* strain producing Class D enzymes of the oxacillinase-48 type was first identified in 2003 in Turkey (Nordmann *et al*., 2011).

1.2.4 *Clostridium difficile* infection and antibiotic use

Clostridium difficile is a spore-forming, Gram-positive anaerobic bacillus which causes a range of gastrointestinal disorders including diarrhoea and fulminant colitis and which can result in sepsis or death (Cao *et al*., 2018; Garey *et al*., 2008). Data from over ten thousand admissions in four surgery hospitals indicate 52 reported cases of *Clostridium difficile* infection (*CDI*); univariate analysis shows an increased risk of *CDI* (OR: 2.80; p=0.002) when antimicrobial

therapy had been given during the six months before admission. The use of antibiotics in the postoperative phase for more than 24 hours was also associated with an increased risk of *CDI*; OR: 5.44, $p<0.001$ (Bernatz *et al*., 2017). A systematic review and meta-analysis of 67 studies found that patients' use of proton pump inhibitor (PPI) increased the risk of developing *CDI* by an odds ratio of 2.34, $p<0.001$ (Oshima *et al*., 2018). As a consequence, PPI and antibiotic use in the previous six months were associated with a higher rate of recurrent *CDI*. As elderly populations are exposed to more medications, the findings suggest that a PPI or H_2 receptor antagonist more than doubles the risk of recurrent *CDI* and that antibiotic exposure is associated with a 63% increased risk of recurrent *CDI* in elderly patients (Cao *et al*., 2018). There is evidence that with every ten-year increase in age the risk of developing *CDI* increases by an odds ratio of 1.07 (Brown *et al*., 2015). An increase in the number of broad-spectrum antibiotics has also been found to result in an increase in the incidence rate of *CDI* by 10.8 per 10,000 patient days (Hiensch *et al*., 2017).

The antibiotics ciprofloxacin/fluoroquinolones, co-amoxiclav (amoxicillin/clavulanic acid), clindamycin and cephalosporins, known as the "4Cs", are associated with a greater risk of *CDI* when compared with other antibiotics (Lawes *et al*., 2017; Brown *et al*., 2015). This is supported by the findings of a meta-analysis of eight studies that the increased risk associated with clindamycin has an odds ratio of 20.43 (95%CI: 8.50–49.09), followed by fluoroquinolones (OR: 5.65; 95%CI: 4.38–7.28), cephalosporins (OR: 4.47; 95%CI: 1.60–12.50) and penicillin (OR: 3.25; 95%CI: 1.89–5.57) (Deshpande *et al*., 2013).

CDI is associated with morbidity, mortality and increased cost. CDI has been associated with an average seven-day increase in length of hospital stay and an increase in mortality by 35% in surgical patients (Bernatz et al., 2017). Hospital-acquired CDI has an incidence rate of 0.8 in every 1,000 patient days, the main factors associated with this incidence being the use of antibiotics in the previous six months (OR=2.8; p=0.002), antibiotic therapy continued for

more than 24 hours after surgery (OR=5.44; p<0.001) and antibiotics used for non-surgery prophylaxis (OR=3.59; p<0.001) (Bernatz et al., 2017).

In peripartum women the incidence rate of CDI is reported as 13.5 per 100,000 pregnancies, increasing by 2% over 10 years (Villers et al., 2015). Pregnancy and labour complications including caesarean section (OR: 3.01), preterm labour (OR: 5.13) and chorioamnionitis (OR: 1.71) have been shown to increase the risk of developing CDI, with a consequent increase in hospital stay and associated costs (Villers et al., 2015). Another review indicates that half of patients (n=7) who developed CDI in the peripartum period were prescribed antibiotic therapy during the month before the incident, but as the sample of 14 patients was so small, no further correlations or odds ratios were calculated in this study (Garey et al., 2008).

1.2.5 The United Kingdom's AMR action plan

The UK's five-year antimicrobial resistance strategy aims to improve the knowledge and understanding of AMR, to conserve and steward the effectiveness of existing treatments and to stimulate the development of new antibiotics, diagnostics and novel therapies (Davies and Gibbens, 2013). It identifies seven key areas for future action, targeting enhanced infection prevention and control practices, optimized prescribing practice, improved professional education, training and public engagement, the development of new drugs, treatments and diagnostics, better access and use of surveillance data, improved identification and prioritization of AMR research needs and strengthened international collaboration (Davies and Gibbens, 2013).

The Scottish Antimicrobial Prescribing Group (SAPG) was established in 2008 and has worked to make the use of antibiotics in Scotland more efficient. Its two main strategies for eliminating the development of AMR are controlling the prescribing of antibiotics and minimizing the use of the 4C broad spectrum antibiotics that are correlated with the development of CDI (Health Protection Scotland & Information Services Division [HPScot & ISD], 2015). The rate of use of the 4Cs in primary care has been reduced by approximately

50% over five years (SAPG, 2014). However, as recently as 2014, the 4Cs were still found to constitute 23% of all antibiotics prescribed in secondary care. Indeed, their use was 9.7% higher than in the previous year, with 12.8% of all antibiotic prescriptions being for co-amoxiclav, 6.6% for cephalosporins, 6% for fluoroquinolones and 2.2% for clindamycin therapy (HPScot & ISD, 2015).

The English Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR) was set up in response to the UK's five-year AMR strategy. ESPAUR reviewed surveillance data between 2012 and 2016 and its findings indicate an overall increase in the rate of antibiotic resistance in *E. coli*, as depicted in Figure 1-1 (Public Health England [PHE], 2017). ESPAUR collected data on antibiotic consumption from primary care, secondary care and dental prescriptions in 2016 and its findings show that penicillins accounted for 45% of total antibiotic prescriptions. Although a reduction of up to 11.5% was observed in use by both dental clinics and general practitioners (GPs), there were increases in both secondary care and inpatient hospital settings, by 28.3% and 2.8% respectively when 2016 figures were compared to the baseline of 2012 data (PHE, 2017a). There was a reported 10% rate of resistance to clindamycin therapy in hospitals in England and Wales (Royal College of Obstetricians & Gynaecologists [RCOG], 2012a), while Scotland reported a rate of 12.1% for clindamycin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) (HPScot & ISD, 2015). Clindamycin has an additional importance in obstetrics, as it is specified in the antibiotic guidelines as a replacement for co-amoxiclav or benzylpenicillin in patients with penicillin allergy status.

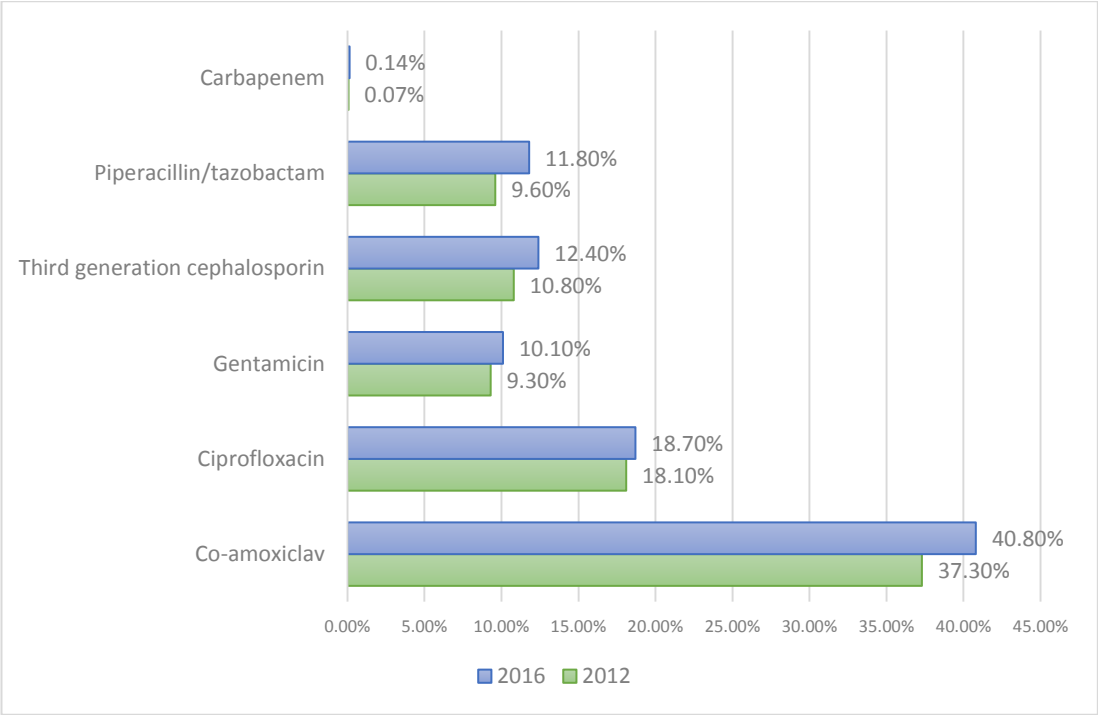

Figure 1-1: Resistance to carbapenem, piperacillin/tazobactam, third generation cephalosporin, gentamicin, ciprofloxacin and co-amoxiclav in *E.coli* pathogens, comparing 2012 and 2016 data, as assembled from ESPAUR

The total antibiotic consumption in secondary obstetric and gynaecological care shows a constant pattern throughout the five years between 2012 and 2016, while the data reported in 2016 show that co-amoxiclav, quinolones and cephalosporins accounted for 44.2% of antibiotic prescriptions in obstetrics and gynaecology (PHE, 2017a).

The key to optimising prescribing practice is the activation of antimicrobial stewardship programmes (AMSPs) that support the better use of antimicrobial therapy by ensuring the prescribing of the right therapy at the right dose, for the right duration and at the right time, aiming to reduce unjustified antimicrobial exposure (Davies and Gibbens, 2013).

1.3 Antimicrobial stewardship

Antimicrobial stewardship (AMS) is defined as “an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness” (NICE, 2015a). The prompt initiation of antibiotic therapy has been proven to reduce mortality and morbidity, particularly in sepsis cases as previously discussed

(Section 1.1), but half of antibiotic therapies initiated were either unnecessary or inappropriate (Pollack and Srinivasan, 2014). AMS aims to achieve the best clinical outcomes, reduce the occurrence of AMR and *CDI* and save unnecessary spending on antibiotic therapy and hospital running costs (Cosgrove *et al*., 2014). Success in AMS depends on support from both the management team and the clinical staff at the hospital. In addition to the AMS team, there is a vital need for a ward-focused antimicrobial team who can evaluate prescriptions at ward level for appropriateness (PHE, 2015). The 'start smart then focus' strategy emphasises the importance of taking smart action by not prescribing antibiotics unless there is clinical evidence of bacterial infection, by clear documentation of indication, dose, duration and review plan, by ensuring that cultures have been obtained prior to any treatment being commenced and by considering antibiotic prophylaxis for surgery patients (PHE, 2015). The 'focus' part of the strategy concerns the vital role of review and follow-up, ensuring that each patient is reviewed within 48-72 hours after initiation of therapy. This review should allow informed and suitable changes to therapy in the light of additional clinical information. Therapy may therefore be stopped or de-escalated to oral therapy or to a narrower spectrum antibiotic, or the patient may be started on outpatient parenteral antibiotic therapy (PHE, 2015). Public Health England recommends an audit to evaluate antimicrobial consumption or de-escalation, as this could contribute to the review and feedback process with the potential to influence the successful implementation of AMSPs (PHE, 2015).

AMS is also important in community settings. The PHE primary care guide for the management and treatment of common infections suggests that antibiotics should be avoided in cases such as acute sore throat. It provides detailed guidelines on expected days until recovery and supports practitioners with scoring tools including the FeverPAIN score. While recommending the use of influenza vaccine in high risk patients to prevent the spread of the disease, it offers detailed guidance on the treatment of unvaccinated patients (PHE, 2017b).

1.3.1 Antimicrobial stewardship programmes

An AMSP is defined as a set of "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by prompting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration" (Goff *et al*., 2017). The initiation and implementation of AMSPs have been considered for more than three decades. According to the CDC, the core elements of a successful AMSP are leadership commitment, accountability, drug expertise, action, tracking, reporting and education. The commitment element requires the job description to be specific about stewardship-related responsibilities and these should be subject to annual review. This should be supported by education and training, ensuring that stewardship is well understood and supported by the stewardship team (Pollack and Srinivasan, 2014). Evidence suggests that large settings require full-time employment of AMS staff, while small settings could develop AMSPs using part-time employment or off-site personnel. In general, AMS should not be placed under the pharmacy and therapeutics (P&T) committee unless the setting is small and the P&T committee's role has been expanded to include the assessment and enhancement of antimicrobial use (Pollack and Srinivasan, 2014). P&T committees were introduced to ensure appropriate and safe drug management and the cost effectiveness of medication; their responsibilities include the evaluation of drug use, monitoring and reporting adverse drug events, approving guidelines for medication management, managing the drug formulary and the authorization of new drugs or the restriction of a new or existing one (Shulkin, 2012).

AMSP leaders cannot achieve success without the support of a team of clinicians, infection prevention specialists, epidemiologists, quality improvement personnel, laboratory staff, nurses and information technologists. Nurses (or midwives) can contribute to the AMSP by ensuring that blood cultures are taken prior to the initiation of antibiotic therapy, by reviewing antibiotic prescriptions during preparation and administration of the drug and by

initiating discussions about the assessment of antibiotic indication, duration and treatment plans (Pollack and Srinivasan, 2014). The guidance provided by Cosgrove *et al*. identifies many categories of knowledge and skills required by AMSP leaders, which include understanding the general principles of AMS, determining different approaches to AMS interventions, understanding antimicrobial therapy, demonstrating a clear understanding of microbiology and laboratory diagnosis, having knowledge of infectious syndromes, understanding methods of measurement and analysis, having access to information technology resources and having programme-building and leadership skills (Cosgrove *et al*., 2014). Each of these categories has its associated skills and knowledge, which are important in assessing the implemented AMSP through the identification of possible gaps and in designing education tools to aid the effective management of the AMSP (Cosgrove *et al*., 2014).

One of the skills required by AMSP leaders is to identify approaches to AMS most likely to enhance the use of antibiotics, which may take the form of broad interventions, pharmacy-driven interventions or infection- and syndrome-specific interventions. An example of a broad intervention is an antibiotic "time out" that requires a re-evaluation of each patient's need for and choice of antibiotic at 48 hours after antibiotic initiation, which is typically the time needed to obtain a more complete clinical picture, including blood culture test results and other relevant laboratory data (Pollack and Srinivasan, 2014). This review should clarify diagnosis and facilitate a review of antibiotic choice, a determination of whether there is an opportunity for antibiotic de-escalation and consideration of antibiotic therapy duration (Pollack and Srinivasan, 2014). This is endorsed by the NICE guidelines on the intravenous use of antibiotics for suspected infection, which recommend the reassessment of each patient after 48 to 72 hours to decide on the necessity of continuing or de-escalating antibiotic therapy (NICE, 2015a). The "time out" intervention is intended to minimize poor practice of the kind identified in a study of six US hospitals, which found that by the fifth day of admission, only 59% of patients had undergone cultures, that 58% of these had negative

results but that antibiotic therapy had not been stopped and that 30% presented with normal white cell count (WCC) and temperature upon initiation of antibiotic therapy (Gelbrand *et al*., 2015). The reassessment of each patient 48 to 72 hours after the start of antibiotic therapy will allow better management and improve potential use of antibiotic resources.

Another broad intervention is prior authorization, which aims to restrict the prescription of certain antibiotics because of their spectrum and to minimize their use by requiring them to be authorized by an expert in infectious diseases and antibiotic prescribing (Pollack and Srinivasan, 2014). The final broad intervention is external audit and feedback, i.e. not conducted by the treating team, to evaluate the effectiveness of antibiotic prescribing (Pollack and Srinivasan, 2014). These key interventions have proven to improve clinical outcome, reduce adverse events, save hospitals money and reduce antibiotic resistance. Nonetheless, Plachouras and Hopkins (2017) deem these interventions to be insufficient and recommend an initiative to combine them with additional behaviour change interventions.

To address the above needs, it is worth exploring a disease- and population-specific approach to allow better assessment and management of antimicrobial therapy, because sepsis is a life-threatening infection that requires antibiotics to be administered during the first hour (Liang and Kumar, 2015). As the identification of sepsis in the obstetric population is complicated by the physiological changes associated with pregnancy (van Dillen *et al*., 2010), this is explored in more detail in the following section.

1.4 Sepsis in the obstetric population

Sepsis was initially defined at the 1991, ACCP/SCCM Consensus Conference as “a host’s systemic inflammatory response syndrome (SIRS)” (Singer *et al*., 2016), and is based on a score obtained using the patient’s temperature, heart rate (HR), WCC and respiratory rate (RR). To support a diagnosis of sepsis, abnormal scores must be obtained on at least two of the indices in the presence of a suspected infection (Vincent *et al*., 2016; Singer *et al*., 2016). A re-evaluation of the definition of sepsis after 24 years of clinical use found it to be deficient

in both specificity and sensitivity, as it failed to capture many true cases of sepsis and identified infections that were not necessarily sepsis (Singer *et al*., 2016). The re-evaluation indicated that the SIRS construct, although useful in identifying patients with infection, has limited specific applicability to sepsis (Singer *et al*., 2016). Sepsis has therefore been redefined as "life-threatening organ dysfunction caused by a dysregulated host response to an infection" (Singer *et al*., 2016). This can be measured using the quick Sepsis-related Organ Failure Assessment (qSOFA), comprising only three indices: mental status, systolic blood pressure (SBP) and RR (Singer *et al*., 2016). In an obstetric population, the identification of sepsis is further complicated by the physiological changes associated with pregnancy. Thus, the tenth edition of the International Classification of Diseases (ICD-10) defines puerperal sepsis as a rise in temperature over a day to above 38 °C occurring between one and ten days after delivery, while the WHO specifies a more prolonged monitoring for puerperal infection detection, which must be between the onset of labour and 42 days post-delivery, with the site of infection limited to the genital tract, in the presence of elevated temperature in addition to other signs, such as pain and vaginal discharge (van Dillen *et al*., 2010).

Mortality from sepsis and severe sepsis respectively is reported at 0.6 and 20.9 per 100,000 pregnancies in the USA, where Group A *Streptococcal (*GAS*)* bacteria were responsible for 50% of direct maternal mortality from sepsis (Acosta *et al*., 2013; Acosta *et al*., 2014). GAS was reported as the most commonly isolated pathogen in postpartum women worldwide and despite the fact that Group B *Streptococcus (*GBS) had a higher prevalence of maternal sepsis, its severity remained limited compared with the disease outcome of GAS (Mason and Aronoff, 2012).

Pathogens causing maternal sepsis vary between individuals and geographical sites. A national case-control study in the UK found a high prevalence rate of *E.coli*, which was detected in 21.1% of severe sepsis cases (Acosta *et al*., 2014). As to the site of infection, the genital tract was the most common, being reported in 31% of cases, followed by the urinary

tract (19.7%), wounds (9%) and the respiratory tract (5.5%), while 26% of cases had no known source of infection. However, the data show differences in both site of infection and pathogen between antenatal and postnatal women (p<0.0001) (Acosta *et al*., 2014). The occurrence of different maternal complications, including those associated with caesarean section delivery, could increase the risk of sepsis (Acosta *et al*., 2014). Clinical data show that receiving a caesarean section exposed women to a five to 20-fold higher risk of developing infection when compared with spontaneous vaginal delivery (SVD) (Van Schalkwyk and Van Eyk, 2010). NICE recommends offering prophylactic antibiotics to all women undergoing caesarean section (NICE, 2011). This therapy should be administered a maximum of 60 minutes before skin incision, with a repeated dose required for prolonged procedures of more than three hours or blood loss greater than 1.5 litres (Van Schalkwyk and Van Eyk, 2010). In contrast, a recent systematic review shows no improvement in morbidity rates associated with the use of prophylactic antibiotics in operative vaginal delivery, which includes the use of forceps and vacuum extraction (Liabsuetrakul *et al*., 2014). However, a case-controlled Scottish study found that operative vaginal delivery doubled the risk of uncomplicated sepsis when compared with SVD (Acosta *et al*., 2012). Uncomplicated sepsis was defined in this study as 'all cases of sepsis not identified by the ICD-9 as either septicaemia, sepsis following abortion, puerperal sepsis, septic shock or acute organ dysfunction associated with sepsis' (Acosta *et al*., 2012).

The recommended prophylactic antibiotic for caesarean section delivery varies among hospitals and countries. The local guidelines of the National Health Service in Greater Glasgow & Clyde (NHSGGC) recommend the use of co-amoxiclav as a first-line prophylactic antibiotic in non-penicillin allergic patients, and clindamycin in penicillin allergic patients (NHSGGC, 2015b). Also, as antibiotic prophylaxis is not limited to caesarean section, pregnant women colonized with GBS should receive intrapartum antibiotic coverage of benzylpenicillin at the onset of labour and repeated every four hours until delivery. The recommended antibiotic therapy in penicillin allergic patients is clindamycin 800 mg every eight hours until

delivery (RCOG, 2012a; NHSGGC, 2015b). Antenatal *GBS* screening is not recommended in all pregnant women, according to the RCOG. Having been GBS positive or prescribed an intrapartum antibiotic (IPA) in a previous pregnancy does not influence the prescription of IPA to women in the current pregnancy, whereas it is strongly recommended that IPA be offered to women who have had a previous baby born with early onset neonatal sepsis (EONS) or who are currently GBS positive. The RCOG also recommends the administration of IPA when pyrexia of more than 38 °C is reported in labour (RCOG, 2012a).

1.4.1 Pathophysiology of sepsis

The pathophysiology of sepsis in obstetric populations is complex (Galvão *et al*., 2016; Guinn *et al*., 2007). There are limited data on pregnant women and the understanding of sepsis has been derived mainly from the study of critically ill or surgical patients (Guinn *et al*., 2007). Pregnancy was once understood to be an immunocompromised period initiated in order for the mother's body not to reject the growing foetus, with the effect of making pregnant women more susceptible to infection (Galvão *et al*., 2016). The emphasis has now shifted to seeing pregnancy as involving immunomodulation, which serves to protect both mother and child (Galvão *et al*., 2016). Pregnancy has pro- and anti-inflammatory periods during which three phases of immunological change occur, roughly corresponding to the three trimesters (Galvão *et al*., 2016). A strong inflammatory response may affect the health of the mother during the first trimester, with implantation and placentation. The second phase is anti-inflammatory, to support foetal development, while the third phase of renewed inflammation is essential in order to prepare for delivery (Galvão *et al*., 2016).

When an infection affects the body, both neutrophils and macrophages are activated to produce inflammatory mediators that activate the CD4 T cells, prompting the release of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1) (Guinn *et al*., 2007). These cytokines activate more neutrophils and macrophages, as well as activating additional immunological features such as the coagulation cascade, inhibiting the

fibrinolytic system and enhancing endothelial permeability (Guinn *et al*., 2007). This produces thrombin, which in complex with thrombomodulin activates protein C, thus inhibiting the anticoagulation balance (Guinn *et al*., 2007). It also generates free radical oxygen, activates nitric oxide production and releases proteases and vasoactive hormones (Guinn *et al*., 2007). As a result of increased production of nitric oxide, a decrease occurs in systemic vascular resistance and vasodilation. This leads to hypovolemia, stimulating receptors that activate the sympathetic nervous system and leading to an increase in heart rate which, in the presence of a reduction in systemic vascular resistance, will result in elevation of cardiac output. This stimulates the production of vasopressin and endothelin, which in turn activate the renin-angiotensin system to enhance sodium ion reabsorption from the renal fluid to maintain vascular tone and intravascular volume (Guinn *et al*., 2007).

These alterations to physiological function can help to fight infection, but in doing so may also damage the immune system (Guinn *et al*., 2007). The CD4 T cells therefore also release anti-inflammatory cytokines to regulate the process. Failure to control the overproduction of anti-inflammatory agents will allow the infection to develop into a pathological condition that is associated with sepsis (Guinn *et al*., 2007). The alteration of physiological functions associated with pregnancy, namely elevated heart rate and WCC, reduced blood pressure and increased cardiac output, can compromise the ability to identify sepsis in its early stages, placing the patient and infant at possible additional risk (Guinn *et al*., 2007).

1.4.2 The birthing process

The process of labour can be divided into three stages, marked by various signs and symptoms. It begins with the dilation of the cervix, which is richly supplied with nerve endings; therefore, this initiates labour-associated pain. The dilation of the cervix also reduces the support of the foetal amniotic membranes, thus beginning the stage of active labour. The second stage runs from the full dilation of the cervix to the delivery of the baby and the last stage from then to the delivery of the placenta (Kovacs & Briggs, 2015; Steer and

Flint, 1999). Surgical delivery is considered in the event of a failure to progress in labour, of maternal or foetal distress, or of complications during normal vaginal delivery (Kovacs & Briggs, 2015). GBS is commonly colonises the lower gastrointestinal and urogenital tracts of women. Its presence is not considered abnormal or treated as an infection, because it does not harm the woman. However, GBS can gain access to the neonate during the peripartum period and this can result in neonatal sepsis (Patras & Nizet, 2018). Although it is not recommended that all pregnant women should receive antenatal screening for GBS, when it is detected intrapartum antibiotic prophylaxis (IPA) should be offered (RCOG, 2017; Olsen *et al*., 2018). There is evidence of a reduction by 80% in early-onset GBS disease when IPA is given during labour to women with positive GBS colonisation (Schrag *et al*., 2016). In Australia, the incidence of early-onset neonatal GBS disease has been reported to have declined from 1.43 to 0.25 in every 1000 live births (RCOG, 2017; Olsen *et al*., 2018). Data from the USA show stability in the incidence of EONS between 2005 and 2014, when it ranged narrowly from 0.79 to 0.77 in every 1000 live births, but during the same period there was a significant reduction in neonatal GBS from 0.27 to 0.22 per 1000 live births (p=0.02). *E.coli* is another pathogen that often colonises the lower gastrointestinal tract and can easily transfer to a woman's genital tract. Up to 13% of women were found to have vaginal colonisation of *E.coli* and in 21% of third-trimester infant deaths *E.coli* was identified in blood culture results (Barcaite *et al*., 2012; Tameliene *et al*., 2012).

One of the complications that can occur after delivery is post-partum haemorrhage (PPH), defined as blood loss of 500 ml or more within the first 24 hours of delivery, which affects 2% of women giving birth worldwide (Kovacs & Briggs, 2015; WHO, 2012). There are several causes of PPH, including uterine atony (failure of the uterus to contract after delivery of the baby), retained placental tissue, coagulation disorder and uterine rupture, and it is worse in women with pre-existing anaemia (WHO, 2012). These complications will require drug therapy to control the condition and ensure patient safety.

1.4.3 Drug categorisation in pregnancy

In 1979 the US Food and Drug Administration (FDA) published the first categorization of drugs used for pregnancy and lactation, introducing a lettering system (A, B, C, D and X) that was used for over three decades (Schatz *et al*., 2016). Medications of category A meant use of the drug was associated with no harm to the foetus; drugs in category B were deemed safe on the basis of animal trials, those on category C had shown adverse events in animal trials, but no human studies were available, and drugs were placed in category D when there was a potential risk of harm to the foetus. Lastly, the use of drugs in category X was associated with risks that outweighed the predicted benefits to the mother and/or the baby (Ciarkowski and Stalburg, 2010).

In 2014, the FDA replaced this system with the Pregnancy and Lactation Labelling Rule (PLLR). Among the many inputs to the development of the PLLR were concerns raised as to the lack of clarity of the existing pregnancy categories, their misinterpretation and misuse. An example of this lack of clarity was that 60% of drugs were assigned to category C, conflating those where animal studies had shown no adverse effects on the foetus with those where no studies had been conducted in either animal or humans. This major category thus contained both drugs with no known risk and others with a possible risk to human health. In addition to abolishing the five categories, the PLLR combines the original sections on pregnancy and on labour and delivery into one section, called “pregnancy”, renames “nursing mothers” as “lactation” and adds a new section on “females and males of reproductive potential”. The first two sections contain four sub-sections: pregnancy exposure registry, risk summary, clinical consideration and data. The pregnancy exposure registry is required only if such a registry exists, while the risk summary summarises the available animal or human data and includes risk of miscarriage and major birth defects. The third section has sub-sections on pregnancy testing, contraception and infertility (Pernia and DeMaagd, 2016).

To prevent maternal complications and associated therapies early identification and management of sepsis in maternity are recommended by the application of early warning scores and care bundles, which are explored in more detail in the following sections.

1.4.4 Maternity Early Warning Score

Since the 1980s, there has been interest in introducing an obstetric scoring system to help in detecting critical illness (Maguire *et al*., 2015). Such a maternity early warning system (MEWS) would be used to monitor women during pregnancy and the peripartum period, with the intention of reducing morbidity and mortality through early detection and management (Maguire *et al*., 2015; Isaacs *et al*., 2014). This can be difficult when the patient's vital signs have been recorded in different places and charts within the clinical notes; reviewing such patients is challenging in the absence of a standardised approach to recording these parameters (Maguire *et al*., 2015). The early warning system has many other names including terms such as 'criteria', 'track' and 'trigger', as tracking the patient's parameters and scores allows the early detection of any clinical deterioration, which then triggers timely intervention (Isaacs *et al*., 2014).

The Confidential Enquiry into Maternal and Child Health (CEMACH) is a UK-wide triennial programme established in 2003 to explore perinatal and childhood mortality (Weindling, 2003). In 2005 CEMACH recommended the use of the modified early obstetric warning score (MEOWS) as shown in Table 1.1 (Singh *et al*., 2012; Ge, 2007).

Table 1.1: The CEMACH MEOWS system, showing the abnormal values of HR, SBP, DBP, temperature, RR, oxygen saturation, neurological response and pain score that are used to trigger the diagnosis of sepsis

	CEMACH MEOWS 2003-2005	
	Yellow	**Red**
Heart rate (beats per minute)	100-120	>120 OR <40
Systolic blood pressure (mmHg)	150-160	>150 OR <90
Diastolic blood pressure (mmHg)	90-100	>100
Temperature (°C)	35-36	>38 OR <35
Respiratory rate (breaths per minute)	21-30	>30 OR <10
Oxygen Saturation (%)	-	<95
Neurological response	Voice	Unresponsive
Pain score	-	2-3

In 2012, the UK Royal College of Physicians standardised a national early warning score (NEWS) within the NHS (Carle *et al*., 2013). There was a clear prohibition of the use of NEWS in pregnant women due to the altered physiological function during maternity (Carle *et al*., 2013). Carle and colleagues therefore designed and validated an obstetric-specific early warning score by the application of univariate analysis and multiple logistic regression, producing a coefficient value to aid in the score-scale development of a NEWS suitable for pregnant women (Carle *et al*., 2013). Table 1.2 details their final scoring system, which was notably based on the scores of a group of patients who had been admitted to critical care units (Carle *et al*., 2013).

Table 1.2: Clinical obstetric early warning score, showing the abnormal values of HR, SBP, DBP, temperature, RR, oxygen saturation and neurological response that are used to trigger the diagnosis of sepsis

	3	2	1	0	1	2	3
Heart rate (beats per minute)	< 60			60-110		111-149	≥ 150
Systolic Blood Pressure (mmHg)	< 80	80-89		90-139	140-149	150-159	≥ 160
Diastolic Blood Pressure (mmHg)				<90	90-99	100-109	≥ 110
Temperature (˚C)	<34.0		34.0 – 35.0	35.1 – 37.9	38.0 – 38.9		≥ 39
Respiratory rate (breaths per minute)	< 10			10-17	18-24	25-29	≥30
Oxygen Saturation (%)				Room air	24-39%		≥ 40%
Neurological response				Alert			Not alert

In 2013 the Irish maternity early warning score (IMEWS) was implemented nationally for use in pregnant women. The system, illustrated in Table 1.3, took a colour-coded approach, using yellow and red for levels of clinical danger, with white for normal parameters (Maguire *et al*., 2015). The escalation guidelines for IMEWS indicate the need for review by the medical team when a patient triggers two yellow responses or a single red one on the scoring chart (Maguire *et al*., 2015).

Table 1.3: The Irish MEWS, showing the abnormal values of HR, SBP, DBP, temperature and RR that are used to trigger the diagnosis of sepsis

	IRISH MEWS	
	Yellow	**Red**
Heart rate (beats per minute)	≥ 100 OR <60	≥ 120 OR <50
Systolic blood pressure (mmHg)	≥ 140 OR <100	≥ 160 Or <90
Diastolic blood pressure (mmHg)	≥90 OR <50	≥100 OR <40
Temperature (˚C)	≥ 37.5 OR <36	≥ 38 or < 35.1
Respiratory rate (breaths per minute)	≥ 20	≥ 25

In the USA, the sepsis in obstetric score (SOS) was designed to identify the risk of obstetric admission to an intensive care unit (ICU) from sepsis. Using data from emergency department (ED) admissions, patients were identified whenever cultures or swabs were considered (Albright *et al*., 2014). The SOS scored each of seven parameters from zero to four, making a maximum score of 28. It was designed to take account of pregnancy-associated physiological

changes and was evaluated by assessing admission to an ICU within 48 hours of ED admission. Table 1.4 provides further details of the scoring system and the values of the parameters (Albright *et al*., 2014).

Table 1.4: Sepsis in Obstetric Score, showing the abnormal values of DBP, temperature, SBP, HR, SpO_2, WCC, % immature neutrophils and lactic acid that are used to trigger the diagnosis of sepsis

Score	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Temperature (˚C)	>40.9	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<30
Systolic blood pressure (mmHg)				>90		70-90			<70
Heart rate (beats/minute)	>179	150-179	130-149	120-129	≤ 119				
Respiratory rate (breaths/min)	>49	35-49		25-34	12-24	10-11	6-9		≤5
SpO_2 (%)					≥ 92%	90-91%		85-89%	<85%
White blood cell count (/µL)	>39.9		25-39.9	17-24.9	5.7-16.9	3-5.6	1-2.9		<1
% Immature neutrophils			≥ 10%		<10%				
Lactic acid (mmol/L)			≥4		<4				

The main differences among these systems are in the cut-off values of parameters that will result in increased clinical observation or a decision on treatment. The temperature cut-off values range from as high as 37.5-38.5 °C to as low as 36-35 °C and the corresponding values for HR, SBP and RR are 100-120 bpm and 60 bpm, 140-150 mmHg and 90-100 mmHg, and 10 bpm and 18-30 bpm respectively. There is some inclusion of laboratory values in the maternity scores; for example, the SOS includes WCC, lactate and neutrophils.

The common problem with all such scores is their non-specificity in identifying deterioration in the patient related to sepsis; in addition, they identify patients who are not septic. An evaluation of the ability of the CEMACH MEOWS to predict morbidity showed a sensitivity of 89% and a specificity of 79%, whereas there was only a 39% positive predictive value and 98% negative predictive value (Singh *et al*., 2012). When Edwards and colleagues evaluated various MEWS scores by applying them to a retrospective cohort of diagnosed cases of chorioamnionitis, they found that the positive predicted values for these scoring systems were low, ranging from 1.42% to 15.4% (Edwards *et al*., 2015). These values provide indefinite identification of abnormalities and illnesses and if used alone would lead to the

illness of some patients being missed because their early warning score values appeared normal, while others not needing treatment would be treated because their values appeared abnormal (Singh *et al*., 2012). The false identification of large numbers of patients means that these women would be prescribed unnecessary antibiotic doses.

1.4.5 Care bundles

A care bundle is a set of practices, usually ranging between three and six in number, that has been proven to enhance patient outcomes and when applied together should provide a better result than if individually implemented (Marwick and Davey, 2009). This quality improvement strategy originated in the USA, was introduced into UK practice in 2002 and has been adopted mainly in ICUs (Clark *et al*., 2015; Fulbrook and Mooney, 2003). The concept of the care bundle originated at the Johns Hopkins University, where the first bundle was produced by searching 35 years of critical care experience reported in the literature from 1965 to 2000. It was then evaluated using critical skills to assess its efficacy in reducing morbidity and mortality in intensive care patients (Fulbrook and Mooney, 2003). The designers of subsequent care bundles have used this published research and linked it to improvements in practice. Each bundle's elements are based either on empirical evidence, guideline recommendations or logical actions. There is an all-or-none approach, whereby all elements within the bundle must normally be implemented together (Borgert *et al*., 2015; Cooke and Holmes, 2007). If any element is medically contraindicated, this should be documented to avoid any suspicion of inadvertent omission and to confirm that this was a positive decision (Horner and Bellamy, 2012). Evaluating compliance with the bundle and with the elements of care within it is an ongoing challenge; although their design and implementation have to be based on evidence or have a strong rational justification, a number of care bundles have not yet been evaluated or undergone peer review (Barochia *et al*., 2010). Therefore, it is essential to measure compliance in order to allow modification and redesign of the bundle if required (Marwick and Davey, 2009).

The importance of care bundles has been demonstrated in cardiac arrest patients, where intervention must be implemented as soon as possible and each minute of delay reduces the likelihood of a positive outcome by 10%. Positive results have also been reported in ventilator-associated pneumonia, where care bundle use was found to be associated with a 44.5% reduction in morbidity (Gao *et al*., 2005).

As sepsis is also associated with mortality, there has been interest in the last two decades in developing a sepsis care bundle, the first of which was the Early Goal-Directed Therapy (EGDT) bundle, whose elements were to be delivered to patients within six hours. This involved the patient receiving a central venous catheter attached to a computerized system to allow continuous monitoring, while treatment for the first six hours occurred in the emergency department, as illustrated in Figure 1-2, prior to inpatient admission (Gao *et al*., 2005; Rivers *et al*., 2001; Wang *et al*., 2009).

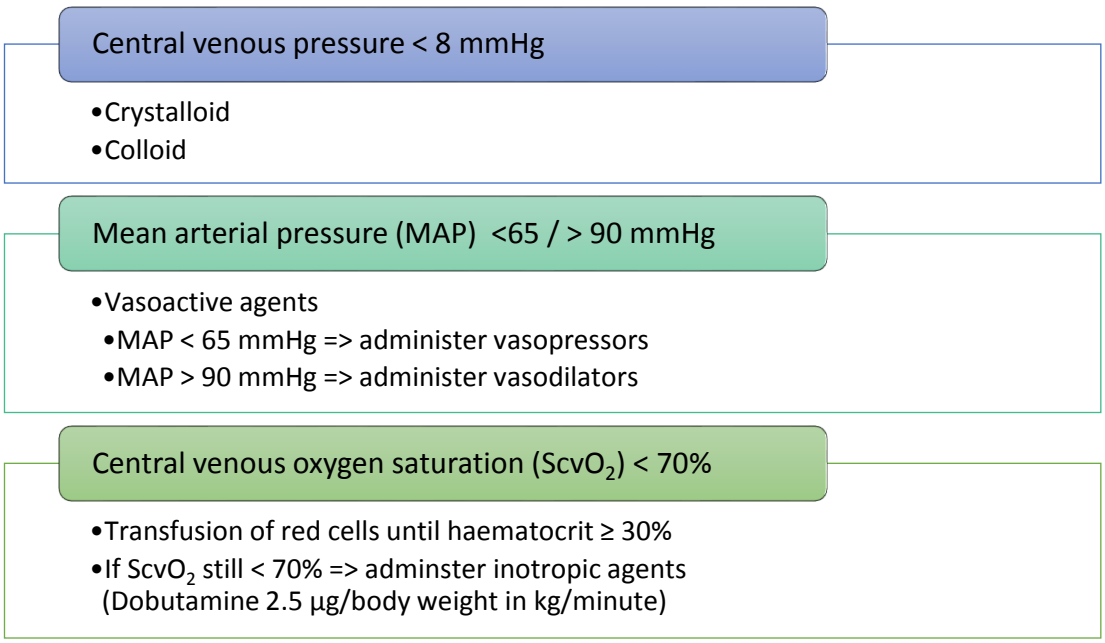

Figure 1-2: Early goal-directed therapy protocol for the treatment of sepsis

The EGDT was proven to reduce mortality rate by 16% and treatment time by about two hours (Gao *et al*., 2005; Wang *et al*., 2009). An intention to treat analysis found that among 263 patients enrolled in the study there was a significant difference in emergency

department treatment time between the EGDT group (mean 6.3 hours) and the standard therapy group (mean 8 hours), $p<0.001$ (Rivers *et al*., 2001). Mortality rate was higher in the standard therapy group compared to the EGDT group, $p=0.009$. This was evaluated again at 28- and 60-day intervals, when there were significant differences at the $p=0.01$ and $p=0.03$ levels respectively (Rivers *et al*., 2001).

Following these results, the Surviving Sepsis Campaign (SSC) adopted the EGDT bundle, aiming to enhance both diagnosis and treatment and to achieve a 25% reduction in severe sepsis mortality within five years (McNeill *et al*., 2008). The SSC is a collaboration between the Society of Critical Care Medicine in the USA and the European Society of Intensive Care Medicine which began in 2002 with the aim of minimizing death associated with severe sepsis and septic shock through the development of awareness and the provision of enhanced care for patients with sepsis (Ward and Levy, 2017). At first, the SSC produced two care bundles: the sepsis resuscitation bundle and the sepsis management bundle (Ward and Levy, 2017). Figure 1-3 illustrates the resuscitation bundle and its six components, to be completed within six hours.

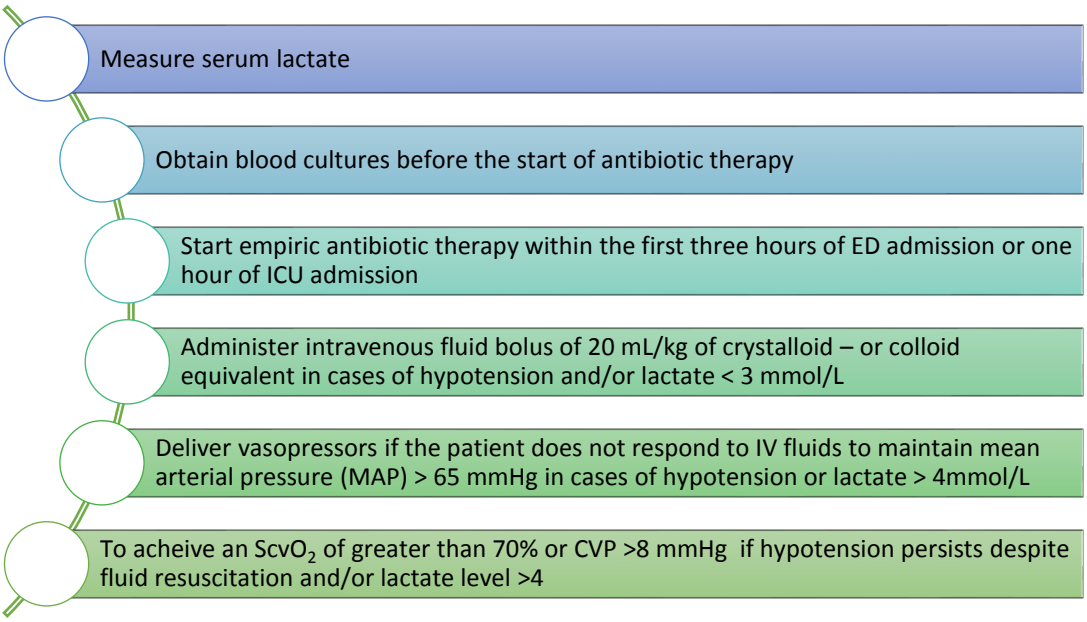

Figure 1-3: The sepsis resuscitation bundle

However, the sepsis guidelines were revised in 2008 and in 2012, dividing the sepsis resuscitation bundle into two parts and revising its aims to focus on early detection and intervention (Ward and Levy, 2017). The first part of the revised bundle consists of four items to be delivered within three hours of the patient being present, while the second part consists of three items to be delivered within six hours (Ward and Levy, 2017). Figure 1-4 details the revised sepsis resuscitation bundle.

First part of the revised bundle: to be delivered within three hours

- Check lactate level
- Obtain blood culture
- Administer IV broad spectrum antibiotic
- ***If patient is hypotensive or has a lactate > 4 mmol/L***
  administer IV fluid (30 ml/Kg)

Second part of the revised bundle: to be delivered within six hours

- Recheck lactate if the initial reading was high.
- **In cases of hypotension not responding to initial IV fluid**
  Vasopressors to maintain MAP >65
- **In cases of persistent arterial hypotension (septic shock) or lactate level >4mmol/L, consider the following:**
  Measure central venous pressure
  Measure $ScvO_2$

Figure 1-4: The revised sepsis bundle

Despite the efforts made to reduce mortality from sepsis by applying the EGDT and SSC resuscitation bundles, the adoption of the SSC bundle within the UK was poor and only 14% of patients in 18 centres were found to have received it (Daniels *et al*., 2010). To improve adoption rates, Daniels and his colleagues designed an operational response to enhance the delivery of care through the introduction of the Sepsis Six Care Bundle (SSCB), which reflects NHS practice and comprises three diagnostic and three therapeutic interventions, to be delivered within one hour (Daniels *et al*., 2010). Figure 1-5 illustrates the SSCB bundle.

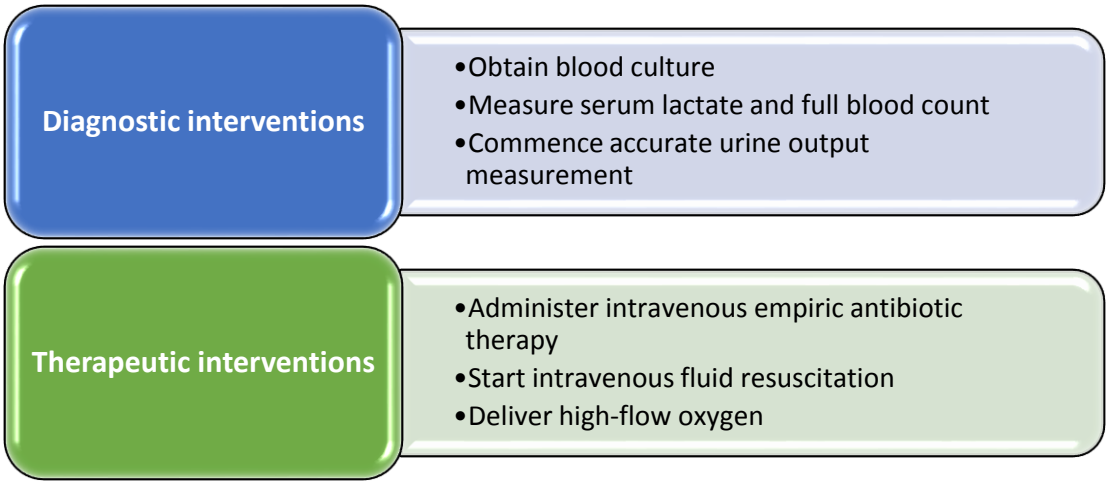

Figure 1-5: The Sepsis Six Care Bundle protocol

Wright and colleagues (2014) from NHS Forth Valley raised concerns after their experience of using the SSCB, noting a 25% increase in the number of blood culture (BC) tests and reporting that the number of positive cultures dropped from 15% to 9% after the SSCB (Wright *et al*., 2014). Uncertainty as to the reason for collecting BCs was reported to be possibly related to abnormalities in the early warning score rather than to suspected sepsis. It was also considered possible that uncertainty over negative BCs was related to their being collected so soon (within the hour), which would tend to produce false negative results and lead to the patient being continued on a broad spectrum antibiotic (Wright *et al*., 2014).

1.4.6 Sepsis Six Care Bundle in obstetric patients

The evaluation of the SSCB in the obstetric population began with retrospective and prospective audits in UK maternity hospitals, on samples of 27 to 174 patients and lasting from three weeks to 15 months (Ratnasekera *et al*., 2014; Howie *et al*., 2015; Francis *et al*., 2015; Edwards *et al*., 2013; Aggarwal *et al*., 2015). Ways of identifying patients with sepsis differ among these studies, including the presence of two or more criteria of SIRS, pyrexia and the administration of antibiotic therapy. Overall compliance with the SSCB was found to be poor, ranging from 50-69.4% in the five studies within the UK (Ratnasekera *et al*., 2014; Howie *et al*., 2015; Francis *et al*., 2015; Edwards *et al*., 2013; Aggarwal *et al*., 2015). The mean

delay in antibiotic administration time was 90 minutes after the one-hour target, while if the antibiotic intervention involved a senior obstetrician it reached a mean of 170 minutes beyond the target of 60 minutes (Ratnasekera *et al*., 2014). Sepsis was most often detected in labour, which represented 50% of the total maternity cases in a Bristol hospital (Edwards *et al*., 2013). Decisions in sepsis cases were taken mainly by senior obstetricians, as reported in 79.4% of cases, whereas in 20.6% of cases the anaesthetist took the decision (Ratnasekera *et al*., 2014). Finally, the mean duration of intravenous antibiotic administration to women with sepsis in postnatal wards was more than two days, with a maximum reported time of 3.3 days, while no data were reported on oral therapy following the IV course of antibiotics (Ratnasekera *et al*., 2014). It is notable that the sepsis bundle started with a wide window of six hours, which was reduced to three hours and finally to the current 60 minutes, consistent with the quicker identification and management of sepsis.

This thesis aims to explore the concept of antimicrobial stewardship in maternity units using mixed methods, by assessing antibiotic use and associated care in suspected peripartum sepsis, investigating the role of the multidisciplinary team and the effectiveness of communication and ward support in the process of assessing and following up treatment.

The structure of the thesis is outlined below. The last section in Chapter 1 sets out the general methodological approach and justifies the methodology adopted to address the research question. It focuses mainly on the mixed methodology approach and discusses some of the methods used in the work described in later chapters.

Chapter 2 reports the quantitative prospective study of a cohort of women treated with antibiotic therapy for suspected or confirmed sepsis. It gives details of the antibiotic therapies prescribed and of the work conducted to investigate the intravenous-to-oral switch, to assess antibiotic discharge prescriptions and to investigate pathogens identified in culture results, along with their sensitivity and resistance patterns. It explains the use of binary logistic regression analysis to review the use of the SIRS diagnostic tool for sepsis,

focusing on the current practice of identifying and managing sepsis in maternity wards by investigating the parameters used to diagnose sepsis and determining which of them was associated with a SIRS score ≥2 in the women concerned. It also reviews other diagnostic tools including qSOFA and various published versions of the MEOWS, highlighting their deficiencies. Finally, it evaluates compliance with the use of the SSCB sticker in women commenced on such care in maternity wards. As to neonates, Chapter 2 reports the use of period prevalence methodology to investigate the use of antibiotic therapy in babies in the first 72 hours of life, evaluating the risk criteria associated with the decision to prescribe antibiotics to these neonates and the prevalence of culture-proven early onset sepsis within the sample.

Chapter 3 reports antibiotic therapies prescribed for non-sepsis women including SSI and urinary tract infection (UTI), it also investigate pathogens identified in culture results, along with their sensitivity and resistance patterns.

Chapter 4 reports the qualitative investigation of midwives use of the SSCB and the concept of antimicrobial stewardship; including their views on identifying patients with sepsis, on de-escalating to narrow-spectrum antibiotics or oral therapy, on the role of microbiologists in the selection of antibiotics and on the support of peers at the ward and hospital levels.

Chapter 5 briefly describes the quality improvement methodology to be used to address the weaknesses in practice identified in Chapters 2 and 4. It sets out a plan for applying the lessons learnt from maternity practice and develops a road map for further improvement and future research in this area.

Finally, Chapter 6 offers reflections on the whole research journey, discusses the broader findings of the research and draws summary conclusions.

1.5 Methodology

This thesis adopts a mixed methodology, combining qualitative prospective and quantitative prospective methodologies. A mixed methodology may be preferred over the traditional research design because answering the research question requires an exploratory understanding and its validation, which cannot be provided by a single approach but demands both quantitative and qualitative elements of research design (Sreejesh and Mohapatra, 2013). A single phenomenon may alternatively have more than one aspect worth exploring, leading the researcher to seek an understanding of both experience and behaviours. In other words, understanding complex phenomena requires researchers to deploy more than one research method within the same project or in response to a single research question (Morse, 2016).

Among the different possible research designs within the mixed-method approach are the simultaneous and sequential alternatives. In simultaneous research, the core and supplemental components are conducted at the same time, while sequential designs involve conducting the supplemental component after the core component has been completed (Morse, 2016). The supplemental component is not complete in itself and could not be published without the content of the core complement, with which it must interface to be valid. Conversely, the core component can be seen as the foundation or backbone of the research project on which all other components of methods or strategies depend – and being the dominant part of the study, it could be published alone. The theoretical drive, in other words whether the study is qualitatively or quantitatively driven, is determined by the direction of the study, which can be identified from the research question. Another important consideration is pacing, i.e. the synchronization between the core and supplemental components (Morse, 2016).

A decision must be made as to where and how the qualitative and quantitative strands will be mixed, whether during the collection or analysis of the data, when interpreting the results or at the level of study design (Creswell and Clark, 2007).

The explanatory sequential design starts with the collection and analysis of quantitative data as the core component, followed by the corresponding stages of the qualitative supplemental component, then the provision of an interpretation (Creswell and Clark, 2007). This is the approach considered in this thesis to provide an explanation of the core quantitative findings through the use of qualitative methods (Creswell and Clark, 2007).

1.5.1 Quantitative research

Quantitative research is the linkage between theory and research through the involvement of numerical data. There are many steps involved in quantitative research methodology, starting with the planning phase of forming a theory and hypothesis, followed by research design and concept measurement, selection of study sites and study subjects. The action phase then includes the collection, processing and analysis of data. Finally, the researcher reports the findings and conclusion through the process of writing up (Bryman, 2015).

Within quantitative research, basic concepts have to be considered including reliability and validity. Reliability, which is the consistency of measurement, can be addressed using stability, internal reliability and inter-observer consistency. Stability is concerned with the change of a measurement over time; measurements should be stable if they are to be reported confidently in the research findings. This is not possible if they fluctuate over time and are not stable. Internal reliability is concerned with coherence and is fundamental in research that uses measurement scales and reports the net results of aggregated scores. Inter-observer consistency is achieved when two or more researchers place their observations of the same phenomena in the same categories. Validity is concerned with having the measured indicator reflect the concept of the research findings and can be

addressed in terms of face validity, concurrent validity, predicative validity, construct validity and convergent validity (Bryman, 2015).

A brief explanation of some quantitative approaches follows. A cohort study is a good method for identifying the incidence and history of an event. It may be the only method available to researchers if a randomised control trial would be considered unethical (Mann, 2003). Randomising patients into treatment and control groups could result in death or undesirable complications for patients in the control group. Cohort epidemiological studies are conducted by following groups of people over a period of time. Prospective or retrospective cohort studies can be considered when dealing with a rare exposure, as selection of study subjects will be based on the exposure of interest (Song and Chung, 2010). A prospective cohort study runs from the present to the future, following an exposure until the event or disease occurs. The exposure should be identified prior to the outcome, to allow the selection of study subjects who will be followed for observation until the development of the disease or event of interest (Song and Chung, 2010; Mann, 2003). By contrast, a retrospective cohort study is a historical study, starting at the present with a disease or outcome and looking back into the past to find exposure (Song and Chung, 2010).

Incidence is the number of new cases of a disease over a period of time; cumulative incidence is the number of cases over a period of time, divided by the number in the population; prevalence is the number of cases existing at a specific point; and period prevalence is the number of cases existing over a specific period of time (Bowling, 2014).

An audit is the process of evaluating current practice against predefined standards. It aims to improve patient outcomes through the achievement of quality in healthcare. It is most often applied to quantitative research methodology, but can also be conducted using observation as part of the qualitative research methodology (Bowling, 2014).

1.5.2 Qualitative research

Creswell and Poth offer a detailed contemporary description of qualitative research that is aligned with the traditional definition as given by Denzin and Lincoln in the SAGE Handbook of Qualitative Research. Their emphasis is on research design and the approach to inquiry (Creswell and Poth, 2017):

> "Qualitative research begins with assumptions and the use of interpretive/theoretical frameworks that inform the study of research problems addressing the meaning an individual or groups ascribe to a social or human problem. To study this problem, qualitative researchers use an emerging qualitative approach to inquiry, the collection of data in a natural setting sensitive to the people and places under study, and data analysis that is both inductive and deductive and establishes patterns or themes. The final written report or presentation includes the voices of participants, the reflexivity of the researcher, a complex description and interpretation of the problem, and its contribution to the literature or a call for change" (Creswell and Poth, 2017).

A common method of collecting data in qualitative research is the interview. It is useful in targeting the participants' world, to explore their experiences, views and meanings, while excluding the interviewer's own beliefs and experiences (Britten, 1995). Interviews can vary in the extent to which they are structured. Fully structured interviews usually take the form of surveys and questionnaires. In unstructured interviews, which rarely occur, the interviewer has no agenda or specific topics to discuss with the interviewees. Semi-structured interviews are widely used in qualitative research. They have the flexibility to allow interviewees to express themselves relatively freely in response to open-ended questions (Britten, 1995; Bryman, 2015). Finally, in-depth interviews allow the interviewer to ask supplementary questions based on information obtained from each interviewee,

focusing on issues of particular interest in order to explore them in further detail (Britten, 1995). During an in-depth interview, the main focus is on capturing the interviewee's opinions, concerns and point of view. The researcher has the flexibility to diverge from the interview guide to gather rich data that will then be coded and analysed to provide a valid meaning (Bryman, 2015).

Among the different methods of interviewing, the most popular is the face-to-face interview, while other methods involve the use of telephones or various applications to facilitate online video or audio link-up. These are popular ways of overcoming the physical barriers that may prevent a person from attending a face-to-face interview. It may also make it easier for busy people with little time in their schedules to participate. Online video interviews have the potential to allow observation of the interviewees' body language, which cannot be observed in a sound-only phone interview (Ritchie *et al*., 2013).

There is some debate about knowledge generation in interviews, as to whether pre-existing knowledge is collected or whether the interviewer's way of conducting the process actually generates the data. In other words, some see the interview as a process of interaction with the interviewee to elicit pre-existing knowledge or beliefs, while others assert that the knowledge obtained did not exist before the interview, but has been generated during the interview itself. Part of the challenge of constructing an interview concerns the researcher's position on whether what is gathered is pre-existing knowledge from the participant's viewpoint or is influenced by the researcher's interests (Ritchie *et al*., 2013).

It is essential to protect the participants from any harm. Masking their identity by removing their names from the data is not enough; instead, the researcher must ensure that the totality of information used in the analysis will not enable recognition of their identity (Creswell and Poth, 2017). The process of data analysis is described in the following section.

1.5.2.1 Qualitative data analysis

1. Data management

Managing the data is the first step in data analysis. It involves organising the data in a named file, stored in a secure and accessible location. In cases of conversion, a clear decision has to be taken at an early stage on the appropriate format for test or audio-video materials. At this stage it must also be decided whether analytical software needs to be used (Creswell and Poth, 2017).

2. Reading

It is important to read the data and to try to make sense of its meaning through reflection and exploration in an initial phase before the start of any coding process Creswell and Poth, (2017) suggest to "Read the transcripts in their entirety several times. Immerse yourself in the details, trying to get a sense of the interview as a whole before breaking it into parts"

3. Coding and categorising

Following the reading, the data must be coded and categorised, as codes and categories are central to the analysis (Creswell and Poth, 2017). A code has been defined as "a term used for attaching conceptual labels to data" (Urquhart, 2012). The aim is to describe the details of what the researcher sees by aggregating the data into a smaller version of codes and categories. Researchers sometimes start with a list of categories and codes, then expand them when reviewing the data. It is recommended to keep the maximum number of codes between 25 and 30, which are combined to produce themes that will be used in the writing process. The source of codes can be in vivo, i.e. emerging from the data and described by participants themselves, taken from the literature, or the researcher's own words to describe the data (Creswell and Poth, 2017).

Coding is employed in many types of qualitative analysis and there are many approaches, including bottom-up, top-down, middle-range and thematic coding (Urquhart, 2012).

1. Grounded theory (GT) is an example of bottom-up coding, where the codes emerge from the data, with no influence from the literature. Coding starts at the word or sentence level, or as line-by-line coding, aiming to reduce the chance of missing any category. Coding at this level has the advantage of providing new insights, which is seen as a strength of GT methodology.
2. Top-down coding occurs when codes emerge from the literature and are applied to the data.
3. Middle-range coding is a combination of bottom-up and top-down coding, whereby initial codes are taken from the literature and more then emerge from the data.
4. Thematic coding is the process of placing codes in larger categories or themes to be applied to chunks of data. It can be "quick and dirty", done by picking a theme from some interviews, or can be reinforced by smaller categories and applied systematically. Thematic coding can mimic the bottom-up and top-down approaches, with the difference being its application at high levels.

The process of quantifying the incidence of codes is termed 'content analysis' (Urquhart, 2012). In purely qualitative research, however, numbers are considered to be of no value in providing an explanation or understanding of a phenomenon (Ritchie *et al*., 2013). Thus, counting the times that a word is used or an action mentioned can be seen as conflicting with the nature of a qualitative study (Ritchie *et al*., 2013; Creswell and Poth, 2017). Instead, every code should receive equal emphasis (Ritchie *et al*., 2013). The aim of qualitative studies is not to produce statistically significant numerical results or to provide the basis for making predictions, but to explore the details of a certain phenomenon without hypothesising an outcome (Pope *et al*., 2002).

Following the completion of the initial coding phase, the researcher should begin looking for categories and themes. Themes are the extensive units of data analysis, each consisting of several codes, so that the final product number of themes. Each can be seen to represent a

family, composed of categories representing the children of themes and subcategories representing their grandchildren (Creswell and Poth, 2017).

4. Representing the data

The final product of data analysis is to represent the findings in the form of text, figures or tables. A decision as to whether to display the data in the form quotes, explanations or both should be taken before this process begins. The assessment of readability will allow the researcher to make modifications whenever needed. It is recommended that the data display format should allow comparisons to be made and patterns to be revealed (Creswell and Poth, 2017).

1.5.2.2 Types of analysis

Four main types of data analysis are known in qualitative research: thematic, framework, grounded theory and narrative analysis. Thematic analysis, which is the most commonly used in qualitative research, produces a 'map' of the data content and serves to summarise variations across the data. The data are reduced by the creation of themes or patterns. Themes can be defined as "recurrent concepts which can be used to summarize and organize the range of topics, views, experiences or beliefs voiced by participants" (Green and Thorogood, 2013).

Thematic analysis can involve a mix of inductive concepts that came from the data and deductive concepts derived from the study's aims or the literature. Framework analysis constitutes a more deductive approach, involving the reduction of data in a thematic framework. Narrative analysis is the use of story-telling to allow the findings to emerge from the data. Finally, GT is a purely inductive method of data analysis that allows theory to be built from the data (Green and Thorogood, 2013).

2 Chapter 2: Difficulties associated with the diagnosis and subsequent management of sepsis in women and babies in maternity units

2.1 Introduction

The physiological changes which occur during pregnancy and labour can affect the SIRS baseline parameters used in the identification of sepsis (Albright *et al*., 2014). Alterations in a woman's normal physiology can mask the initial phase of sepsis and delay diagnosis, thus potentially delaying clinical intervention and subsequent recovery (Cordioli *et al*., 2013). These physiological changes, especially within the third trimester, in particular, an elevated heart rate and low blood pressure, increase the diagnostic challenge (Arulkumaran and Singer, 2013). As explained in Section 1.4, despite the challenges associated with sepsis diagnosis, when sepsis is suspected, antimicrobial intervention should be delivered as quickly as possible on the basis of expediency (Yealy *et al*., 2015). This is by intravenous administration of broad-spectrum antibiotics until clinical data indicates the possibility of de-escalation or cessation of antimicrobial therapy (Arulkumaran and Singer, 2013; RCOG, 2012a; NICE, 2016; Dellinger *et al*., 2013). Initial care should be considered and delivered within one-hour as recommended by the RCOG and the SSC (RCOG, 2012a; Dellinger *et al*., 2013). The choice of antimicrobial agent should follow local guidelines and policy, which are mainly based on the epidemiology of antimicrobial resistance in the particular hospital and/or geographical area (RCOG, 2012a; Dellinger *et al*., 2013). However, initiating broad spectrum intravenous antibiotic treatment should prompt daily clinical review and de-escalation to a narrower-spectrum antibiotic and/or intravenous-to-oral switching as soon as is clinically appropriate (Dellinger *et al*., 2013; National Clinical Effectiveness Committee, 2014).

The recognition that patient deterioration can be limited by the early detection and management of sepsis has led to the application of care bundles as a mechanism for minimizing harm and enhancing patient care (Resar *et al*., 2012). The SSCB was recently

introduced into the maternity wards of the health board examined. The documentation of what care has and has not been delivered is communicated within the healthcare team in the form of a sticker attached to patients' notes, with the aim of delivering all six elements of the bundle within one hour of sepsis being provisionally diagnosed.

Babies newly born to women who have been treated for suspected sepsis during labour will be commenced on IV antibiotic as prophylaxis against EONS. There are divergent definitions of EONS, but the RCOG (RCOG, 2012b) defines it as 'an infection affecting neonates prior to their seventh day of life'. NICE guidelines and local hospital policy however, consider EONS to be an infection commencing within the first 72 hours (West of Scotland Neonatal Managed Clinical Network, 2017; NICE, 2012). The NICE guidelines list a number of criteria, risk factors, red flags and clinical signs for babies (refer to Table 2.8) which help to drive the decision on antibiotic therapy (West of Scotland Neonatal Managed Clinical Network, 2017; NICE, 2012). A red flag indicates that the baby needs to have antibiotic therapy. While the presence of a single risk factor or an abnormal clinical sign in the neonate does not require the administration of antibiotic therapy, closer monitoring of such babies is encouraged (NICE, 2012).

One of the risk factors and clinical indicators for babies to be treated is being born to a woman who was commenced on a sepsis protocol. This means that both mother and baby can be treated with an antibiotic where sepsis is suspected but not confirmed by culture. Decisions made in response to the mother's condition should be carefully considered when they directly affect the baby and account should be taken of the adverse effects of unnecessary antibiotic therapy. A review of the evidence on which these risk factors and clinical indicators are based concluded that low quality evidence had been used to support this list (National Collaborating Centre for Women's and Children's Health, 2012). Maternal GBS colonisation as a risk factor has been assessed as weakly predictive of culture-proven infection and moderately predictive of clinical infection, based on a study of 823 babies

conducted in 1996. The same study found that gestational age < 37 weeks was weakly predictive of culture-proven infection and moderately predictive of clinical infection. There is high quality evidence from a 1998 study of 1367 babies that clinical chorioamnionitis in babies with very low birth weight of < 1500 g can be used to predict culture-proven infection and clinical diagnosis of early onset sepsis. The evidence becomes weaker with an increase in birth weight. Maternal fever with a temperature > 37.5 offers low quality evidence of infection in babies at 48 hours of life, according to a study of 72 babies conducted in 1983 (National Collaborating Centre for Women's and Children's Health, 2012).

Babies exposed to antibiotics, especially in the early days of life, have the potential to develop a number of diseases later in life (Martin *et al*., 2016). In a recent study of 36 newborn babies, 16 (44.44%) were exposed to a prophylactic dose of intrapartum antibiotic prior to caesarean section, while seven babies (19.44%), although delivered vaginally, were exposed to antibiotics for prolonged rupture of membranes or infection. The remaining 13 babies (36.11%) were not exposed to intrapartum antibiotics. All babies' microbiota from four sources (maternal oral, placental, maternal faecal and babies' oral swabs) were tested on the first day of life. Analysis shows that 65% of the babies' oral microbiota consisted principally of mothers' oral microbiota. Results in respect of intrapartum antibiotics support the clustering of the microbiota on the basis of intrapartum antibiotic exposure (R=0.21, *p*=0,002), whereas delivery method was found to have no effect (Gomez-Arango *et al*., 2017). Intrapartum antibiotic exposure has also been found to have longer-term associations, with the development of asthma later in childhood, with an increased risk of developing obesity, particularly in males, and with the development of irritable bowel syndrome and coeliac disease (Cotten, 2016).

The aim of antimicrobial stewardship in the treatment of sepsis in pregnancy is to optimize clinical outcomes for both women and babies while reducing the unnecessary use of antimicrobial therapy, supporting the empirical treatment of suspected infection until

culture results prove otherwise. Antimicrobial stewardship encourages clinicians to "discontinue antibiotics after 48 hours if blood cultures are negative and ongoing infection is not suspected" (Patel and Saiman, 2012).

2.2 Aims and objectives

2.2.1 Aims

To evaluate antimicrobial stewardship in suspected sepsis and the delivery of the Sepsis Six care bundle in maternity settings.

2.2.2 Objectives

1) To assess the prescription of antibiotic therapy and the SSCB in women suspected of having sepsis.
2) To evaluate the impact of the microbiology report on the choice and de-escalation of antibiotics.
3) To assess babies' antibiotic exposure resulting from antibiotic treatment delivered to women with suspected sepsis.

2.3 Methodology

2.3.1 Sites and setting

A prospective observational cohort study was conducted in three maternity hospitals in a single Scottish health board region that recorded 12,233 live births in 2015 (NHS National Services Scotland and ISD, 2016). Data collection ran from Monday 11th April 2016 for a period of 12 weeks. Once collected, individual patient data were immediately anonymised and held electronically on a secure server until analysis.

The study was introduced to the clinical team by having an appointed person in each site introducing the researcher (NA) and the study aim to the teams working in the maternity and neonatal wards. This was done either in person or by email.

2.3.2 Study participants

Methods used to identify patients for inclusion in the study varied among the three hospitals, depending on the absence or presence of specialised clinical pharmacy services. The process is illustrated by the flowchart in Figure 2-1.

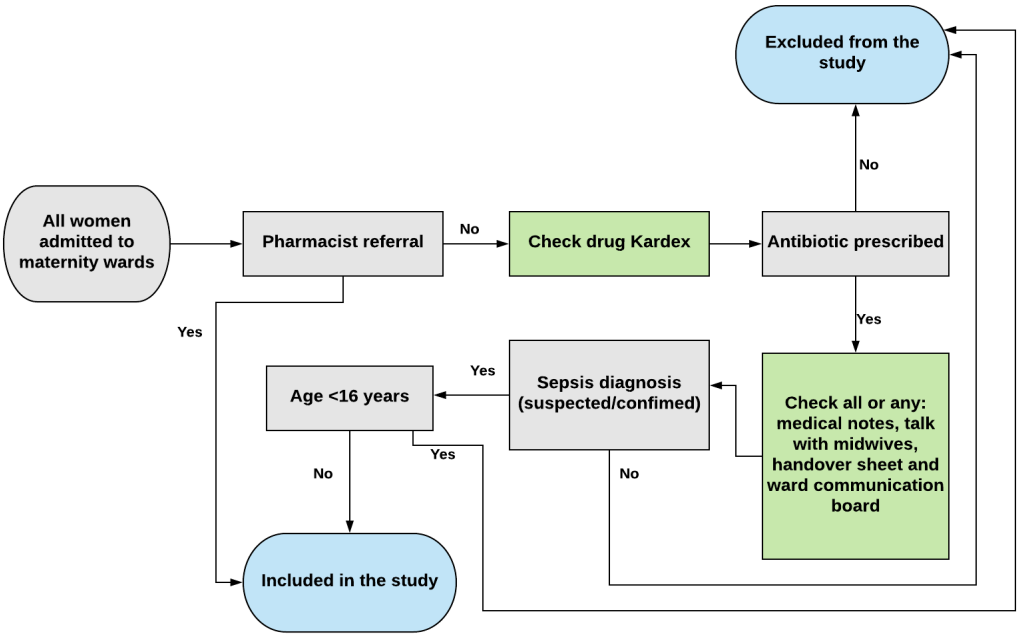

Figure 2-1: Flowchart illustrating the process of identifying patients in the study

Pharmacist referral is equivalent to the selection process demonstrated in the flowchart, the only difference being that it was done by the specialised pharmacist working in the obstetric ward.

Data on each identified patient were collected from the clinical notes, drug Kardex, patient handheld notes and TrakCare® (an electronic patient information system adopted at the hospital study sites). Follow up with any changes in therapy or laboratory results were recorded for all patients until discharged from the ward.

2.3.3 Data collection

2.3.3.1 Patient medical note and/or handheld

Demographic data were collected on age, weight, body mass index (BMI), allergy status, parity and gestation whenever available. Patients were categorised as either antenatal, labour, postnatal or postnatal readmission. Data were captured on the unit to which each woman was admitted, i.e. antenatal/postnatal ward, intensive therapy unit (ITU) and/or high dependency unit (HDU). The complete data from the Sepsis Six sticker were also captured for individual patients as shown in Table 2.1.

Table 2.1: Sepsis Six Care bundle sticker

Data when Sepsis Six delivered	Day number:
What are the SIRS? Temp □ HR □ RR □ WCC □	Time zero:
Sepsis Six bundle:	
1. Oxygen to achieve saturation >94%, ≤98%	Yes □ No□ Time:
2. Blood culture and relevant swabs	Yes □ No□ Time:
3. Take lactate, FBC, CRP, U+E, Coag, G+S +/- ABG	Yes □ No□ Time:
4. Intravenous antibiotic	Yes □ No□ Time:
5. IV fluid challenge	Yes □ No□ Time:
6. Note urine output, fluid balance, consider catheter	Yes □ No□ Time:
Care delivered within 1 hour of suspected/diagnosed The name of the provider of sepsis six was written Yes □ No□	Yes □ No□ Designation:

Key: SIRS: systemic inflammatory response syndrome; **HR**: heart rate; **RR**: respiratory rate; **WCC**: white cell count; **FBC**: full blood count; **CRP**: C-reactive protein; **U+E**: urea and electrolytes; **coag**: coagulase test; **G+S**: group and save; **ABG**: arterial blood gas; **IV**: intravenous.

2.3.3.2 Patient drug Kardex

Information about antibiotic therapy was collected from the patient's drug Kardex. Information about antibiotic therapy prescribed throughout the patient's stay in the hospital wards was of interest. Thus, data were collected on antimicrobial name, drug dose, route of administration, frequency and number of doses or days of therapy where possible. The number of doses was rounded to the nearest number of days for the purpose of analysis.

Information on therapy not prescribed by a medic—on the last page of the drug Kardex—and given by the midwife as needed by the patient was not included.

2.3.3.3 Patient electronic health record

All laboratory results covering haematology and biochemistry were captured from TrakCare®, in addition to any discharge medication that was recorded in the patient's immediate discharge letter (IDL) ®; a document containing a patient's admission summary and listing patient medication at discharge. Microbiology data on pathogens detected, resistance and sensitivity, if obtained, were checked and captured from TrakCare® for each patient. Information about specimens, specifically cultural yields, growth, sensitivity and resistance, were obtained from each patient's TrakCare® where available. Any comments and advice from microbiologists that were communicated by telephone and reported in a patient's clinical notes were also captured.

Also captured was the action taken by healthcare providers following the microbiology advice and/or report, from three possible alternatives: either to escalate to another antimicrobial therapy that the detected pathogen was sensitive to, to de-escalate from the broad-spectrum antibiotic(s) or to continue with the current treatment plan. Any changes in the route of drug administration were also recorded. IDLs were also accessed for patients who were treated for sepsis, had their therapy discontinued or de-escalated and were then discharged home with no antimicrobial therapy reported in their IDL.

Following the application of the Sepsis Six care bundle, a number of laboratory tests were expected to be requested for all patients. These include but are not limited to blood culture or relevant swab, full blood count, C-reactive protein (CRP), urea & electrolytes and coagulase blood test. The decision on whether to include arterial blood gas in the list of tests was left to the healthcare provider (consultant, middle grade or junior doctor). Therefore, it was not obtained for all patients. Finally, liver function test data were obtained in parallel with the other tests for most patients.

2.3.3.4 Patient early warning chart

Information about the patient's temperature, heart rate, respiratory rate, blood pressure and mental status was collected from the MEOWS that was located with the patient's handheld notes. The first reading recorded in the data collection form was not the first measurement on the MEOWS chart but taken at the time closest to when sepsis was called. The data collected were limited to the following: temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation and neurological status: either 'alert' or responsive to 'voice'. Labour reference values for SIRS parameters differ in some ways from those for general obstetric wards. SIRS reference values are shown in Table 2.2.

Table 2.2: NHSGGC local guidelines for the modified labour and maternity abnormal SIRS criteria that are used to trigger the diagnosis of sepsis

	Modified SIRS criteria for maternity wards	**Modified SIRS criteria for labour**
Temperature	< 36˚C or > 38 ˚C	≥ 37.5 ˚C on two separate occasions at least 2 hours apart
Heart rate	> 100 beats per minute	> 110 beats per minute
White cell count	< 4 or > 16 x 10^9/L	> 20 x 10^9/L
Respiratory rate	> 20 breaths per minute	> 22 breaths per minute
Systolic blood pressure	< 90 mmHg	< 90 mmHg
Mental status	Altered mental status	Altered mental status

2.3.4 Study phases

During the pilot phase, the data collection methods were assessed and evaluated by applying them to patients admitted to one maternity unit during March 2016. For a total of four weeks, data were captured on 29 patients in the labour, antenatal and postnatal wards. No pilot was considered necessary at the other two units, mainly because all three maternity units were within one health board, so similar structures and systems were assumed to be operative at all three sites.

The main reason for conducting the pilot was to ensure that appropriate data were collected to satisfy the research aims. The results of the pilot allowed changes to be made to the data collection forms explained in section 2.3.3. These were considered and approved prior to data collection for the main study. Data using the final collection tool were then collected for a period of 12 weeks. The pilot study allowed researcher NA to understand the reality of the clinical data. It was expected that only one antibiotic therapy would be found to have been prescribed to each patient, but in reality there were often changes in drug therapy, in dose and/or in route. The antibiotic table in the data collection form was therefore expanded to include more spaces in order to accommodate such changes. The microbiology report was similarly expected to specify only the organism that was detected, but it was found that in practice there would sometimes be more than one microbiology report (i.e. on multiple specimens collected) and that it would be necessary to collect data on other parameters including sensitivity and resistance.

2.3.5 Babies with suspected sepsis

A period prevalence study was conducted in the same settings for the same health region. Data were collected on babies reported to have been prescribed antibiotic therapy in the first 72 hours of life, including both term and pre-term babies. Excluded were babies who had undergone surgery whenever the indication was clearly stated in the medical notes. Data were collected on each baby's weight, gestation, mode of delivery and the unit to which the baby was admitted. Information about the CRP level within the first 72 hours of life was collected. As blood culture specimens varied according to the baby's condition and admission unit, the only information collected was the result of the culture/swab, recorded as either the pathogen detected or the fact that there was "no growth". Information on antimicrobial therapy prescribed throughout the first 72 hours of life that was captured included drug name, dose, route and frequency.

Further information was collected based on the NICE guidelines on neonatal infection. This comprised data on risk factors, red flags and clinical indicators, which appeared on the data collection form as a check list. Information was completed from each baby's medical notes, including the admission papers for the reason for admission to the unit.

Failure to follow up led to the exclusion of one baby (SN: 208) as at the point of data entry no CHI number was given to the baby. It was later found that two babies had been born on the same day with the same surname. The researcher was not able to check TrakCare®.

2.3.6 Ethical consideration

This study was considered a service evaluation, as routinely recorded information was collected to evaluate a development in current service delivery within a single centre of Greater Glasgow & Clyde. It did not generate new knowledge, but rather evaluates and assesses the quality of the current service (Twycross and Shorten, 2014). The Scientific Officer of the West of Scotland Research Ethics Committee confirmed that the proposed study did not require ethical approval and Caldicott approval was granted. As no new data were being generated it was not considered appropriate to seek NHS research ethics committee or Research & development (R&D) approval. However, University departmental ethics approval was sought from the Strathclyde Institute of Pharmacy and Biomedical Science (SIPBS) Research Ethics Committee and a decision to approve was made prior to the data collection. This was done to ensure good adherence to ethical principles requiring that data be anonymized and securely stored (Twycross and Shorten, 2014).

2.3.7 Statistical analysis

All analysis was performed using the IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp), using a significance level of 5% for data interpretation. The Shapiro-Wilk test of normality was performed on all data to assess its goodness of fit to a normal distribution. Median + range was used for non-parametric data and mean ± standard deviation (SD) for

parametric data. Other data are reported using number and percentage (%). The Mann-Whitney U test was applied to patients' demographic data to assess the differences in these parameters between culture-positive and culture-negative patients. Mann Whitney was also used to assess differences in CRP between positive and negative culture specimens and between the different SIRS scores. The Mann-Whitney U test was performed to assess the median distribution of numerical data with a non-parametric distribution between two groups; the Wilcoxon rank sum test would have provided equivalent outcomes and both of these tests are equivalent to the t-test, which can be applied to parametric data (Petrie and Sabin, 2013). The Kruskal-Wallis test was used to compare numerical data with a non-parametric distribution in more than two groups, was performed to detect differences in CRP level between different modes of delivery (Petrie and Sabin, 2013).

A binary logistic regression is performed when the outcome is binary, e.g. disease vs disease-free outcome. It determines which of a number of variables present are associated with the outcome and assesses the probability of an individual developing the outcome when the particular covariates occur (Petrie and Sabin, 2013). The binary logistic regression test was performed to assess the SIRS criteria (i.e. WCC, HR, RR, temperature) in addition to SBP, CRP and mental status in determining the diagnosis of sepsis in maternal women. Binary logistic regression was also used to determine the risk factors associated with CRP>10 mg/L in babies.

First, to assess the criteria for diagnosing sepsis, all parameters collected from each patient's MEOWS and electronic health records were recorded as continuous data, except for mental status (0= alert, 1=voice, 2=unresponsive). The continuous data for WCC, CRP, HR, RR, SBP and temperature were converted into categorical data (0=within normal range, 1=abnormal) using the "transform" function to "record into different variables". Next, individual patient scores were calculated to categorise the patients into two groups (group1= SIRS <2, group2= SIRS ≥2) using WCC, RR, HR and temperature. SBP, CRP and mental status were not used to

calculate the SIRS score, but were used later in the binary logistic regression test to assess whether they influenced the outcome.

Patients who were identified and treated in labour had different SIRS reference values from those patients who were identified and treated in wards. The SIRS labour reference values have been modified to accommodate the labouring and delivery process; they therefore have a different range from that of the SIRS reference values for women diagnosed and treated before or after the incidence of labour. These differences were aggregated when conducting the analysis.

Binary logistical regression was performed on datasets to determine which parameters (among WCC, RR, HR, SBP, CRP, temperature and mental status) were more likely to be associated with these women having a trigger for sepsis (SIRS ≥2). In the SPSS program these parameters were the "covariates", and the outcome of group1= SIRS <2, group2= SIRS ≥2 were the "dependent" variable. The method of entering the covariates into the logistic regression model was selected as "forward: conditional"; which means that the covariates were added one by one to the model, which would then stop when no significant change was obtained by adding further covariates.

There were four main outputs of this analytical test: 1) a "classification table" that determined the accuracy of the model's prediction of sepsis; 2) a "variables in the equation" table that determined which parameters from the covariates had been selected for the model, providing additional data including the *p*-values of these variables and at which step the "forward: conditional" model stopped; 3) a "constant" value used in the equation to add further values based on the logistic regression model; and 4) a table of "variables not in the equation" and their *p*-values to justify not including them in the model.

The equation of the binary logistic regression (explained in detail in the result section) gave the predicted probability of having sepsis for each individual patient in the analysis. It could also be used for patients not in this study when the values of the parameters were known.

The main outcome of the binary logistic regression analysis is to provide a model for future patients, determining their probability of having sepsis on a range from 0 to 1, where anything above 0.5 means a good probability and the closer the value is to 1 the greater the patient's chance of having sepsis. This probability as an output of the logistic regression can be visually presented using the receiver operating characteristic (ROC) curve.

An ROC curve is the sensitivity (true positive rate) of the binary logistic regression model in identifying sepsis plotted as a function of the 1-specificity of the binary logistic regression model in falsely identifying sepsis (false positive rate). A perfect model will have an ROC curve close to the upper left corner, which represents 100% in both sensitivity and specificity, the highest possible accuracy of a diagnostic test and a probability of 1 on the 0 to 1 scale of the binary logistic regression model (Zweig and Campbell, 1993; Kleinbaum and Klein, 2010). As this test is predictive, the result may differ from actual data. The proportion of cases with a positive test result which are correctly diagnosed is called the positive predicted value (PPV), while the proportion of those with a negative test result which are correctly diagnosed is the negative predicted value (NPV) (Altman, 1990).

The result is represented by the area under the ROC curve; the larger the area under the curve (AUC), the better the discrimination of the model and the closer to 1 (Kleinbaum and Klein, 2010).

2.4 Results for women

2.4.1 Demographics

A total of 89 women with a mean age of 29.8 ± 5.3 years were identified with suspected or confirmed sepsis from a total of 2690 pregnancies. This gave an incidence rate of 3.3% of women with suspected or confirmed sepsis. Almost half of the women (46.1%, n=41) had their babies delivered by emergency caesarean section, 1.1% (n=1) by elective caesarean section, 24.7% (n=22) by spontaneous vaginal delivery and 15.7% (n=14) by instrumental

delivery, while data were missing/not obtained for 13.5% (n=11) of women, of whom 63.7% (n=7) were diagnosed with sepsis in their antenatal period. Most cases (85.4%, n=76) of sepsis diagnosed during hospital admission were reported in the labour (46.1%, n=41) and postnatal (39.3%, n=35) wards. In 89.9% (n=80) of cases, women were treated in maternity wards, while 7.9% (n=7) of the women were treated in high dependency units and 2.2% (n=2) were treated in an intensive care unit. No women were recorded as being underweight. Twenty-two women (27.8%) were obese; of these, 45.5% were class I obese (BMI 30-34.9 kg/m^2); 27.3% were class II obese (BMI 35-39.9 kg/m^2) and 27.3% were class III obese, with BMI ≥40 kg/m^2. Table 2.3 summarises the additional demographic data.

2.4.2 Systemic inflammatory response score

MEOWS and Full Blood Count (FBC) results were used to calculate the inflammatory response score, as sepsis diagnosis required at least two abnormal SIRS indices and the suspicion of infection. This evaluation showed that only 46 patients (51.7%) had a SIRS score of two or more, 27 (30.4%) scored less than two and 15 patients (16.9%) had a single or multiple missing parameter recorded at the point of sepsis diagnosis.

2.4.3 Microbiology reporting

Assessing the microbiology reports, a total of 120 blood cultures or swabs taken from 89 women were analysed. The data for four women were missing. The majority of specimens showed “no growth” of a pathogen (60%; n=72). Figure 2-2 summarises the positive results of cultures or swabs based on specimens. One case each of *Clostridium perfringens* and *E. coli*-associated sepsis (n=2) were associated with ICU admission and prolonged hospital stay of 30-31 days duration.

Table 2.3: Patients' demographic data upon admission to hospital prior to giving birth

Demographic/maternal data	Overall Median (range)	Culture positive Median	Culture negative Median	P-value from Mann-Whitney U test
Weight (kg)	70 (44-154)	73	69.6	0.526
BMI (kg/m^2)	25.3 (18.7-55.1)	24.7	25.3	0.355
Parity	0 (0-8)	1	0	0.176
Gravidity	0 (0-10)	0	0	0.230
Gestation age (weeks)	39.5 (13-41)	39	40	**0.045***
and additional days	4 (0-6)	4	4	0.686
Length of hospital stay (day)	4 (1-31)	4	4	**0.007***
Estimated blood loss (ml)	900 (100-5000)	983	825	0.698

*Significant at $p<0.05$

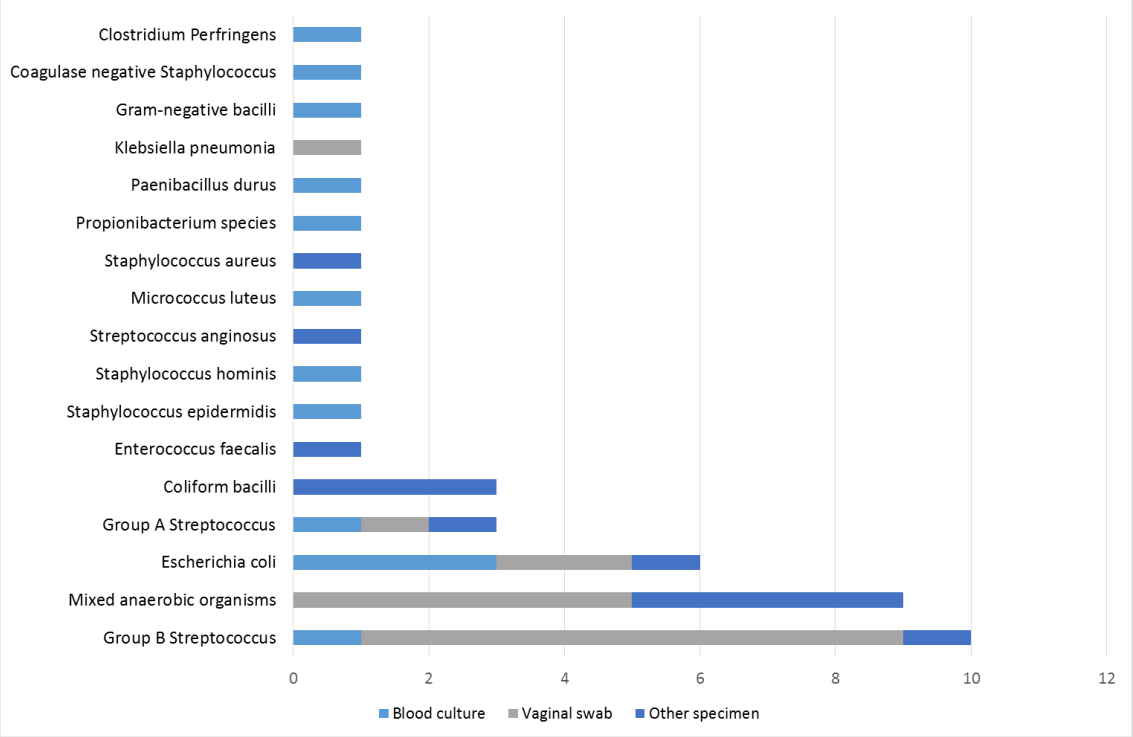

Figure 2-2: Pathogens isolated from clinical specimens from women with suspected sepsis

The number of isolated pathogens from blood culture, vaginal swab or other specimen of urine culture, placental swab, skin swab or wound swab.

2.4.3.1 Antibiotic resistance patterns

Of a total of 48 microbiologically-positive specimens, 66.7% (n=32) were reported as being sensitive and/or resistant to certain antibiotics. Changes of antibiotic therapy after a microbiology report were observed in 28.12% (n=9) of cases.

Seven incidents of resistant microbes were reported in six patients. The patient who experienced clindamycin and clarithromycin resistance was diagnosed with a *group B streptococcal* infection. Resistance to ampicillin/amoxicillin was reported in two cases of *E. coli* infection, while resistance to clarithromycin was reported in two additional cases of GBS infection. Finally, resistance to trimethoprim was reported with *coliform bacilli* infection. Appendix B provides a summary of both antibiotic sensitivity and resistance in pathogens isolated from women's cultures. All of these were limited to resistant microbes and did not include clinical antibiotic resistance in any patient. Changes to therapies were based on antibiotic susceptibility.

2.4.4 Antimicrobial therapy

A total of 313 antibiotic prescriptions were collected during the study period. Table 2.4 lists the antimicrobial therapies administered, ranging from 1 to 17 therapies per patient, with a median of 3 antibiotic therapies per patient. Duration of therapy varied between hospital admission and discharge, having a median of 2 (1-5 days) for antibiotics prescribed in the ward and a median of 7 (3-14 days) for IDL antibiotic prescriptions.

The five most commonly prescribed antimicrobials were amoxicillin/clavulanic acid (co-amoxiclav), gentamicin, metronidazole, flucloxacillin and clindamycin (Table2.5). Gentamicin was prescribed intravenously (IV) at various doses depending on patient-specific factors such as weight and creatinine clearance. Doses ranged from 160 mg to 400 mg every 24 or 48 hours. There was limited gentamicin therapeutic drug monitoring, as therapy was most commonly stopped following a single dose. Trimethoprim was prescribed as a monotherapy without inclusion of sulfamethoxazole.

Table 2.4: Antibiotic categories and the number of prescriptions prescribed for women with suspected sepsis

Antibiotic name	Number of prescriptions (%)			
	Total **(100%)**	SIRS ≥2 **(59.4%)**	SIRS <2 **(28.8%)**	Unknown **(11.8%)**
Penicillins	213 (68.05%)	124 (66.7%)	59 (65.5%)	30 (81.1%)
Cephalosporin, carbapenems and other beta-lactams	7 (2.24%)	7 (3.7%)	0	0
Aminoglycosides	40 (12.78%)	24 (12.9%)	12 (13.3%)	4 (10.8%)
Macrolides	5 (1.60%)	2 (1.1%)	3 (3.3%)	0
Clindamycin	14 (4.47%)	10 (5.4%)	2 (2.2%)	2 (5.4%)
Vancomycin	5 (1.60%)	2 (1.1%)	3 (3.3%)	0
Trimethoprim	2 (0.64%)	2 (1.1%)	0	0
Metronidazole	25 (7.99%)	13 (6.9%)	11 (12.2%)	1 (2.7%)
Quinolones	2 (0.64%)	2 (1.1%)	0	0
Total	**313**	**186**	**90**	**37**

Table 2.5: Route, dose and frequency of some antibiotic therapies prescribed for women with suspected sepsis

	Route	N (%)	Dose			Frequency
Co-amoxiclav (n=180)	IV	77 (42.8%)	600 mg (n=1)	1200 mg (n=76)		TDS
	PO	103 (57.2%)	375 mg (n=3)	625 mg (n=100)		
Metronidazole (n=25)	IV	8 (32%)	500 mg (n=8)			TDS
	PO	16 (64%)	400 mg (n=16)			TDS (n=15) BD (n=1)
	PR	1 (4%)	1000 mg (n=1)			OD
Flucloxacillin (n=17)	IV	9 (52.9%)	1000 mg (n=5)	2000 mg (n=4)		QDS
	PO	8 (47.1%)	250 mg (n=1)	500 mg (n=4)	1000 mg n=3)	
Clindamycin (n=14)	IV	7 (50%)	450 mg (n=1)	600 mg (n=4)	900 mg (n=2)	450 mg: 1 dose only 900 mg: TDS (n=1) 900 mg: QDS (n=1) 600 mg: QDS (n=2) 600 mg: TDS (n=2)
	PO	7 (50%)	300 mg (n=6)	350 mg (n=1)		QDS

Key: IV: intravenous, PO: per oral, PR: per rectal, OD: = omni die (every day), BD: = bis die (twice daily), TDS: ter die sumendum (to be taken three times daily), QDS: = quater die sumendum (to be taken four times daily)

2.4.5 Intravenous to oral switch

There were 91 antibiotic prescriptions initiated in the 88 patients, 93.4% (n=85) were prescribed as IV and the remaining 6.6% (n=6) were delivered orally from the outset. In 85.7% of the 91 cases (n=78), patients initiated on IV antibiotics were switched after an average of 48 hours to oral (PO) therapy, leaving only seven patients with no oral switch, either because another IV antibiotic therapy was initiated (n=2) or cessation of IV therapy after 24 hours (n=5). Six antibiotic switches were deemed inappropriate (NHSGGC, 2017). Two of these involved a 300 mg PO dose of clindamycin prescribed following a 900 mg IV dose; in two other cases, 1200 mg IV co-amoxiclav was de-escalated to 375 mg PO; in one case, 2000 mg IV flucloxacillin was de-escalated to 250 mg PO and in the final case, 500 mg IV clarithromycin was de-escalated to 500 mg PO erythromycin.

2.4.6 Immediate discharge letters

The IDLs of all 89 patients were assessed, revealing that 18 women (20.2%) were discharged without antimicrobial therapy. Six of the 18 patients had been considered septic based only on the single clinical criteria of “pyrexia in labour” and antimicrobial therapy was subsequently discontinued after 24 hours. There were no documented reasons for discontinuation of antimicrobial therapy for the remainder. Among the 18 patients, only two had a positive culture. Upon further investigation we found that one patient was discharged after 31 days and completed her antibiotic therapy during her stay and that the other patient had coliform bacilli in her urine culture.

Patients’ IDLs revealed that 61.8% (n=55) of the women were discharged on 625 mg PO co-amoxiclav three times daily (TDS). This included many patients where no pathogen was isolated and who were initiated on 1200 mg intravenous co-amoxiclav TDS.

The length of antibiotic courses following discharge were available for only 59.5% of women, with an average length of 6.4 days. In 50% of the IDLs the length of the antibiotic course was

7 days; only 8% had more than a week of antibiotic therapy and 42% had less than a week, half of these being of five days' duration.

2.4.7 Sepsis Six sticker

Only 37.1% (n=33) of patients had the Sepsis Six sticker on their medical notes. Oxygen was delivered to 27.3% (n=9) of these 33 patients; blood culture and/or swabs were taken from 97% (n=32); lactate, full blood count and further blood tests were taken in 97% (n=32) of cases; 93.9% (n=31) received an intravenous antibiotic; intravenous fluid challenge was delivered in 93.9% (n=31) of cases and a catheter was used in 78.8 % (n=26) of patients to monitor urine output. Whether the SSCB had been delivered within one hour of sepsis being diagnosed could not be determined in the absence of a time zero, which was not recorded on the Sepsis Six stickers of six women. Only two cases of Sepsis Six care were delivered within one hour, at 35 and 40 minutes from time zero.

2.4.8 Diagnosis criteria for sepsis

2.4.8.1 SIRS criteria and the application of binary logistic regression

Prior to the analysis, all cases with any missing data were excluded. A total of 73 women were included in the analysis, after 16 had been excluded for missing data at the point of sepsis diagnosis. The binary logistic regression model gave an overall accuracy of 81.1% when WCC, HR, RR and temperature were used to identify sepsis. This model is not 100% accurate in predicting sepsis, but from the available data it had a PPV of 84.8% and an NPV of 75%.

The model suggests the use of temperature, WCC, RR and HR to predict sepsis in patients; it did not include CRP, SBP and mental status because they were not significantly associated with the outcome (i.e. having sepsis). The four variables included in the model were multiplied by a value called the "unstandardized beta weight" which can be obtained from the "variables in the equation" table from the output data. In addition to these values, the model output included a "constant" value to be added to the other variables.

The predicted probability of having sepsis can be calculated using the following regression equation:

$$Probability\ of\ sepsis\ = -63.56 +\ 1.343 * Temp +\ 0.236 * RR + 0.165 * WCC + 0.061 * HR$$

Each of the variables included in the equation above has an odds ratio, showing for example that with a one unit increase in the temperature while holding the other variables constant, there is a fourfold increase in being diagnosed with sepsis (OR=3.83; 95%CI:1.53-9.55).

By simply looking at the equation and the odds ratios of the variables, an understanding of the whole model can be obtained. However, this does not reveal which variable on its own has the strongest impact on the diagnosis, i.e. its coefficient without the influence of other variables. This coefficient, ranging from zero to one, is called the "standardized beta weight". It can be calculated using a statistical package, but not SPSS. Therefore, a paper was presented at the annual meeting of the Southwest Educational Research Association in Texas explaining the standardized coefficient for making comparisons among variables in logistic regression. The paper was supplemented with a function sheet to calculate the standardized logistic regression coefficient using Microsoft Excel. Three values are needed prior to any calculation: the SDs of temperature, WCC, RR and HR, the mean of the predicted probability of the logistic regression model and the unstandardized coefficient of each of the variables (i.e. temperature, WCC, RR and HR) (King, 2007). Further mathematical functions are explained in Appendix A. The findings show that the highest value of standardized beta weight was for the WCC coefficient (0.265), followed by temperature (0.257), respiratory rate (0.239) and finally heart rate (0.217). Table 2.6 shows the unstandardized beta weight, the standardized beta weight, *p*-value and odds ratio for each parameter.

Table 2.6: Unstandardized and standardized beta weights of parameters included in the binary logistic regression equation

	Unstandardized beta weight	Standardized beta weight	*p*-value	*OR* (95%CI)
Temperature	1.343	0.257	0.004	3.83 (1.53-9.55)
Respiratory rate	0.236	0.239	0.056	1.26 (0.99-1.61)
White cell count	0.165	0.265	0.002	1.18 (1.06-1.31)
Heart rate	0.061	0.217	0.010	1.06 (1.01-1.11)

Figure 2-3 shows the predicted probability of the binary logistic regression model and the predicted probability of individual parameters. Calculations were based on patient data and the binary logistic equation presented above. Any change in a patient's dataset will result in a change in the predicted probability and the ROC curve. The grey "reference line" indicates 0.5 AUC; any curve above this represents a better probability than under the reference line. The larger the AUC the better the model. The predicted probability of the binary logistic model gave an AUC of 0.877.

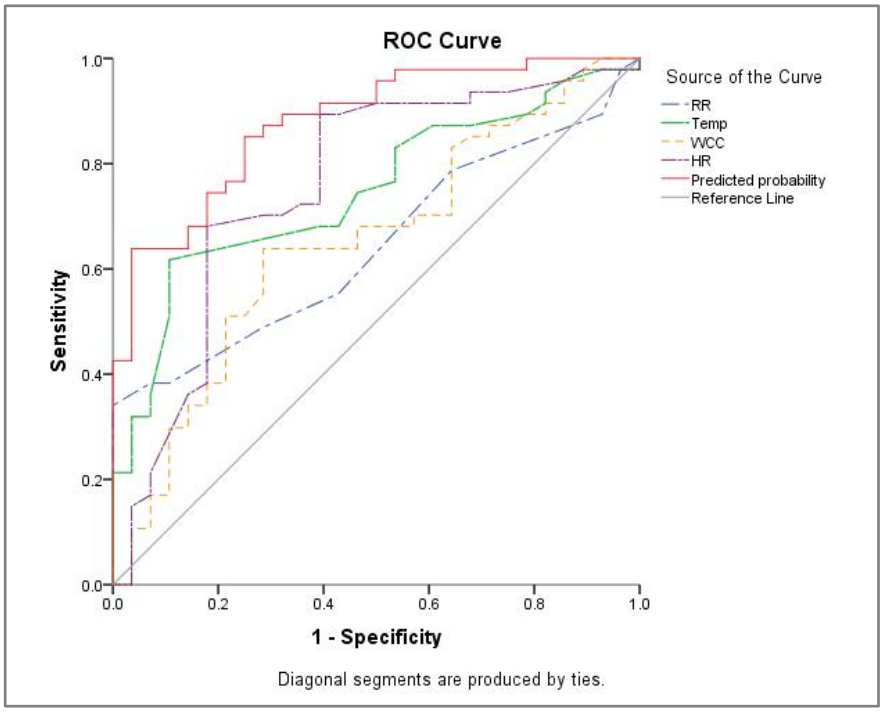

Figure 2-3: ROC curve for the predicted probability of the binary logistic regression model using RR, HR, WCC and temperature in identifying sepsis, and predicted probability of individual SIRS parameters

2.4.8.2 Quick SOFA

Applying the new definition of sepsis as sepsis-related organ failure, the findings using the qSOFA criteria of respiratory rate, systolic blood pressure and mental status indicated that only two patients (2.7%) were at risk of organ failure.

2.4.8.3 Different MEOWS reference

Three different MEOWS were applied and compared to the SIRS criteria. Table 2.7 sets out the abnormal ranges for these three scales (Edwards *et al*., 2015). The findings show that more cases were detected using MEOWS C and B as these criteria were able to place 74.3% (n=55) of patients in the sepsis group, while fewer cases were detected using MEOWS A, where the criteria identified only 47.3% (n=35) of the patients. The SIRS criteria fell between these two values, detecting 62.2% (n=46) of patients as having sepsis (Figure 2-4).

Table 2.7: The abnormal ranges of MEOWS A, B and C for temperature, heart rate, respiratory rate and systolic blood pressure to trigger the diagnosis of sepsis

	MEOWS-A	MEOWS-B	MEOWS-C
Temperature(˚C)	< 36 or ≥ 38	< 36 or ≥ 38	< 36 or ≥ 38
Heart rate (bpm)	<70 or ≥110	<50 or ≥100	<50 or ≥100
Respiratory rate (bpm)	≤ 10 or > 20	≤ 10 or > 20	≤ 10 or > 20
Systolic blood pressure (mmHg)	<100 or ≥ 150	<100 or ≥ 160	<100 or ≥ 150

Upon reviewing the criteria, it was found that they all used the same reference values of temperature, RR, HR and SBP (Edwards *et al*., 2015). However, discrepancies were detected in reported cases of sepsis detected in labour, as different criteria were applied to this group of patients in the cohort.

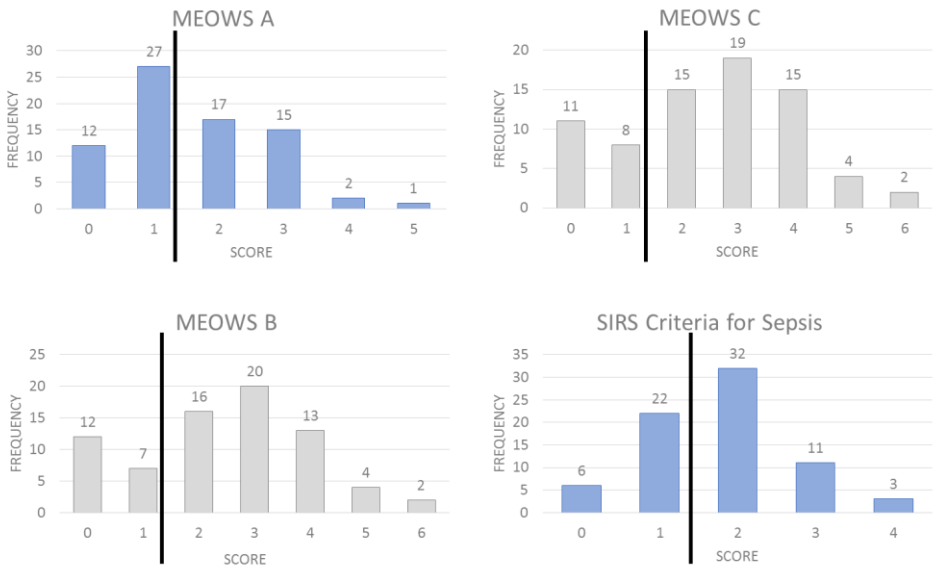

Figure 2-4: The number of patients identified with score of ≥2 (after the vertical black line) using SIRS, MEOWS A, B and C scoring system to trigger the diagnosis of sepsis

2.5 Results for babies

2.5.1 Demographics

Data on 215 babies were captured throughout the data collection period, representing newborns who were prescribed antibiotic therapy at the point of data collection. The main mode of delivery experienced by the babies was caesarean section, as reported in 47% (n=101) of the cases, followed by SVD (32.1%, n=69) and instrumental delivery (11.2%, n=24). Failure to access some medical notes resulted in missing data on mode of delivery in 9.8% of the cases (n=21). The babies' weights are categorised in Table 2.8.

Table 2.8: Neonates' birth weight data presented as number and percentage of each weight category

Weight categories	Number of neonate (%)
Extremely low birth weight of < 1000 g	5 (2.4%)
Very low birth weight of < 1500 g	11 (5.4%)
Low birth weight of < 2500 g	56 (27.3%)
Normal weight at birth between 2500 g and 4200 g	125 (58.1%)
Weight of more than 4200 g at birth	8 (3.9%)
Missing data	10 (4.7%)

Data on gestational age at delivery indicated that seven babies (3.3%) had a gestational age of less than 28 weeks, 10 babies (4.7%) were between 28 and 31 weeks and 77 (35.8%) between 32 and 36 weeks, while 103 babies (47.9%) had a gestational age of more than 37 weeks. Data on 18 babies (8.4%) were missing. The neonates' unit of admission varied: 44.7% (n=96) of babies were given antibiotics in a neonatal ICU, while 31.6% (n=68) were in a postnatal ward, 11.6% (n=25) in a special care baby unit and 4.2% (n=9) in a high dependency unit. Only one baby had been readmitted following discharge into a paediatric intensive care unit, but this was within the first three days of life.

The CRP level was considered in these babies to be within the first 72 hours of life, with a maximum reported CRP level of 131 mg/L and the lowest reported as < 1 mg/L. A third of the babies (33.3%; n=72) had an abnormal CRP of greater than 10 mg/L and the overall median value was found to be 4 mg/L. The median value for the group of babies with CRP > 10 mg/L was 28 mg/L, while the median for babies with CRP ≤ 10mg/L was 0 mg/L.

2.5.2 Antibiotic therapy

Based on the local guidelines, the first line of therapy in early onset neonatal sepsis is a combination of benzylpenicillin and gentamicin. This has been reported widely and in the study it represented 90.4% of the cases (n=176 and 173 respectively). However, there were also 9.6% of cases where cefotaxime was prescribed to babies at high risk of sepsis.

New doses of each baby's antibiotic were calculated from the baby's weight and the results were compared to the prescribed dose in each baby. Only four babies (1%) were found to have more than 10 mg (10%) difference in their benzylpenicillin dose and more than 1 mg (10%) difference in their gentamicin dose, while cefotaxime dose differences ranging from 11 to 49 mg (6-30%) were observed in nine patients (2.3%). Doses for seven patients were missing. It should be noted that the NHSGGC health board specifies that dose rounding should not routinely exceed 10% of dose, rather than the criteria being expressed in numbers of milligrams.

Antibiotic therapy was not limited to these antibiotic agents, as the following antibiotics were prescribed during the first 72 hours of babies' lives and replaced the initial treatment or were added to it in response to culture results: flucloxacillin (n=4), metronidazole (n=5), vancomycin (n=9), fluconazole (n=7), amoxicillin (n= 2) and penicillin V (n=1).

2.5.3 Microbiology report

Relevant cultures or swabs were not reported in 13.5% (n=29) of the cases, either having not been obtained from the babies or never having been received by the microbiology laboratory for analysis. More than three-quarters (78.1%, n=168) were stated in their microbiology report to have no growth. Figure 2-6 shows 18 pathogens (8.4%) detected with respect to gestational age.

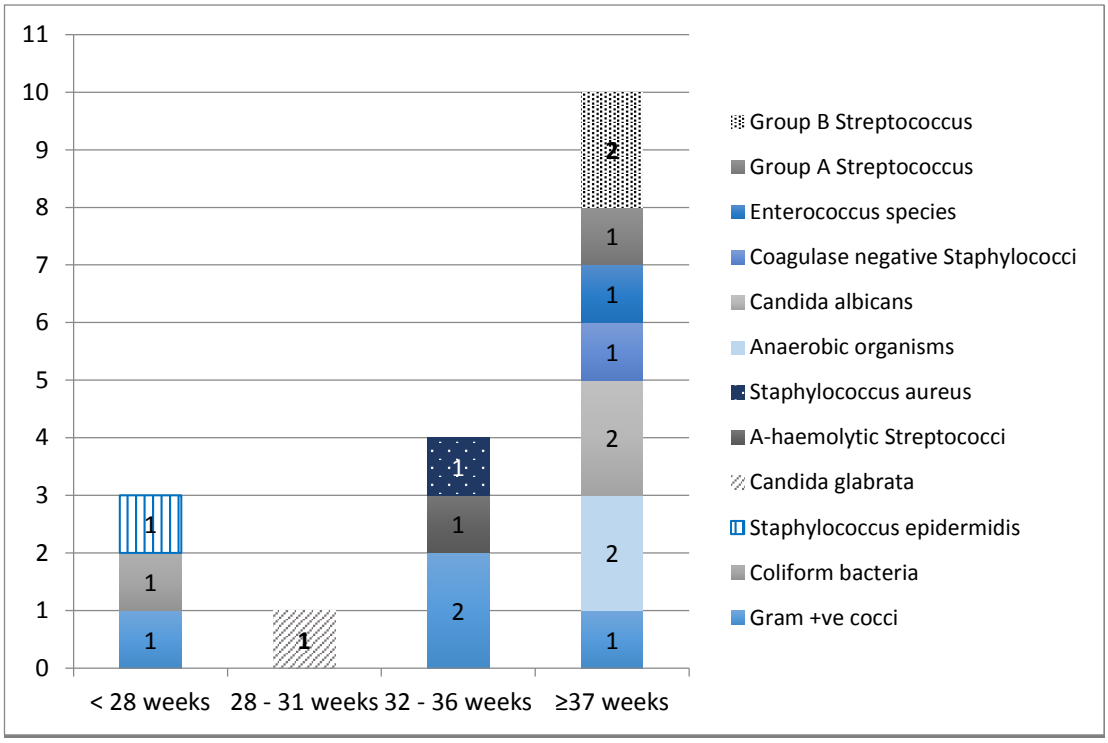

Figure 2-5: Pathogens identified from babies' specimens, presented by gestational age

2.5.4 Risk factors and red flags

Amongst the 215 babies, there were only 183 cases (85.11%) of completed early onset neonatal sepsis risk factors/flags collected during the study period. The red flag most often reported was parenteral antibiotic treatment given to the woman for confirmed or suspected

invasive bacterial infection, which was recorded in 24% (n=44) of the babies, followed by respiratory distress starting more than four hours after birth, as reported in 14.2% (n=26) babies. The risk factors most often reported were maternal GBS colonisation, bacteraemia or infection in the current pregnancy in 9.8% (n=18) of babies, pre-labour rupture of membranes in 20.2% (n=37) and preterm birth following spontaneous labour (before 37 weeks' gestation) in 38.3% (n=70). Furthermore, suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth was reported in 14.2% (n=26) of the sample, while intrapartum fever higher than 38 °C or confirmed or suspected chorioamnionitis was reported in 7.1% (n=13) of babies.

Signs of respiratory distress were identified in 29% (n=53) of the study babies and the need for mechanical ventilation in a preterm labour was reported in 8.2% (n=15). Table 2.9 lists the total number of babies who presented with each risk factor, clinical indicator or red flag. The total number exceeds the size of the sample (n=183) because some babies presented with more than one risk factor. The absence of some risk factors from the table does not mean that they were not experienced in the sample; some which did occur may not appear because of poor documentation of the sepsis risk factors on the sheet assigned to them in babies' medical notes.

Table 2.9: Risk factors, clinical indicators and red flags for 183 babies used in identifying risk of infection and potential need for antibiotic prescribing

Red Flags	**n**	**%**
Parental antibiotic for mother with confirmed or suspected infection – not IPA	44	24.0
Suspected/confirmed infection in another baby in multiple pregnancy	4	2.2
Respiratory distress starting more than four hours after birth	26	14.2
Seizures	1	0.5
Need for mechanical ventilation in term baby	0	0
Sign of shock	0	0
Risk Factors		
Invasive GBS infection in a previous baby	2	1.1
Maternal GBS colonisation, bacteraemia or infection in the current pregnancy	18	9.8
Pre-labour rupture of membrane (spontaneous)	37	20.2
Preterm birth following spontaneous labour (before 37 weeks gestation)	70	38.3
Suspected/confirmed rapture of membrane for more than 18 hr in preterm birth	26	14.2
Intrapartum fever >38 ºC OR confirmed/suspected chorioamnionitis	13	7.1
Clinical Indicators		
Altered behaviour or responsiveness	0	0
Altered muscle tone (e.g. floppiness)	6	3.3
Feeding difficulties	5	2.7
Feed intolerance	0	0
Abnormal HR	10	5.5
Sign of respiratory distress	53	29.0
Jaundice within 24 hr of birth	6	3.3
Sign of neonatal encephalopathy	0	0
Need for cardiopulmonary resuscitation	1	0.5
Need for mechanical ventilation in a preterm labour	15	8.2
Unexplained excessive bleeding, thrombocytopenia or abnormal coagulation	0	0
Oliguria persisting beyond 24 hr after birth	0	0
Persistent foetal circulation	0	0
Altered glucose homeostatis	10	5.5
Metabolic acidosis	0	0
Hypoxia	2	1.1
Apnoea	7	3.8
Local sign of infection (e.g. skin, eye)	2	1.1
Temp <36 ºC or >38 ºC	1	0.5

* **IPA: intrapartum antibiotic**

2.5.5 Binary logistic regression

For those sepsis factors that were reported more than ten times, a binary logistic regression was applied to determine the association between CRP and the risk factors, to determine which factors could be related to CRP >10 mg/L. The model derived from the binary logistic regression stopped at step 2, having a chi-squared value of 10.537 which was statistically significant at p=0.005, with an overall accuracy of 64.5%. Only two variables were included in the equation: Sign of respiratory distress showed a negative association with CRP > 10 mg/L (p=0.006; r= -0.10), while preterm birth before 37 weeks had a positive association with CRP > 10 mg/L (p=0.019; r= 0.10).

The area under the curve of predicted probability = 0.629. The AUC for sign of respiratory distress = 0.421, which is less than 0.500 (the reference line); this explains the negative association with CRP > 10 mg/L. For preterm birth of less than 37 weeks, AUC = 0.563. Therefore, the predicted probability gives a better prediction of the association of CRP > 10 mg/L with the sepsis risk factors. These findings mean that signs of respiratory distress in babies were not associated with CRP > 10mg/L, but gestational age < 37 weeks was associated with CRP > 10 mg/L. This association was very weak, as shown by the coefficient values above: R=-0.10 and R=0.10 respectively.

2.6 Discussion

The apparent incidence of sepsis in this sample was 331 in every 10,000 pregnancies. This appears high relative to the literature, which reports the incidence of sepsis as 10 in every 10,000 pregnancies (Acosta *et al*., 2013). However, this study included all suspected or diagnosed cases that were treated with antibiotics, whereas Acosta *et al*. (2013) reported only confirmed cases from a retrospective cohort study and excluded cases where antibiotic therapy may have been initiated for suspected sepsis. In this study, sepsis was mainly diagnosed within the intra-partum (46.1%) and postpartum (39.3%) periods. This is in agreement with a recent study in Ireland which reported figures of 36% and 47.1%

respectively for intra-partum and postpartum sepsis (Knowles *et al*., 2015). The median length of stay in hospital was four days (IQR: 3-6 days), similar to a recent US study of maternal sepsis (Acosta *et al*., 2013). In comparison, the reported length of stay for a general obstetric population is reported to be 3 days (IQR: 2-4 days) (Covvey *et al*., 2015). The proportion of patients admitted to an HDU or an ICU were 7.9% and 2.2% respectively, slightly lower than those reported in the Irish study (Knowles *et al*., 2015). Obesity was observed in 27.8% of this sepsis cohort, slightly higher than the 22.2% of women who gave birth in Scotland with a BMI >30 kg/m^2 (NHS National Services Scotland and ISD, 2016). Obesity is known to increase the risk of developing infection 3.5-fold when compared with non-obese women (Bamfo, 2013). An emergency caesarean section was observed in 46.1% (n=41) of septic women, which is similar to other studies and is associated with a 20-fold greater risk of developing infection than for spontaneous vaginal delivery (Bamfo, 2013). The presence of at least two abnormal SIRS criteria is a factor aiding the clinical identification of sepsis. Nonetheless, only 51.7% of the patient cohort met these criteria and 30.4% exhibited only one abnormal SIRS criterion or none.

2.6.1 Antibiotic therapy and microbiology report

Adherence to local guidelines was high, where co-amoxiclav with or without gentamicin as first-line therapy for suspected sepsis is recommended, with clindamycin the preferred substitution for co-amoxiclav in penicillin-allergic women (NHGGGC, 2015b). A wider comparison of this empiric therapy both nationally and internationally is difficult because of wide variances in patterns of antimicrobial resistance. The emphasis on early antibiotic treatment has emerged from studies of non-obstetric severe sepsis or septic shock that in most cases needed ICU admission to commence such treatment for sepsis (Minderhoud *et al*., 2017). This direction of care was associated with efforts made in accident and emergency (A&E) to use the SIRS criteria along with their suspicions of infection to identify patients at risk of organ failure. Since analysis of blood tests to confirm sensitivities and organ function

can take time, the recommendation is to start antibiotic therapy within the first hour in the absence of blood results. The SSC emphasises the importance of administering antibiotics to patients within the first hour of suspected sepsis, with very limited information regarding methods of screening, while their data were reported in ICU patients (Minderhoud *et al*., 2017). Despite the change in sepsis definition and the emphasis on the application of qSOFA (sepsis-3) to replace severe sepsis, clinical practice settings still use the SIRS criteria (Minderhoud *et al*., 2017).

A&E data for adult non-obstetric patients reported in the Netherlands indicate that 30% of patients treated for suspected sepsis showed no evidence of infection. The decision to stop antibiotics based on negative culture results was reported by day five in 32% of patients (Minderhoud *et al*., 2017). In the present study, 60% of the cultures analysed showed no evidence of infection and 20% were discharged with no further antibiotic course. The authors suggest that this may have resulted from a fear of antimicrobial resistance developing when treatment was stopped before anticipated course duration. The literature however shows that antibiotic de-escalation is safe, whereas unnecessarily prolonged antibiotic use can promote antimicrobial resistance (Minderhoud *et al*., 2017). There is a lack of timely follow-up in the management of sepsis in both obstetric and non-obstetric settings. Where antibiotic therapy was initiated in cases of suspected sepsis, review of the ongoing need for antibiotics and switch to oral therapy was not consistently carried out.

The overuse of antibiotics that are prescribed for different indications can raise the cost of healthcare, increase adverse drug effects and promote antimicrobial resistance, which is acknowledged to constitute a global crisis (O'Neill, 2016). The impact of antimicrobial resistance is not limited to infectious diseases, but could also interfere with cancer treatment, organ transplants and many other major surgeries (Shallcross and Davies, 2014).

In our study, the main pathogens observed were GBS, mixed anaerobic organisms, *E. coli*, coliform bacilli, GAS and gas-forming infections. Previous studies recorded comparable

findings (Knowles *et al*., 2015). *E.coli* is the most common pathogen associated with maternal sepsis and is reported to be associated with up to 31% of genital tract-related sepsis cases in the obstetric population (Sáez-López *et al*., 2016). *S.pyogenes* and *E.coli* are common pathogens in clinical cases of chorioamnionitis, and combinations of Gram-positive and Gram-negative bacteria are common in maternal sepsis, according to the RCOG (RCOG, 2012a). Coliform bacteria have been reported in cases of urinary sepsis, while *Clostridium perfringens* is a less common pathogen (RCOG, 2012a). Although 60% of microbiology specimens did not isolate a pathogen, this did not negate the clinical diagnosis of sepsis, as antibiotic therapy should not be discontinued on the sole basis of a negative microbiology report (Lucas *et al*., 2012).

Globally, GBS data show that resistance to clindamycin and erythromycin ranged from 1% to 43% and from 3% to 54% respectively. Cases are reported of clindamycin-resistant GBS in early onset neonatal infection after exposure to intrapartum clindamycin (Clifford *et al*., 2011). An Australian study found that resistance of GBS to clindamycin and erythromycin was low, at 6.4% and 4.2% respectively, with half of erythromycin-resistant isolates showing cross-resistance to clindamycin (Garland *et al*., 2011). By contrast, GBS has a global susceptibility to benzylpenicillin, which has therefore been chosen as an empiric intrapartum antibiotic for women with positive GBS within NHSGGC (Berg *et al*., 2014; NHSGGC, 2015b).

2.6.2 Sepsis diagnostic criteria

2.6.2.1 Maternal fever

Pyrexia in labour was the leading single clinical reason to initiate antibiotic therapy in this study cohort, despite 30% of women being known to experience intrapartum pyrexia. Pyrexia is attributable to various sources of infection including chorioamnionitis, but may also arise from epidural analgesia (Segal, 2010). Elevation in temperature is accompanied by many other maternal changes at delivery, including tachycardia and altered respiratory rate, which in most cases normalise quickly (Segal, 2010). This may explain the proportion of patients

where cessation of antibiotic therapy occurred within 24 hours post-delivery with reversion to normal physiological status. Since 1989, an association has been found between epidural analgesia and maternal temperature. A suddenly elevated temperature has been observed in 0.6% to 11% of women given an epidural (Sharpe and Arendt, 2017). The incidence of maternal fever has always been related to infection, but a double-blind placebo controlled trial in which 400 women received either a prophylactic dose of cefoxitin or placebo prior to the epidural found that maternal fever occurred in 38% and 40% of participants respectively (p=0.68) (Sharpe and Arendt, 2017; Sharma *et al*., 2014). This indicates that maternal fever was not associated with actual infection, but rather with placental inflammation which was not reduced by the prophylactic antibiotic (Sharma *et al*., 2014). Nevertheless, temperature ≥ 38 °C may provide some evidence of infection when associated with other maternal risk factors or complications. Evidence shows that among the reported 3.3% of mothers having intrapartum fever, 3.1% were diagnosed with suspected chorioamnionitis (Towers *et al*., 2017). The USA CDC recommends that "well-appearing new-borns whose mothers had suspected chorioamnionitis should undergo a limited evaluation and receive antibiotic therapy pending culture results" (Towers *et al*., 2017). Chorioamnionitis may be suspected in cases of maternal fever alone and this will lead to the newborn being commenced on antibiotic therapy as well, with the aim of preventing neonatal infection (Towers *et al*., 2017). In the present study, among the neonates who had been commenced on IV antibiotics, the decision in 13 cases (17.1%) was based on suspected chorioamnionitis, while another 44 (24%) were based on parental antibiotics for the mother with confirmed or suspected infection and only 29 of mothers had a positive blood culture. A cohort study of 421 women with maternal fever found only one baby with a positive blood culture for *E.coli*, whereas when 5645 women without pyrexia were evaluated, the researchers found only four babies with positive blood cultures: one for *E.coli* and three for GBS infection (Towers *et al*., 2017).

2.6.2.2 Sepsis scoring systems

The early identification and management of sepsis in maternity are recommended (Shankar-Hari *et al*., 2016), as delay in diagnosis or treatment can lead to maternal mortality and morbidity, which are associated with a delay in administering the appropriate therapy and management to these women (Bauer *et al*., 2015). There is limited applicability of the various biomarkers due to the non-specific or non-sensitive nature of these criteria, arising from the altered physiological function of pregnant women (Cordioli *et al*., 2013), which could lead to under- or over-treatment. Use of clinical judgement is recommended to facilitate the diagnosis of sepsis and it is unsafe to rely solely on laboratory tests (Kibe *et al*., 2011).

The binary logistic regression model findings indicate a false positive value of 15.2%, meaning that those patients were less likely to develop sepsis but were identified as having it, while 25% were false negatives, i.e. identified as less likely to develop sepsis when they actually had it. Varied results are reported in the literature on evaluating MEOWS: having a low PPV ranged between 1.4% and 5.1%, and AUC ranged from 0.52 to 0.72 (Edwards *et al*., 2015). Another evaluation of the Sepsis in Obstetric Score for identifying the risk of ICU admission found specificity and sensitivity at 99.2% and 88.9% respectively (Albright *et al*., 2014). It seems that research on sepsis is underreported, as most published literature focuses on cases of deterioration in obstetric women and evaluates their admission to intensive care.

The standardized beta weights of the variables included in the equation show that white cell count had the highest coefficient of 0.265, followed by temperature, then respiratory rate and heart rate, while the odds ratio of developing sepsis increased fourfold with every one unit increase in temperature. The model was not tested for decrease in temperature, because of limitations in the available temperature values in patient data. These findings emphasise the importance of WCC and temperature in the identification of sepsis. Given the low coefficients, these findings need to be tested in a larger cohort, where culture-proven sepsis is used as a diagnostic cut-off and these parameters are compared with a non-sepsis

obstetric control group. The variables not included in the equation, i.e. SBP, CRP and mental status, should receive less attention from a statistical point of view when assessing a patient's condition, given their indiscernible effects, which were not observed in this cohort. It is proposed that the qSOFA definition should be able to identify women at an early stage of severe maternal infection to allow healthcare practitioners to initiate treatment (Bonet *et al*., 2017). The definition of severe maternal sepsis excludes the early stage of sepsis and delays the initiation of treatment for these women. The new definition of maternal sepsis is "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period" (WHO, 2017). When applied to our sample, this criterion had unpromising results in being able to determine sepsis. It seems that it can be used for very sick women to determine their requirement for ICU admission, but has limited applicability to a general obstetric population.

The SIRS and qSOFA definitions were retrospectively applied to the study cohort to determine what the outcome would be if the latter were considered in obstetrics. According to our findings, although the SIRS criteria are both less sensitive and less specific in diagnosing patients with sepsis, they have the advantage of not leaving matters to such a late pathophysiological stage where organ failure becomes a real concern. This is especially important, since obstetric women are often found to deteriorate very quickly (Banfield and Sister, 2015). The qSOFA criteria, introduced since the new sepsis definition, provide uncertainty of both action and result. The sensitivity of qSOFA in emergency rooms has been reported at 63%, while NEWS has been shown to predict mortality and ICU admission in an advanced way compared to qSOFA. There is a lack of clarity on the best methods to use in identifying sepsis in non-ICU settings (Minderhoud *et al*., 2017).

2.6.2.3 Laboratory biomarkers

The gold standard for sepsis diagnosis is blood culture, although the time required to process the test makes it necessary to use another method to identify and diagnose sepsis in order

to ensure early diagnosis and management (Vijayan *et al*., 2017). In the present study, when cultures had been taken for analysis, decisions to treat patients were based on WCC, CRP, MEOWS abnormalities and patients' clinical history. For some wards including labour and triage, the blood results for CRP and WCC would be processed very quickly, but in postnatal and antenatal wards this would take longer. It is clear that at the point of diagnosis there was limited evidence to guide the decisions and that MEOWS and patient clinical history were mainly relied on. In labour wards, routine blood tests would be taken and analysed following admission, so for some women in the labour and postnatal wards, the CRP and WCC results might be available to guide the diagnosis. However, CRP appeared to be a poor prognostic indicator in this cohort, with no differential observed between mode of delivery, SIRS score or clinical specimen results. The lack of specificity of CRP is problematic and despite its wide use in clinical practice, CRP is not a definite marker of sepsis alone (Pierrakos and Vincent, 2010). A study of women in labour and a control group of maternity women not in labour found that CRP level was significantly higher in labour, in premature pre-labour rupture of membrane (PPROM) and after labour; $p<0.001$ in all cases. The true value of CRP ranged from 250 mg/L after labour to 384.4 and 409.6 mg/L in labour and in PPROM respectively (Eyada *et al*., 1994). A comparison between vaginal and caesarean deliveries in 160 women found no significant difference between the two groups, $p=0.190$, with mean CRP values in caesarean and vaginal deliveries reported as 7.0±6.8 and 5.8±3.7 respectively (Erkaya *et al*., 2014). An increase in women's CRP values after caesarean delivery has been reported, with a mean of 77 ±31 mg/L on the second day, decreasing to about 33 mg/L on the sixth day after surgery. A significant difference was found between women who had their caesarean section after the onset of labour or those who had it after the rupture of membranes (Keski-Nisula *et al*., 1997). Univariate analysis shows that elevated CRP after caesarean delivery was associated with onset of labour, rupture of membranes, length of operation and type of anaesthesia (Keski-Nisula *et al*., 1997).

Compared with procalcitonin (PCT), CRP has lower specificity; its popularity in clinical practice is due to its greater availability (Pierrakos and Vincent, 2010). PCT starts to rise at four hours following the onset of infection and will peak at 8-24 hours, thus providing an earlier indication of infection than either CRP or WCC levels which rise slowly and peak at 36 hours (Kibe *et al*., 2011). The absolute selectivity of PCT is not great, as it can be elevated in cases of renal impairment, abdominal surgery or trauma and may also be elevated in women undergoing caesarean section. A meta-analysis comparing PCT and CRP found respective odds ratios of 15.7 [95%CI; 9.1-27.1] and 5.4 [95%CI; 3.2-9.2] for their diagnostic accuracy (Kibe *et al*., 2011). The American College of Critical Care Medicine and the Infectious Diseases Society of America recommend PCT as "an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations" and grade it as providing Level 2 evidence (Kibe *et al*., 2011). Considering the time these biomarkers need to rise above the normal range, the present study has found that decisions on diagnosis could be made on WCC and CRP levels that were taken before the onset of suspected sepsis. Although new blood tests were collected and analysed, the initiation of antibiotic therapy and the time these biomarkers need to rise make it more complicated to assess the value of these test in the diagnosis of sepsis. Lactate is another biomarker used in the practice observed in the present study, but it has a very limited application and was used in very few patients. A limitation of lactate level is that increased values have been reported with cardiac arrest, trauma and both severe sepsis and septic shock (Zhang *et al*., 2014). In healthy individuals lactate has an expected half-life of 20 minutes. There is limited use of lactate as a prognostic for sepsis because it lacks specificity; an increase in lactate level may occur in non-sepsis cases such as patients with hepatic impairment (Wittayachamnankul *et al*., 2016). A lactate level ≥ 4 mmol/L is associated with mortality, OR=4.89 (Wittayachamnankul *et al*., 2016; Kang and Park, 2016). Lactate clearance (LC) is the reduction in lactate level following a therapeutic intervention in comparison to baseline lactate before the therapy and the literature indicates that LC of 10% six hours after revival has the potential to enhance the survival rate and reduce

mortality (Wittayachamnankul *et al*., 2016). Nonetheless, LC is not used to determine therapeutic discontinuation or de-escalation as an endpoint for sepsis cases (Kang and Park, 2016). However, because PCT has a good response time, both elevating and falling more quickly than CRP, it could act as a good antimicrobial stewardship aid in reducing unnecessary antibiotic therapy (Vijayan *et al*., 2017). Thus, the decision to reduce antibiotic exposure could be driven by the serum PCT level (Vijayan *et al*., 2017). PCT cannot stand alone in the diagnosis of sepsis, however; it aids the early identification of sepsis but does not detect the pathogen causing the infection. The Gram stain and culture analysis process is fundamental to the provision of complete diagnostic information to determine the treatment plan (Vijayan *et al*., 2017). Although the literature widely discusses different biomarkers, PCT was not used in the present study, and the application of biomarkers was mainly limited to CRP and WCC, while lactate was used in very few patients. Martín and colleagues recommend the design of a scoring system based on combined biomarker values including CRP, PCT and lactate to aid physicians in their treatment decisions, arguing that this approach has the potential to reduce the use of antibiotics and of blood culture tests (Martín *et al*., 2004). However this approach would not be possible in our study population as only a combination of weighted CRP, WCC and lactate could be used. In addition, from the findings of the logistic regression, temperature and WCC were the main indices in the prediction of sepsis. Thus, it might be worth exploring an equation combining CRP, WCC, lactate and temperature through the application of a further regression model and further evaluation based on new patient datasets with non-sepsis individuals as controls.

2.6.3 Sepsis Six care bundle

The data show poor compliance with the Sepsis Six package with only 37.1% of the women having the SSCB recorded in their case records. This is comparable with an audit by Deutsch *et al*., who found only 50% adherence to a care bundle, which improved following the provision of education for the multidisciplinary team (MDT) (Aggarwal *et al*., 2015). Another

retrospective audit in an obstetric hospital reported compliance with a care bundle at 69.4%, having pyrexia in labour as the main driver for blood culture or other relevant microbiology culture analysis (Francis *et al*., 2015). Pyrexia in labour was also the main driver of sepsis diagnosis in our study. A third audit found that only 11.9% of sepsis cases had pyrexia in labour (Ratnasekera *et al*., 2014). Compliance with the Sepsis Six bundle was poor across all studied maternity units. Some studies indicate that the education and involvement of MDTs enhances compliance (Aggarwal *et al*., 2015). However, the rapid turnover and rotation of junior doctors are challenges to such enhancement. During pregnancy, women undergo alterations to physiological functions which must be considered when managing maternity patients with sepsis (Guinn *et al*., 2007). It is important to clarify the reference values of SIRS; the conflict of having separate reference values for labour is not justified. It is known that labour can change a woman's SIRS values and more effort in managing such patients is essential.

2.6.4 Babies treated with antibiotic

The diagnosis of neonatal sepsis is very challenging because of the lack of specific signs and symptoms in babies. Therefore, it is very common for the diagnosis of EONS to rely on clinical observation and maternity history (refer to Table 2.9). Studies reveal an 8.8-fold increase in the prescription of antibiotic treatment for suspected infection when compared with the culture-proven diagnosis of infection (Patel and Saiman, 2012). This high number of broad spectrum antibiotic prescriptions in the absence of culture-proven sepsis increases concerns for the development of multi-drug resistance (Patel and Saiman, 2012).

About half of the babies who were treated with antibiotics for a suspected infection had been delivered by caesarean section. Evidence shows that infants born by caesarean section are five times more likely to develop sepsis than infants born by vaginal delivery (Moges *et al*., 2017). Low birth weight of less than 2.5 kg is associated with a threefold greater likelihood of developing sepsis when compared to neonates of normal birth weight and this difference

increases to 12-fold in those under 1.5 kg, while neonates whose gestational age is < 37 weeks are nine time more likely to develop sepsis than those of 37 weeks and older (Moges *et al*., 2017). About one third of babies' weights were below 2.5 kg; therefore the associated length of stay and complications could be related to low birth weight rather than the suspecting of early onset sepsis. The mother's maternity data are limited to those collected in the risk factor table, indicating that 13 infants experienced chorioamnionitis or maternal temperature > 38 °C. This is a little confusing, as chorioamnionitis was given equal attention to maternal temperature > 38 °C, which is not ideal. Throughout the data collection it was observed by researcher NA that babies born to women diagnosed with chorioamnionitis were unwell and required neonatal ICU admission and a longer stay in hospital. When compared to babies born to women with maternal temperature > 38 °C, most of these babies were treated at postnatal ward level and had shorter stay in hospital. The 94 neonates who were given IV antibiotics had a gestational age less than 37 weeks. The empiric antibiotic therapy for babies in the first 72 hours of life is reported in 95% of cases to be a combination of aminoglycoside and benzylpenicillin or ampicillin (Fjalstad *et al*., 2016), while the data for this study show that 90.4% of the babies had benzylpenicillin and aminoglycoside as their empiric antibiotic.

The fact that culture-proven EONS is rare, occurring in 32 per 1000 babies in the first day of life and 35 per 1000 in the second, could lead clinicians to overuse antibiotics for neonates with suspected infection (Esaiassen *et al*., 2017; Rønnestad *et al*., 2005). Among babies with a positive culture result, the pathogens isolated were Gram-positive bacteria in 65.5% of the cases (Moges *et al*., 2017). It has been shown that GBS is one of the most significant pathogens and the leading cause associated with EONS (Sgro *et al*., 2011; Blackburn *et al*., 2014). We reported 18 cases of positive cultures, GBS being identified in only two of these, which could be explained by the fact the women in labour who were tested for GBS during the antenatal period had received IPA treatment. Antenatal screening for pregnant women

should be considered, while it is reported in the literature that one third of women with positive GBS have not been exposed to IPA because delivery occurred very soon after admission. Despite the presence of other risk factors that required the mother to have IPA treatment, a third of women (34%) did not receive it when needed (Kuhn *et al*., 2010). The IPA exposure of mothers in our study cannot be evaluated because data on IPA were not considered and collected as part of the research aims and objectives. IPA can be given as a single or multiple prophylactic dose prior to caesarean section, following rupture of membranes or a GBS positive culture (Gomez-Arango *et al*., 2017). A recent systematic review has shown that antibiotic treatment commenced on babies with unproven EONS has adverse effects (Esaiassen *et al*., 2017). A prolonged duration of antibiotic treatment ≥ 4 days for ELBW babies increases their risk of developing necrotizing enterocolitis, while exposing these babies to third generation cephalosporins has the potential to increase the risk of developing invasive fungal infections, primarily Candida spp. (Esaiassen *et al*., 2017). Candida infections are associated with several risk factors, including thrombocytopenia, birth weight, gestation age, mechanical ventilation, length of stay, central vascular access, antibiotic use, steroids and third-generation cephalosporins (Benjamin *et al*., 2003; Sanami *et al*., 2015). There were three cases of reported Candida infections in our study; however, these babies were not exposed to third-generation cephalosporins but were treated with benzylpenicillin and gentamicin as first line therapy. CRP has a limited application in diagnosing EONS, as reported figures range widely between 4 mg/L and 267 mg/L in babies with diagnosed EONS (Kuhn *et al*., 2010). CRP has a reported PPV of 80% and an NPV of 48.9%. When it was used to assess patients throughout the first 72 hours of life, the data show that on the day of admission CRP had a normal value in 36% of cases, decreasing to 32% by the end of the third day. This variation emphasises the lack of accuracy reported in the literature, as CRP was able to endorse the diagnosis of EONS in only 70% of cases (Hisamuddin *et al*., 2015).

Only minimum quantities of CRP pass the placenta; therefore, the CRP level obtained from the baby usually results from the endogenous de novo hepatic synthesis that starts quickly in the presence of a stimulus. Not every elevated CRP value indicates an infection, as there are other possible causes of raised CRP (Hofer *et al*., 2012). CRP levels were found to be abnormally raised in cases of pre-labour rupture of membranes (PROM), prolonged labour and maternal fever (Hofer *et al*., 2012). A 2009 study found that in the absence of infection in the mother, CRP level in newborns was not related to mode of delivery (Kaya *et al*., 2009). However, this finding is contradicted by a recent study which included positive GBS and intrapartum antibiotics and which found that neonates born by vaginal delivery or emergency caesarean section had significantly higher CRP at 48 hours after delivery compared to elective caesarean section, while neonates of mothers who completed a course of IPA for GBS had lower CRP compared to others (Perrone *et al*., 2017). CRP level is expected to increase following antibiotic treatment and then to decrease after 16 hours as it reaches its half-life (Hofer *et al*., 2012).

2.7 Limitations

This study does not report any obstetric or non-obstetric medical conditions that were experienced by the women in this study. Information obtained regarding the birthing experience (labour) was limited to that explained above. Information on the total scores reported for the MEOWS readings was not recorded as part of the data collection. The MEOWS chart data were presented mostly as symbols, i.e. either an upward arrow or a black dot, rather than the actual reading, which made the estimation of the value the only option. In addition, the times recorded on the MEOWS chart were unclear on a very few occasions, where it was not possible to be sure which figures were hours and which were minutes, as the time was recorded on a different line in an italic font. Where possible in such cases, times were estimated on the basis of the previous and following times. Some measurements reported on the MEOWS charts were placed under a blank day and time box, which made it impossible to assign a day or time to these data. There was no consideration of the rotation

of hospital staff, as the main aim was to evaluate the practice, not individual practitioners. However, all of the data were collected within one hospital rotation and reflect medical practice during the study period. The absence of a control group, a limitation of this study, was due to limited resources of time and the small number of researchers involved in collecting the data. This study has also found that the use of the Sepsis Six care bundle is limited, but it is not yet known if this is due to the difficulty of diagnosing sepsis in obstetric women. The initiation of some antibiotic therapy seems in this audit to be common in women who have not been commenced on the SSCB. The negative outcomes of antibiotic therapy in early life should drive a more structured approach to eliminating unnecessary antibiotic use. The list provided within the NICE guideline "antibiotics for the prevention and treatment of early-onset neonatal infection" is based on out-of-date or low quality studies.

The analysis performed for the binary logistic regression was limited by the absence of a control group and by the small number of patients in this cohort. Therefore, the findings are limited to what was observed in this study and cannot be generalized without first being tested on a larger cohort with the inclusion of a control group.

2.8 Conclusion

The lack of highly specific and sensitive panels of biomarkers to inform accurate sepsis diagnosis in the obstetric patient hinders effective antibiotic stewardship. In the absence of effective biomarkers, clinical reliance on SIRS criteria and CRP values presently drives apparent over-diagnosis of sepsis and initiation of antimicrobial prescribing. This was compounded by the frequently negative microbial cultures, 60% in this cohort, sampled from patients, which reduces the possibility of antimicrobial de-escalation from the initiated empiric (broader spectrum) regimes. The challenge of diagnosing sepsis in both women and neonates leaves an unsatisfactorily large number of individuals exposed to antimicrobial therapy when it is not needed. Further research is required to extend antimicrobial stewardship into obstetric settings for both women and babies. Fundamental to the success

of this process is the integration of other healthcare professionals such as physicians, midwives, nurses and pharmacists.

3 Chapter 3: Additional data on non-sepsis antenatal and postnatal antibiotics

3.1 Introduction

Medications are prescribed during pregnancy to manage various medical conditions and antibiotics account for 80% of these prescriptions (Kuperman and Koren, 2016). Antibiotic therapies were found to have been used in 19.7% of pregnancies in Germany and 40.8% in the USA (Jonge *et al*., 2014). More broadly, a fifth of women in Europe were prescribed antibiotics during pregnancy, while data from the USA show double the rate (Kuperman and Koren, 2016). A recent study conducted in the Netherlands into antibiotic prescriptions dispensed in community pharmacies before, during and after pregnancy found that among 19,577 prescriptions over 16 years, at least one antibiotic was prescribed during pregnancy in 20.8% of cases. Beta lactams were the antibiotic class most commonly prescribed, as amoxicillin comprised 59.1% of all antibiotic prescriptions. No category X antibiotics were prescribed and only 2% and 0.8% of prescriptions were of category C and D drugs respectively (Jonge *et al*., 2014). As explained in section 1.4.3, category X is associated with risks that outweighed the benefits to mother and/or baby. Category C use is correlated with adverse events, based on animal trials, and category D use represents a potential risk to the foetus (Ciarkowski and Stalburg, 2010). Antibiotic therapies were used prophylactically in women undergoing a caesarean section; however, infections were reported in 27% of 100 women who were diagnosed with wound infections, post-partum endometritis and urinary tract infections. *Staphylococci*, *enterococci* and *anaerobes* were among the most common pathogens isolated from women diagnosed with endometrial infections (Liu *et al*., 2016). Studies show that the rate of infection-related complications was 30% higher when a caesarean section was performed after labour and rupture of membranes in the absence of antibiotic prophylaxis. If instead prophylactic antibiotics were used in caesarean section, there was a reduction of up to 65% in wound infections and post-partum endometriosis (de Tejada, 2014).

According to a literature review study, there has been a noticeable increase in the last two decades in the prescription of antibiotics for the symptomatic treatment of respiratory, urinary or genital infections in obstetrics, prompting concerns that problems will arise from overuse, including an increased risk of developing drug resistance (de Tejada, 2014).

Up to 70% of caesarean deliveries are performed as emergency interventions and despite antibiotic prophylaxis being recommended, the infection rate in these women is up to 12% (Tita *et al*., 2016). Co-amoxiclav is the first line antibiotic prophylactic for caesarean section, while amoxicillin is prescribed in conjugation with co-amoxiclav in women of 100 kg and over based on a discussion with the manufacturer (Wockhardt). However, a SAPG report recommended the standard dose to be used in obese patients (SAPG, 2017).The antibiotic should be administered intravenously 60 minutes before skin incision as previously mentioned in Chapter 1 (NHSGGC, 2015a). Cephalosporins have also been used to prevent infection in women undergoing caesarean section. Azithromycin has been evaluated as a single dose administered in conjugation with a cephalosporin antibiotic in a randomized control trial of 181 women vs cephalosporin alone, resulting in a reduction in endometritis (RR=0.62) and wound infection (RR=0.35) (Tita *et al*., 2016). The estimated risk of SSI following caesarean delivery is 5% and this rate is expected to be higher when labour begins before the caesarean delivery and in obese women (Moulton *et al*., 2017). SSI is a very common complication following obstetric and gynaecological surgery, but its incidence has been shown to be reduced by the use of antibiotic prophylaxis (Liu *et al*., 2016). Factors associated with the surgical site including the use of alcohol-based antiseptics and suture closure of the incision have also been found to reduce the SSI rate (Moulton *et al*., 2017).

Pre-labour rupture of membranes happens in 10% of pregnancies, more than half of these cases occurring at term. Around 60% of women experiencing PROM develop chorioamnionitis as a result and those in whom PROM is prolonged for more than 24 hours have a 40% higher risk of developing chorioamnionitis (Ismail and Lahiri, 2013). PROM also

increases the risk of complications including early onset neonatal sepsis and wound infection (Ismail and Lahiri, 2013; Kenyon *et al*., 2001). As to preterm PROM and the subsequent greater risk of complications associated with gestational age, antibiotic use is found to reduce the rates of both maternal and neonatal infection (Kenyon *et al*., 2001). Both UK national and Glasgow local guidelines recommended the use of erythromycin as a prophylactic antibiotic for a maximum of ten days during the antenatal period when PROM occurs in term or preterm babies (NICE, 2015b; NHSGGC, 2015a)

3.2 Methodology

3.2.1 Study design and setting

A period prevalence study of non-sepsis antibiotic use to treat infection in obstetric wards within NHSGGC.

3.2.2 Study subjects

The study subjects were all women admitted to postnatal or antenatal wards who were prescribed antibiotics for a clear and defined diagnosis excluding sepsis. Also excluded were all antibiotics prescribed prophylactically for PROM, caesarean section and GBS. This study was part of the larger cohort described in Chapter 2.

3.2.3 Data collection

The demographic data collected included patients' age, gestational age, parity, gravity if possible and allergy status. Patients' weight and BMI were collected when available. Length of hospital stay and mode of delivery for postnatal admission were also captured, in parallel with the number of days post-delivery.

Data were collected on the diagnosis and the named antibiotic prescribed for each patient. The sources of this information were the patients' drug Kardexes for antibiotics prescribed

during time in hospital and IDLs for those prescribed for treatment at home after discharge. Information on each antibiotic included the drug name, dose and route of administration.

Data were collected on microbiology reports and were included only if a culture or swab was taken from the patient. Data thus obtained included pathogens detected and sensitivity or resistance reported where possible. In addition, data were collected on some blood results, including WCC and CRP.

3.3 Results for postnatal wards

3.3.1 Demographic data

A total of 49 patients were identified as women treated for infection postnatally during the data collection period. The mean age of the sample was 31 years; the youngest patient was 18 years old and the oldest was 41 years. The median patient weight was 71 kg, the highest weight was 149.9 kg and the lowest was 43 kg. Only three patients (5.9%) weighed less than 50 kg and four (7.8%) weighed over 100 kg. As to allergy status, three-quarters of the patients (n=36) were recorded as (No Known Drug Allergy) NKDA, while six women (12.24%) had a penicillin allergy that affected the choice of antibiotic in their treatment journey. The remaining six patients for whom data were available were reported to have another allergy, either to some other therapy or to food.

The patients' length of stay in the hospital wards ranged from one day to 12 days with a median of four days, while reported postnatal readmission following delivery ranged from two days to 42 days. Data on mode of delivery show that more than half of patients underwent emergency caesarean section (n=27), followed by spontaneous vaginal delivery (n=8) and elective caesarean section (n=5). The least common mode of delivery reported was operative vaginal delivery.

3.3.2 Antibiotic therapy

Almost two-thirds of patients (63.3%) started their antibiotic therapy via the IV route and the remaining 36.7% were given oral antibiotic therapy.

The total number of antibiotic prescriptions reported in the postnatal wards during the study period for the sample of 49 patients was 57, the majority of these therapies being with IV co-amoxiclav in 33.3% of treatments (n=19), followed by PO flucloxacillin in 19.3% (n=11). The indication and diagnosis named for each patient are presented in parallel with the antibiotic prescribed for each diagnosis in Table 3.1 (refer to page 93). Based on the data obtained, IV gentamicin was prescribed for PROM, while for cases that presented wound abnormalities including wound infection, wound haematoma, wound drain and wound cellulitis the main antibiotics prescribed were flucloxacillin and co-amoxiclav (14 and 8 prescriptions respectively).

3.3.3 Microbiology report

Analysis of the microbiology reports for all patients shows that 32.7% of women (n=16) had missing data and that 42.8% (n=21) had no growth detected in their microbiology report. Data on all of the patients whose microbiology reports indicated a positive result are presented in Figure 3-1. The microbiology reports referring to sensitivity or resistance to antibiotic therapy are presented in Table 3.2. Analysis of the data on these PO patients showed that about a half of them (55.6%) had not been assessed for culture or swab analysis and that no sample was withdrawn from these patients, while the microbiology reports on the 44.4% who were assessed showed that no growth was detected in their samples.

Table 3.1: Diagnoses of postnatal infection and antibiotics prescribed

Diagnosis	Antibiotic
Query infection	PO Co-amoxiclav
Arm cellulitis	Combination of (IV Flucloxacillin - IV Clindamycin)
Chest infection Lower respiratory tract infection	PO Cephalexin PO Doxycycline IV Amoxicillin PO Clarithromycin
Endometritis	IV Co-amoxiclav
Foul smelling	IV Co-amoxiclav
Hematoma (back to theatre) Vaginal hematoma Vaginal pack Vaginal restoration – surgery prophylactic	IV Co-amoxiclav PO Co-amoxiclav
Large blood loss PPH	IV Co-amoxiclav PO Cephalexin PO Metronidazole Combination of (IV Gentamicin - IV Co-amoxiclav)
Mastitis	Combination of (IV Flucloxacillin - IV Benzylpenicillin) Combination of (IV Co- amoxiclav – PO Flucloxacillin)
Positive low vaginal swab	IV Co-amoxiclav
PROM	IV Gentamicin
Upper respiratory tract infection	IV Co-amoxiclav
Wound infection Wound cellulitis Wound drain Wound erythema Wound hematoma	IV Flucloxacillin PO Flucloxacillin Combination of (IV Co-amoxiclav, IV Metronidazole) IV Vancomycin PO Co-amoxiclav Combination of (IV Clarithromycin - IV Metronidazole) IV Clindamycin PO Doxycycline IV Co-amoxiclav

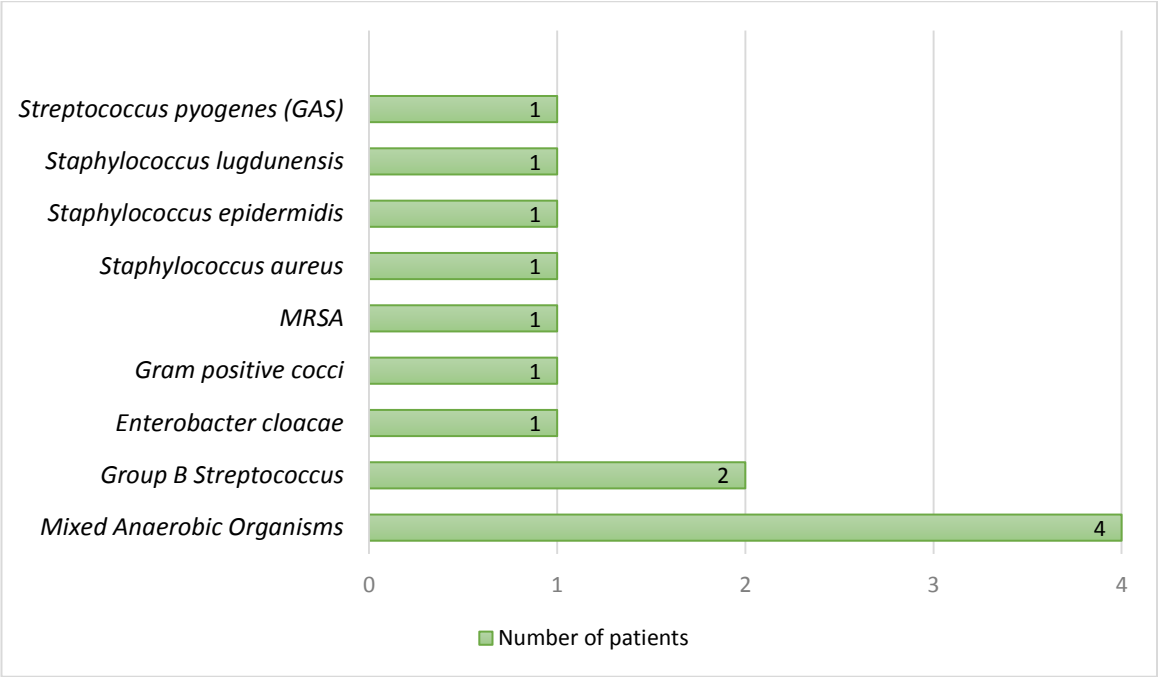

Figure 3-1: Pathogens isolated from clinical specimens of women with postnatal infection

3.3.4 Antibiotic therapy on discharge letter

A total of 34 patients were discharged with oral antibiotics, the majority of them being prescribed either co-amoxiclav, as reported in 44.1% of cases (n=15), or flucloxacillin in 35.3% of cases (n=12). One patient was discharged with amoxicillin, one with ciprofloxacin, three with doxycycline and two with metronidazole. Only two patients were discharged with a combination of antibiotic therapy: The first was diagnosed with mastitis and discharged with co-amoxiclav 625 mg, flucloxacillin 1000 mg and metronidazole 400 mg; the second was diagnosed with wound infection and discharged with doxycycline 100 mg and metronidazole 400 mg.

The duration of antibiotic therapy was stated in only 22 IDLs and averaged six days; ten patients were discharged with a seven-day course of therapy and another ten with five days of antibiotics, while only two had a more than seven days of antibiotics on their IDLs (eight and ten days).

Table 3.2: Isolated pathogen and related sensitivity and/or resistance in postnatal infection

Pathogen	Sensitivity	Resistance
Enterobacter cloacae	Ciprofloxacin Gentamicin Tazocin	Co-amoxiclav Ampicillin/ amoxicillin
Group B *Streptococcus*	Clarithromycin Penicillin	
Group A *Streptococcus*	Clarithromycin Penicillin	
Staphylococcus aureus	Clarithromycin Flucloxacillin	
Staphylococcus lugdunensis	Clarithromycin Flucloxacillin	
Mixed anaerobic organisms	Co-amoxiclav Amp/amoxicillin Aztreonam Ciprofloxacin Gentamicin Temocillin Metronidazole	
MRSA		Flucloxacillin

3.3.5 Biomarkers

The median values of WCC and CRP were 12 x 10^9/L and 66 mg/L respectively. Examination of patients' data showed that WCC was abnormal in only 21.9% (n=25) of women and CRP values were abnormal in only 49% (n=24).

3.4 Results for antenatal wards

3.4.1 Demographics

The data of 37 patients who were admitted to antenatal wards with an infection that required antibiotic therapy were captured. Data obtained on patient parity and gravity were significantly different from the normal distribution as reported by the Shapiro-Wilk test ($p<0.001$). Parity and gravity had a median of one with a range of 0-4 for both parity and for gravity. Data on patient allergy status indicate that only five had presented with penicillin allergy. Data from 34 women show that three-quarters of patients were admitted during

their third trimester, 17.6% during their second trimester and only 5.9% during the first. The mean reported weight of women in the sample was 66.6 kg. Approximately one-half (17/33, 51.5%) of them weighed between 50 and 70 kg, 27.3% (9/33) weighed between 71 and 90 kg, 15.2% (5/33) weighed less than 50 kg and only two patients (6.1%) presented with a weight above 90 kg, neither of them over 100 kg. Overall mean BMI was found to be 24.2 kg/m^2. Only four women were at class I obesity (BMI 30-34.9 kg/m^2), 11 women were overweight (BMI 25-29.9 kg/m^2), 12 were at a healthy weight (BMI 18.5-24.9 kg/m^2) and only five were underweight (BMI <18.5 kg/m^2). BMI data were missing in four patients.

3.4.2 Diagnosis and therapy

Information reported on diagnosis indicated that the most common condition suspected or diagnosed was UTI, in 59.5% of the sample (n=22), while the second most common diagnosis was pyelonephritis, reported in 24.3% (n=9) of cases. Only two women (5.4%) were reported to have UTIs with pyelonephritis and another two had lower respiratory tract infections (LRTI). One patient had a GAS infection and another had moderate hydronephrosis. Diagnoses and corresponding therapies are listed in Table 3.3

Table 3.3: Diagnosis of antenatal infection and antibiotic prescribed

Diagnosis	Therapy
Group A *Streptococcus*	PO Amoxicillin
LRTI	IV Co-amoxiclav PO Co-amoxiclav PO Oseltamivir phosphate
Moderate hydronephrosis	IV Co-amoxiclav
Pyelonephritis	IV Co-amoxiclav IV Gentamicin PO Cephalexin
UTIs	PO Cephalexin IV Co-amoxiclav IV Gentamicin PO Nitrofurantoin PO Trimethoprim
UTI + Pyelonephritis	IV Co-amoxiclav PO Nitrofurantoin

3.4.3 Microbiology report

Almost half of patients (n=17) presented with no growth in their culture or swab, while four patients (10.8%) had missing data; therefore, there was no sample for analysis and no identification of the pathogen causing the infection. *Coliform bacilli* were reported in 27% (n=10) of the sample, making this the most common pathogen isolated from women in their antenatal period. In two cases (5.4%), *mixed anaerobic* organisms were found to have grown in the culture or swab and there was one case each of *E. coli*, *S. aureus* and Group A *Streptococcus*.

Resistance to co-amoxiclav was reported (n=3) in two cases of isolated *coliform bacilli* and one *E coli* isolate. Four cases of ampicillin/amoxicillin resistance to *coliform bacilli* were recorded. Five cases of trimethoprim resistance were observed, with four cases seen in *coliform bacilli* isolates and one in an *E. coli* isolate.

3.4.4 Antibiotic therapy on discharge letter

The antibiotics most commonly prescribed in IDLs were cephalexin, as reported in 29.7% (n=11) of discharge prescriptions, followed by co-amoxiclav (n=7) trimethoprim (n=6) and amoxicillin (n=4). Nitrofurantoin was prescribed only twice and clarithromycin in only one discharge letter.

The length of antibiotic course in was only available in 23 IDLs with an average of 6.5 days. In 56.5% of these women (n=13) it was a seven-day course of antibiotic therapy, one had a 10-day course and five patients were discharged with a five-day course.

3.5 Discussion

Postpartum infection is considered a major cause of pregnancy-related mortality and morbidity worldwide. Caesarean section increases up to 20-fold the risk of postpartum infection, which occurs in up to 20% of women undergoing caesarean section (Lyimo *et al*., 2013). In half of postnatal cases, the antibiotics prescribed for wound-related infections were

not those specified in the NHSGGC guidelines. The first-line therapy for wound infection is oral flucloxacillin or clarithromycin, while metronidazole and gentamicin may be added, depending on the severity and condition of the infection. The treatment of these women with the broad-spectrum antibiotic co-amoxiclav lacks justification.

The use of single or multiple doses of prophylactic antibiotics has been evaluated in the literature and the evidence favours a single prophylactic dose (Lyimo *et al*., 2013). As to time of administration, a randomized trial found no significant differences in infection outcome dependent on whether the antibiotic was given before skin incision or after cord clamping (Francis *et al*., 2013). Obesity and diabetes were found to increase the risk of post-caesarean section infection, OR=1.43 (95%CI: 1.09-1.88) and OR=1.18 (95%CI: 0.76-1.82) respectively (Leth *et al*., 2011). Other research investigated the preoperative use of skin antiseptics to minimize surgical site infection. In a randomized trial, over 1000 women were treated with either a chlorhexidine-alcohol or an iodine-alcohol preparation. SSI was found to occur in significantly (p=0.02) fewer women in the chlorhexidine-alcohol group (4%; n=23) than the iodine-alcohol group (7.3%; n=41) (Tuuli *et al*., 2016).

The present study found that a significant number of women had received antibiotic treatment for a post caesarean section wound-related matter. The study did not investigate the appropriate use of antibiotic prophylaxis, but it was considered briefly as part of the health board evaluation of 14 women over 100 kg weight, which found that 12 women had not received an additional dose of amoxicillin. When this finding was shared in an action meeting, healthcare providers discussed the increased incidence of post caesarean section wound-related infection and concluded that skin preparations and antibiotic doses should both be considered before conducting another audit on this matter.

Postpartum haemorrhage is a major cause of maternal mortality, accounting for a quarter of maternal deaths worldwide. The main drug used in the management of PPH is oxytocin, while ergometrine, tranexamic acid and misoprostol are also used (Chandraharan and Krishna,

2017). The use of antibiotics is considered only where PPH is associated with a retained product and where the woman has to return to theatre for manual removal of placenta; in such cases a single prophylactic dose of ampicillin or first-generation cephalosporin is required (WHO, 2009). The woman diagnosed with PPH was given a combination of IV gentamicin and IV co-amoxiclav, then discharged with oral co-amoxiclav. As the diagnoses of these women were taken from the patients' medical notes, the decisions as to the treatment lack justification.

One postnatal woman had a positive culture for MRSA, which as stated in the literature is not very common, affecting only 0.5-2% of pregnant women (Beigi *et al*., 2009). A five-year study in a Birmingham women's hospital found that only 42 of a total of 6500 maternal women had positive *MRSA* results. The obstetric incidence of *MRSA* colonisation is reasonably low and the rate of transmission to infants is minimal (Gray and Martin, 2010).

During the antenatal period certain physiological changes occur in women which make it very common to observe UTIs, particularly after 12 weeks gestation. Pyelonephritis is among the main reasons for antenatal hospital admission (Zanatta *et al*., 2017). A Brazilian study found that *E.coli* was the most common pathogen causing pyelonephritis in pregnant women and that ceftriaxone was prescribed in 97% of these cases (Zanatta *et al*., 2017). To reduce inaccuracy in diagnosis and to achieve the gold standard, a urine culture is required to determine the pathogen(s) and the associated sensitivity and/or resistance (Kranz *et al*., 2017). However, for economic and practical reasons this was not possible in the current practice of the wards participating in the present study, where physical assessment and urinalysis were used instead, with urine culture being performed in most but not all patients. Culture was omitted in three cases of lower UTI and one case of LRTI only. The NHSGGC guidelines for maternal antibiotic use state that the first-line therapy in cases of UTI is cephalexin and that in cases of upper UTI and pyelonephritis it is co-amoxiclav with or

without gentamicin (NHSGGC, 2015a). The study found overall good compliance with these guidelines.

3.6 Conclusion

Good compliance with the antibiotic guidelines was observed in this period prevalence study. Women were treated for clear diagnoses that were justified in most cases, which indicates reasonably good practice and communication within the multidisciplinary team. Culture analysis was not performed in all patients because the associated resources of cost and time were limited. Instead, physical assessment with/without relevant tests were in place to support diagnosis. An action meeting to reduce the incidence of SSI associated with caesarean section and to review the protocol clearly indicated the determination of the healthcare board under investigation to drive better practice. Further assessment and intervention are recommended to ensure the delivery of better care to patients.

4 Chapter 4: A qualitative study of the implementation of the SSCB and antimicrobial stewardship in maternity units

4.1 Introduction

There are implementation strategies for every care bundle and these are recognised as ways of increasing the adoption of clinical practice (Proctor *et al*., 2013). The literature refers to the existence of more than 70 implementation strategies, each composed of either a single strategy or multiple strategies (Powell *et al*., 2017). Many frameworks of multiple strategies have been published and these tend to have in common six key processes which have been found to reflect the variations among them. These are planning, education, financing, restructuring, managing quality and attending to policy context (Proctor *et al*., 2013). The Replicating Effective Programs Framework, for instance, has four implementation phases: the precondition strategies that aim to identify needs and barriers; then pre-implementation, which includes developing a working group; next, the implementation phase, which covers training, assessment of any technical issues, feedback and consideration of any improvements; and finally the maintenance and evolution phase, when there is a need to revise the programme after delivery (Proctor *et al*., 2013). There is a reported lack of clarity in implementation, including in the identification, development and examination of these strategies, arising from the inconsistent use of terminology and the absence of the details needed to enable the replication of the implementation programme (Powell *et al*., 2015).

Improvements in communication, diagnosis and clinical outcomes have been identified when monitoring and feedback to clinicians were considered. There is little literature on the mechanisms of the feedback provided, with most authors simply comparing the outcomes of receiving feedback versus no feedback (De Jong, 2016). The theoretical concept of feedback intervention is based on the finding that clinicians will consider feedback to which their attention is directed if they find it effective. The person who gives the feedback must have credibility and relevance to the receiver for it to be accepted (De Jong, 2016).

The lack of supply of any required care, including stickers or equipment, along with a deficiency in healthcare providers' skills, has been found to have a negative impact and can interfere with the achievement of good management of sepsis (Jacob *et al*., 2012).

Antimicrobial stewardship has been defined as "coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy and route of administration" (Barlam *et al*., 2016). The aim of AMS is to enhance patient outcomes and antibiotic susceptibilities, thus reducing adverse antibiotic drug events like *CDI* (Barlam *et al*., 2016). The use of pre-authorisation procedures with or without a prospective audit and feedback is a strongly recommended strategy to implement AMS (Barlam *et al*., 2016). A didactic education approach using passive education practice and pamphlets could emphasise the fundamentals of AMS in clinical practice (Barlam *et al*., 2016). MacDougall and Polk (2005) explain the roles of certain individuals in implementing a successful antimicrobial stewardship programme. These include hospital administrators, microbiologists, infectious disease physicians, infection control staff, hospital epidemiologists and pharmacists, but the authors do not describe the roles of nurses or midwives. In the UK context, the SAPG consists of a wider collaboration of antimicrobial pharmacists, infectious disease specialists, infection prevention specialists, microbiologists, leadership teams, public representatives, the pharmaceutical industry, information and antimicrobial surveillance scientists, veterinary medicine practitioners, quality improvement experts, dentistry practitioners and primary care clinicians (Nathwani *et al*., 2011). The SAPG now includes nurses and no longer includes veterinary medicine practitioners (SAPG, 2018).

The 'start smart then focus' programme supports the fundamental role of the ward and the impact of nurses and midwives in successfully minimizing the threat of antimicrobial resistance (Bennett, 2016). The importance of their contribution to AMS comes from their close contact when monitoring patients' condition, assessing any drug allergy and patient

medication history, along with administering the antibiotics (Bennett, 2016). In collaboration with NHS boards and other stakeholders, the SAPG aims to "enhance the quality of antimicrobial prescribing to reduce unnecessary antibiotic use". This is mainly achieved by minimizing patients' exposure to broad-spectrum antibiotics while increasing the use of narrow-spectrum agents, thus developing better use of antibiotics and minimizing undesirable outcomes such as resistance, *CDI* and death (Nathwani *et al*., 2011).

Antibiotic de-escalation is defined as "changing an initially covering antibiotic regimen to a narrower spectrum regimen based on antibiotic susceptibility testing results within 96 hours" (Paul *et al*., 2016). Patients with suspected sepsis are expected to be given a broad-spectrum antibiotic; this therapy will be reviewed after the culture results have been obtained (Lee *et al*., 2015).

Inter-professional communication is a key concept in delivering better care, as enhancing communication has been found to improve patient care and health quality (Johnston *et al*., 2014, O'Leary *et al*., 2017). Conversely, poor communication within the healthcare team has been identified as one of the main reasons for adverse events (Popovici *et al*., 2015). The demanding workload, the need to develop and update patient care plans and the spreading of the team across many wards makes this communication very challenging. Therefore, healthcare professionals usually rely on methods of communication that include the involvement of technological communication methods (O'Leary *et al*., 2017).

Pagers and smartphones are the main methods of communication among healthcare professionals (Johnston *et al*., 2014). The use of pagers is very widespread in the USA, where a recent survey found that they were provided in 80% of hospitals and were used in 49% of the communications between healthcare professionals, while 21% used smartphones, 20% used mobile phones and 4% used hands-free communication devices (O'Leary *et al*., 2017). Pagers have a negative impact on workflow, they lack feedback and do not allow users to triage the incoming communication, while smartphones have the advantageous ability to

triage communications, although their multifunctional properties also negatively affect their efficacy (Johnston *et al*., 2014). On the other hand, pagers have the advantages of low cost and no requirement for Wi-Fi or signalling services, but the need to respond with a phone call is a distraction for the physician. Furthermore, the majority of pager contacts are reported to be non-urgent, thus unnecessarily disrupting the flow of work in the healthcare setting (O'Leary *et al*., 2017).

The quality of communication is reported to be critical at handover during shift or ward changes. The exchanging of information between practitioners to plan and deliver patient care makes a valuable contribution to patient safety, so that any deficit in this process can impact negatively upon patients' health through the missing of treatment or tests, or by delaying clinical procedures (Popovici *et al*., 2015). The frequency of handovers may cause information to be incomplete or misleading, thus reducing the effectiveness of inter-professional communication. The increased adoption of technology within hospital settings may facilitate enhanced communication and better information transfer between wards and professionals, but it has been found that poor evaluation of such technology prior to its use in hospitals has had adverse consequences (Popovici *et al*., 2015).

It was reported in Chapter 2 that patterns of over-diagnosis and over-treatment have developed relating to maternal sepsis. Particular challenges are the fear of having to deal with sick women whose condition deteriorates very quickly and the poor specificity and sensitivity of the SIRS criteria in diagnosing sepsis. Whether these have driven non-compliance with the SSCB and interfered with its implementation is still not known, which is why we have explored this more deeply with midwives using qualitative methodology.

4.2 Aims and objectives

4.2.1 Aims

To understand the factors and issues affecting optimal compliance with implementation of the SSCB and antimicrobial stewardship in maternity units.

4.2.2 Objectives

1. To investigate the availability and applicability of individual care within the SSCB.
2. To evaluate the prescription and de-escalation of antibiotics to women with suspected sepsis.
3. To evaluate the methods used in communications regarding patient care across maternity wards.

4.2.3 Methodology

As in-depth interviewing is a robust method of providing rich data descriptive of interviewees' experiences, opinions or knowledge in an area of interest, this method was selected for the quantitative study. The use of open questions is a fundamental tool of this method, allowing participants to provide detailed information about the facts, rather than limiting their responses to 'yes' and 'no' or some other closed set of possibilities. Nonetheless, the use of closed question is also useful in many cases, especially where further understanding and clarification are needed. Non-leading questions can take the interviewee in a certain direction that the interviewer wants to explore and investigate, thus helping to elicit robust data about certain feelings, thoughts or actions (Ritchie *et al*., 2013).

4.2.3.1 Study method and participants

An in-depth interview was conducted with each participant enrolled in the study. Participants were midwives working in NHSGGC maternity wards who had knowledge of the Sepsis Six care bundle. The condition 'knowledge of the bundle' did not limit participation to those who had used it; awareness of its existence was sufficient for enrolment in the study.

4.2.3.2 Study sampling

In this study, sampling was not based on probability but on certain criteria for inclusion. The recruitment strategy here was to apply such purposive sampling, with guided criteria for recruitment, as opposed to convenience sampling based on opportunity and chance. Staff were approached based upon their working in maternity wards and their pre-existing knowledge of the Sepsis Six care bundle. Potential participants were excluded from the study if they did not meet either of these two conditions.

Recruitment for the study was intended to be by the snowball method, where an email was sent to the lead contact in each of the three maternity wards, asking any healthcare provider who was interested in participating in the study to contact the researcher, NA, via email to arrange a convenient time and place for interview. However, opportunity sampling was also employed, having NA approach each maternity ward and ask the staff available about their interest in participating in the study. There were then two successive cycles of sampling over a seven-week period: each cycle occurred over three weeks.

4.2.3.3 Developing the research materials

4.2.3.3.1 Participants' invitation letter

A letter was developed to provide information for the lead midwife or senior charge midwife in each maternity ward, making them aware of the study by providing a summary of its background and aims. This invitation letter (appendix F) highlighted the criteria for inclusion in the research and clarified some points of interest. Contact information was provided so that anyone interested in participating could contact the researcher, NA, to ask for further details or seek clarification of any points.

4.2.3.3.2 Participants' information sheet

All prospective participants declaring an interest in taking part received an information sheet (appendix G) designed to give them fundamental information about the study. It also highlighted the importance of the desired outcome, to improve sepsis care for women in

NHSGGC maternity wards. It stated the criteria for the inclusion of healthcare providers in the study. It explained what taking part involved and described potential risks and benefits. It emphasised that all data would be anonymised and handled confidentially, and stated that participants would be free to withdraw from the study at any time. It noted that the expected benefits at ward level would arise from the ability to identify factors facilitating and hindering the provision of the complete Sepsis Six care bundle within an hour of sepsis being suspected, thus helping to develop a quality improvement methodology to improve sepsis care in maternity wards within NHSGGC. This information sheet also carried details of the sponsor of this study as part of a PhD programme, the University of Strathclyde, and provided further information on the applicable ethical standards. Finally, the researcher's email address and contact information were provided.

4.2.3.3.3 Consent form

A consent form was developed to ensure that participants had given their fundamental agreement prior to the start of the interviews (appendix H). They were asked to confirm that they had fully understood all of the information given in the participants' information sheet and that they had been given the opportunity to ask questions. Participants were assured that their enrolment in the study was completely voluntary and that they could withdraw at any point without giving a reason. They were required to confirm that they understood that the interviews would be audio-recorded and transcribed and that the data obtained would be anonymised. Before being interviewed, each participant was required to sign and date two copies of the form, one to keep themselves and the other for the researcher's records.

4.2.3.3.4 Interview guide

The interview guide (appendix I) was designed primarily to identify the topics to be discussed with the participants. There were also many reflective questions based on the information obtained from each interviewee.

4.2.3.4 Validation of interview guide

The interview guide was seen by the clinical risk manager at PRM, who validated it in terms of its topics, as well as by a qualitative research associate within the SIPBS Institute (EDC), by both academic supervisors (GA and ABM) and by the clinical supervisor (JG), all of whom validated it in terms of its topics and the formation of the questions themselves.

4.2.3.5 Ethical approval

An ethics application was completed and submitted to both the SIPBS ethics committee and the NHS Caldicott prior to the start of the study. In addition, it was approved by the West of Scotland NHS R&D, who had seen the interview guide and approved it as a service evaluation not requiring an NHS ethics application.

4.2.3.6 Pilot

A pilot interview was conducted with one participant, allowing the researcher to gain additional interview skills and to make sure that everything was captured following the use of the interview guide and further reflection on the interviewee's answers.

4.2.3.7 Data storage

The audio files of the interviews were stored in the University of Strathclyde Sharefile application, allowing only access by the researcher. The transcribed data were also stored in Sharefile, in a folder accessible only to the interviewer herself and the two academic supervisors.

4.2.3.8 Data analysis

Data were transcribed from the audio files to a Word document using an intelligent verbatim transcription that excluded all hesitation fillers (e.g. 'um' and 'er') and laughter, with no account for pauses, and included a very small amount of editing to correct grammar (Salonga, 2018). The transcribed files were then uploaded into the NVivo qualitative data analysis software (QSR International Pty Ltd.) Version 11, 2017.

The data analysis followed a thematic approach, starting with the assignment of codes, then aggregating these into categories and finally into major themes, to be presented in the findings section.

4.2.3.9 Validation

A 20% validation of each transcribing cycle was conducted. The first cycle was validated by another PhD student (NW), while the validation of the second cycle was carried out by another PhD student (AM). There were no major problems that might affect the content of the interviews or their analysis, as the validation process only highlighted minor changes that were limited to some prepositions, the singular and plural of some words and other mostly trivial changes.

4.3 Findings and discussion

A wide variety of experiences were recorded from 13 participants across three different sites within the same health board. All 13 participants (Table 4.1) were either midwives or senior midwives working in maternity wards, labour wards or triage/maternity assessment units.

Table 4.1: Demographic data for participants in interviews on SSCB and antimicrobial stewardship

Participant number	Hospital	Ward	Length of interview (min:sec)	Experience (years)
1	A	Postnatal ward	19:37	17
2	A	Antenatal ward	19:54	10
3	A	HDU labour ward	23:24	14
4	B	Postnatal ward	37:52	17
5	B	HDU labour ward	08:40 08:59	1
6	B	Antenatal ward	27:54	14
7	C	Postnatal antenatal ward	32:30	33
8	C	Labour ward	26:49	21
9	A	Postnatal ward	62:04	8
10	B	Maternity assessment	35:40	20
11	B	Postnatal ward	39:00	20
12	C	Labour ward	43:14	9
13	C	Postnatal ward	42:27	16
		Total	428:06	
		Mean ±SD	33 ± 12:24	15.25 ±8.10

Key min: minute; sec: second; HDU: high dependency unit

Their experience was not limited to midwifery, as some had been nurse practitioners prior to their midwifery training, while some also had independent prescribing status. There was a reported belief that midwives have the experience of dealing with healthy women who have experienced pregnancy and childbirth, while nurse practitioners have the additional experience of dealing with a broader range of patients with a variety of health-related conditions.

> *"if you have previous nursing experience you're used to sicker people, whereas midwives are used to well people, and it's to be able to see the deteriorating patient quickly because the golden hours can't be wasted."* (Participant.7).

Participants had an average of 15 years of experience in maternity wards. Their experience with the SSCB varied, from involvement in the implementation process, education and follow-up on education to its non-availability and limited use of the sticker within the same health board. In this section participants were mostly refer to as "midwives", this does not mean generalisation to include all midwives or all participants into a single view or quote. But rather these data were captured from either one participant or multiple participants, where each quote received an equal attention.

The three main themes emerging from the findings were barriers to implementing the SSCB, antimicrobial stewardship and communication within the multidisciplinary team. Table 4.2 summarises the themes and categories identified from the results

Table 4.2: Themes, categories and sub-categories identified from the result after applying thematic analysis approach to the transcribed data from 13 interviews

Themes	Categories	Sub-categories
Barrier to implementing the Sepsis Six care bundle	Failure to realise the objective of the bundle	
	The inappropriateness of the bundle components	
	Failure to safety monitor patients after the initiation of the bundle	
Antimicrobial stewardship	Unnecessary therapy	
	Antibiotic prescribing	The midwife's role in relating to commencement of antibiotic prescribing
		The verbal prescription of antibiotics
		The initiation of gentamicin therapy
		Rapid identification and management
	Antibiotic de-escalation	The role of multidisciplinary team
		Criteria for deciding on antibiotic de-escalation
Communication within the multidisciplinary team	Ward-level communication	Support related communication
		Criteria for referring to medical staff
		Escalating the referral to medical staff
		Patient's admission unit
		Role of practitioner/ward in patient transfer
	Tools of communication	The patient's immediate discharge letter
		The SBAR approach
		Documentation of patient care

4.3.1 Barriers to implementing the sepsis six care bundle

4.3.1.1 Failure to realise the objective of the bundle

The SSCB sticker, which reflects the bundle itself, was not introduced to participants; it had not been explained and they were unaware of its components. This lack of awareness may be explained by the failure of the midwives themselves to realise the importance of the bundle. Alternatively, the fault was said by midwives to lie within the ward in the absence to initiate any explanation of the bundle by senior midwives and medical staff to their team.

Midwives failure to visualize the sticker shows that they were unable to commence its application to patients and thus to improve their practice.

> *"I don't think that I can tell you what the sticker looks like. I'm not sure that anyone has ever shown me the sticker and what to do with it."* *(Participant.9)*

Midwives felt that the bundle had not been explained and that following the instructions given on the sticker could lead to better practice. The SSCB would be commenced for all women with two SIRS risk factors. This assumption had emerged in the absence of explanatory guidelines and lack of clarity regarding the correct practice.

> *"If they want to introduce it to the postnatal ward [it's essential] that they explain it to people before they do, because I was just told 'Sepsis Six – there is a drawer with packs in it'."* *(Participant.4)*

Despite the support available at ward level, that included the introduction of the bundle and working toward enhancing the awareness of manging sepsis, it was still not integrated into midwives' practice to the point of realising that SSCB is not just *"another sticker"* *(Participant.3)*. Opposition to the implementation of the new bundle was typified by the remark that *"people don't like changes"* *(Participant.3)*.

Some midwives believed that they are able to work efficiently without the need for the SSCB. This contradicts the bundle's values and aims, and represents a challenge to the amendment of midwives' behaviour.

> *"Some people are like 'Oh, we're already doing that! Why do we need a sticker?'."* *(Participant.3)*

Some midwives complained that obtaining and using the sticker could be inconvenient in practice and that they would prefer to have the same content as a page within the patients' notes, to which they could turn whenever it was needed.

> *"I suppose with it being a sticker, then you have to go and get it, and stick it in. Whether this is the best thing, or should it be something somewhere in the notes, a page that you turn to, 'We are now doing sepsis'."* *(Participant.9)*

The priority was seen as being to care for the patient and to commence whatever care she needed at the point of suspecting sepsis. Participants did not feel that they should give priority to looking for a sticker before taking care of the patient. They believed that the sticker was meant to be used before commencing application of the Sepsis Six, but in practice they found it difficult to justify giving attention to the sticker itself prior to delivering the care.

> *"Someone who's unwell, would I go and get the sticker so I could follow the list, or would I wait until everything had been dealt with and then get the sticker, so 'I did that, I did that'."* *(Participant.9)*

Access to the SSCB is fundamental when compliance is a requirement. Following the implementation of the bundle, the achievement of better practice is challenged by too little effort being made to provide the stickers or to update the old supply. Midwives believed that the sticker was absent from their wards and they did not seem to know where to look for it.

> *"Not that I'm aware of! I'm been brutally honest with you."* *(Participant.4)*

Initiating and following up sepsis treatment purely on the basis of personal experience could not ensure an outcome similar to that of treatment initiated and followed up according to the sepsis six guidelines.

> *"We don't have the sticker so we do not follow it the way that they possibly do."* *(Participant.4)*

The workload of medical staff requires them to be in different places within a short period of time. They are required to review each diagnosis of sepsis within the first hour to ensure that treatment of these women has been satisfactorily considered. A member of the medical staff is required to be present in the ward within an hour of sepsis diagnosis and the woman should have her blood culture taken, then her antibiotic therapy should be commenced. Doctors' inability to be present within the first hour is a challenge in many situations.

> *"If the doctor is so busy that you can't get hold of a doctor … Because we are not allowed to prescribe antibiotics and do the blood culture. That's the only kind of barrier that I would think. We can't do them because we need medical staff."* *(Participant.13)*

4.3.1.2 The inappropriateness of the bundle components

There is an argument about sepsis cases in maternity and whether it is appropriate to deal with these in postnatal wards. Participants strongly approved of the steps of care involved in the SSCB, but were concerned that the need for all of these was not considered in postnatal women diagnosed with sepsis.

> *"Somebody in a postnatal ward who requires a Sepsis Six sticker, to me, should not be in the postnatal ward. She should be transferred out of the postnatal ward, if they require all the criteria that is on it."* *(Participant.4)*

Women with sepsis who do not require high dependency care are not transferred from the postnatal ward. These women do not need the full SSCB. Participants believed that women

with no need for the care bundle specified in the Sepsis Six protocol did not merit transfer to a labour ward for close monitoring.

> *"The other ones who don't merit transfer do not need all the steps that are involved in Sepsis Six."* *(Participant.4)*

Instead, there is a belief that SSCB should not be delivered as a bundle to all patients diagnosed with sepsis. Its availability suggests a reference that is in place to help and guide when there is a need; healthcare professionals would rather apply their own personal experience and judgement in evaluating the care in the bundle for their patients.

> *"Everything. If ever it's needed, it's all there, but you can use it, or the medical staff can use their judgement to say 'Right. Actually, she does not need that'."* *(Participant.13)*

These opinions were not limited to their own practice with patients. Midwives encourage teamwork and their ability to communicate within the team has been observed to emphasise these behaviours. The confidence and courage to take a stand on patient care, to discuss with colleagues the appropriateness of care and to involve a senior person in these conversations reflects their strong belief that this care should not be given to every patient diagnosed with sepsis.

> *"If it's, a new midwife …, we'll say 'Look, she might not need that. Do you want to discuss that with ... a doctor?' Or if it's maybe a junior doctor [and] we felt what happened, in our experience, that we wouldn't normally do that, we'd say 'Can you just double check with your registrar?' ... So we'll get them to check with somebody more senior"* *(Participant.13)*

Individualized patient care can save patients from being exposed to unjustified treatment. An unnecessary catheter can cause a woman pain and expose her to trauma following her experience of giving birth, while the prescription of antibiotics should be justified to avoid

exposing the mother and the baby to an unwarranted therapy that can lead to drug resistance and conflict with the principle of antimicrobial stewardship.

> *"Some people will be catheterized unnecessarily or possibly commenced on IV antibiotics unnecessarily. So that's my concern of having the sticker."* *(Participant.4)*

Instead, the practice of following the protocol and delivering the six elements of care within the bundle was believed to have no bad outcomes, so that if it had been commenced no damage would have been caused.

> *"You wouldn't get into trouble … for it. They would maybe just get you to read up your protocol again but you would not be doing anybody any harm."* *(Participant.12)*

Nevertheless, these decisions supported by the protocol stand in the front line between midwives' behaviour and their personal beliefs. Their practice in these cases will be to satisfy the requirements of the Sepsis Six protocol by ensuring its completion, while their feelings will be with their judgment that the bundle is superfluous, which they have disregarded.

> *"None of us have a crystal ball that can tell what's going to happen in the future, so you just have to go with the protocol and [against] your judgment sometimes."* *(Participant.13)*

Some midwives did not see the name 'Sepsis Six' as representing the exact number of care elements that should be delivered to each patient, as only four of the six would initially be commenced in maternity patients diagnosed with sepsis, while the applicability of the remaining two (oxygen and catheter) would depend on the situation.

> *"I think four out of the six, because we don't always give oxygen, we don't always do urine. It just depends."* *(Participant.10)*

Others, however, believed that the bundle was in place as a set of initial responses to be applied indiscriminately to all patients, with the possibility of modifying the care given later. For them, the bundle should be treated as a set of elements that must be initiated within an hour of every diagnosis of sepsis.

> *"I think the fact that it's a set of guidelines for sort of immediate initial management for patients over a one hour period ... I can kind of get that that would fit everybody, because it's almost like an emergency response as a first response and you will do all of these and then once we've got the results of all these investigations we can then tailor the plan from there."* *(Participant.9)*

A catheter cannot be considered for a patient without having knowledge of the history of the illness and the reasons for their presence in the ward. The midwife has to be aware that there are various types of sepsis and that identifying what type a patient has can influence the decision to catheterizing her.

> *"Depends on what they've come in with, what they're in with, what type of sepsis they're in with."* *(Participant.2)*

The aim of fitting a catheter is to monitor the patient's urine output and it is sometimes possible to do so without catheterizing her, but when this cannot be done a catheter should be considered.

> *"Catheter… most of them need that, but there are occasions when you can avoid that if you manage to measure, but I think the majority of people end up with one."* *(Participant.6)*

Participants believed that a catheter should also be considered when close monitoring of the patient was not possible, such as in a ward setting.

"Probably yes, in the ward, because you are not with your patient all the time." *(Participant.3)*

However, they believed that monitoring the patient closely would be preferable, to avoid the disadvantage of catheterization, i.e. that it is an uncomfortable and unpleasant process for the patient.

"They're not very comfortable, the catheter's not comfortable." *(Participant.3)*

Oxygen saturation should be lower than 94% to commence the patient on oxygen therapy. In practice, it was found that oxygen was not considered necessary for all septic patients on maternity wards. The catheter can be postponed while monitoring the patient's urine output, since if she has good diuresis there will be no need for her to be catheterized.

"Just personal experience and when … the medical staff come to see the patient like that. 'Oh, she does not need oxygen' or 'She is up. Just monitor her urine output at the moment.' Obviously, sometimes they change. If maybe then they've not got good urinary output then they will catheterize them, but if they monitor it and they've got good diuresis, then sometimes they won't necessarily do it." *(Participant.13)*

There were two views of oxygen. Some midwives saw it as a drug and believed that unnecessary oxygen could be harmful for the patient. Nonetheless, if a woman's saturation seemed acceptable at the point of diagnosis with sepsis, the midwife should continue to monitor her and check her saturation more closely afterwards.

"Oxygen can be harmful if it's administered when you don't actually need it. But again, they need to be sure that they will be going back and checking on them, if they're not going to start it." *(Participant.3)*

Other midwives believed that oxygen would do no harm if delivered to a patient whose saturation was above 94%.

"If you give oxygen you are not going to do her any harm." *(Participant.7)*

Intravenous fluid is part of the SSCB; however, midwives felt that they should use their experience and personal judgement, as if a woman was able to drink three jugs of water, there would be no need for the midwife to put up a bag of fluid for her.

"Not in every patient we need IV fluid as well, if she's got three jugs of water there and she is drinking it all." *(Participant.1)*

The SSCB sticker was not accepted because it duplicates the work of the existing sheet. It replaced an earlier format of an A4 paper that's been display in large font, with further information. This was popular and seen as having advantages over the later sticker, which was smaller and contained fewer instructions.

"This is in fact before the sticker came in. This is what we used. I think why we tend not to use the stickers is because we are using this, so it is like double work … It is bigger, and you can put it in front of the notes. The sticker's smaller. Actually, I like this, but I like paper. I like things like that. The sticker is quite small." *(Participant.10)*

4.3.1.3 Failure to safely monitor patients after the initiation of the bundle

Even when successfully initiated, the SSCB will not deliver its potential benefits if not followed by successful monitoring. It was acknowledged that midwives' ability to triage patients in the wards is limited to the first hour. The prolonged care of these women will not be successful in the context of the requirement to prepare and check all intravenous antibiotic doses in busy wards.

"You can prioritize somebody for an hour or so, but after that I think it can become a workload issue, because … making up all these antibiotics and checking them and giving them takes quite a lot of time." *(Participant.9)*

Safety and efficacy should be ensured for all maternity women, most of whom are healthy. Midwives looking after patients in maternity wards should not experience the stress of knowing that nobody is available to look after the ward. The requirements of time and effort to care for sick women could be met by having a stable patient discharge system. Instead, negative outcomes for other women and babies who are admitted to the same ward as septic women are underreported and their safety is compromised by the fact that busy midwives have to deal with the preparation, checking and delivery of IV antibiotics more than three times a day.

> *"We had two women on IV antibiotics and one of them was on three different kinds and one on two different kinds and there are only two midwives on the wards … because they need two midwives to check each dose, it's … too much of a workload because it means the two midwives are in the drug room doing that and there is actually nobody looking after the rest of the patients."* *(Participant.9)*

There is another important aspect of safety and accountability affecting other women in the ward who experience maternal complications other than sepsis. The limited resources of staff and time will fundamentally affect the care given to these women. It is difficult to triage patients and to set priorities rapidly in order to focus on delivering what is most important first.

> *"It is very difficult because you might have somebody with sepsis, but also somebody who'd come in with no foetal movement and you discovered that they don't have a heart rate. So you are dealing with that, …, you're dealing with labouring patients; you are dealing with people who are bleeding."* *(Participant.10)*

The pathway of care for women suffering sepsis can be communicated by midwives to their supervisors or ward coordinators. They should not experience feelings of discontent in the

workplace by themselves, as support and help can be provided. It should be remembered that the midwives inability to handle the stress of treating women suffering trauma can cause harm to both patients and healthcare worker more than good.

> *"Any good midwife would flag up and go 'I can't do this, it's unsafe'. You need to go to your supervisor, go to your coordinator and just say 'I'm not prepared to do it.' It's your name that's at risk. In a court of law it would be you that's in trouble."* *(Participant.11)*

There are vital components of trust and confidence in midwives' words that have to be perceived by their superiors before the provision of any support, including transfer of patient care. Midwives asserted that while it is important to speak out when workload is not manageable, no action should normally be taken against these women. There is an issue of workload experienced by midwives working with sepsis women in maternity wards.

> *"It's an ongoing thing. I think having women on the ward who've been treated with sepsis, that there is definitely workload issues there."* *(Participant.9)*

4.3.2 Antimicrobial Stewardship

4.3.2.1 Unnecessary therapy

In the wards under investigation, sepsis was diagnosed on the basis of SIRS criteria. This led to patients being commenced on intravenous antibiotic treatment for flu-like symptoms because they had two abnormal SIRS criteria. Midwives believed that experience in assessing these women was fundamental and that understanding the physiological changes that occur during and after labour could explain many observed abnormalities in SIRS criteria.

> *"A lot of them as well as things like mastitis, their milk, whenever the lady's milk comes in, her temperature rises as her cholesterol changes to breast milk, her pulse goes up. I've had women commenced on IV*

antibiotics, because, and I know they're feeling that way because the milk comes in, and it's like flu like symptoms they've got." *(Participant.4)*

Midwives believed that some abnormalities in the women's MEOWS charts as part of the sepsis risk factors should not always be taken into consideration without assessing the history of the patient and the whole picture of her experience in and after labour. By contrast, medical staff would like to move directly to prescribing an IV antibiotic as a precaution.

"If somebody has a raised temperature, the doctor wants them to go onto IV antibiotics." *(Participant.4)*

There was an essential aspect of using the person's experience in assessing and reviewing women in maternity. The sole use of the protocol did not constitute a comprehensive practice and could drive unnecessary therapy. Looking at the patient, taking her history and understanding the situation could enlighten the practitioner before commencing antibiotic treatment.

"Certainly, we don't have a problem reviewing people, but sometimes when you jump in too quickly it can be somebody's due paracetamol at that point. It's a whole variety of… When sick people come in you know that they're sick. If they are walking in smiling, then you know that they are not septic." *(Participant.10)*

A negative aspect of implementing the Sepsis Six care bundle in the postnatal ward was that women were commenced on IV antibiotics as a precaution when any parameters were outside the normal reference range.

"Possibly commenced on IV antibiotics unnecessarily. So that's my concern with having the sticker." *(Participant.4)*

The regulation behind the start of antibiotic therapy was unrestricted, allowing healthcare providers to prescribe IV antibiotics to a wide group of patients prior to reviewing any blood results.

> *"We do jump into antibiotics … too much, instead of waiting on all these results to come back. We've already had a couple of doses sometimes."* *(Participant.1)*

Midwives were concerned about the practice of being *"IV antibiotic happy"*, reporting that it would sometimes seem as if all of their patients were receiving IV antibiotics and that this was disturbing.

> *"I know that is one of the things that does concern us, because we are quite IV antibiotic happy. We are, if sometimes you think everybody's on IV antibiotics."* *(Participant.10)*

They were, however, satisfied with all women being recorded on a sepsis chart, if this action could save one woman's life. Sepsis is a serious illness and should be treated as such, even if that meant prescribing antibiotics to all women in order to prevent one undesired outcome that might occur.

> *"No, if it's going to save a life … at the end of the day, if this helps one person, then you've got to do it … So even if everybody who comes in postnatally goes onto a sepsis chart, then that's the way this going to have to be."* *(Participant.10)*

The readmission of women to the hospital ward was driven by referrals by community midwives who lacked experience in symptoms related to breast milk. Such women would be commenced on IV antibiotics based on a temperature of 37.6 °C and a slightly elevated pulse.

> *"I think we overprescribe antibiotics, so we get a lot of people in just in caution … Now when these women are coming in and we are treating*

them because the community midwives will go out, check their temperature, the temperature setting at 37.6 or something, their pulse is slightly raised. That's a normal physiological thing during breast feeding. All these women are coming in getting IV antibiotics, they're absolutely fine when their inflammatory markers come back. So it is just a matter of experience of knowing is that breast milk or is it sepsis." *(Participant.10)*

The fact that a woman's condition can deteriorate if untreated with antibiotics was seen as the reason for commencing IV antibiotic treatment very quickly. As the patient's future condition was unknown, the possibility that it would deteriorate very rapidly drove this action.

"With it being so important … I would rather be treated when it's needed treated, to save anything from getting worse then, but yeah, probably there is a lot! It's the whole antibiotic things as well, I've jumped in and given people IV antibiotics and if they've not necessarily needed them." *(Participant.13)*

While the presence of SSCB encourages the prescription of IV antibiotics as part of the bundle, midwives confirmed that it was only one dose of therapy, after which a review should be considered for the blood result and a decision should be made on the need for continued administration of the antibiotic.

"They don't prescribe dose after dose after dose of antibiotic. It's just one and then we'll get the blood results back and then take it from there. They have to follow up, so when you start on Sepsis Six they get a one-off dose of antibiotic so you can't give any more after that. The doctor has to follow up the patient after that, checking their blood results and then prescribe what is required for that." *(Participant.12)*

A belief was reported that antibiotics could be commenced for a raised CRP, without the need to commence the women on the full Sepsis Six protocol.

> *"They started on antibiotics for a raised CRP, but not necessarily the Sepsis Six."* *(Participant.12)*

4.3.2.2 Antibiotic prescribing

4.3.2.2.1 The midwife's role in relating to commencement of antibiotic prescribing

Although the diagnosis of sepsis is not purely a midwife's decision, knowledge of the risk factors and the ability to start the SSCB has been reported by midwives. Nevertheless, the term "decide" seems to indicate certainty of action, compared with the more flexible notion of suspecting sepsis.

> *"It's not my job to decide if somebody is septic."* *(Participant.4)*

It was seen as the midwife's responsibility to provide information related to the patient's condition, to develop a case scenario and to provide all of the details and evidence, while the medical staff were responsible for deciding on the treatment pathway.

> *"They* [the midwives] *will advocate for the patient, because obviously what they're doing is they're making sure that all the evidence is there for the medical staff, but they don't choose then the treatment pathway. It's a medical decision because it's outwith the norm."* *(Participant.7)*

On other occasions, the midwife might be observed to be involved in the discussion of patient care. However, the registrar would lead the decision-making by prescribing a one-off dose of IV antibiotic that will be discontinued or continued depending on the blood results.

> *"It's a discussion between us all. Normally it's the registrar who will say: 'Give them, just give them an antibiotic, just give them a one-off antibiotic. Let's see how things go. Wait for the blood result, because*

we've got this time concern of an hour. Just give her antibiotics and we will wait for the blood result to come back'." *(Participant.10)*

The credibility of the antibiotic decision was not a matter for the midwives, who stated that their role was limited to the administration of the antibiotic after it been prescribed by the medical staff.

"We will be administering their medication as it's been prescribed." *(Participant.4)*

Senior midwives had more authority to prescribe antibiotics than junior midwives. A guide was available to help midwives to determine which antibiotics they were able to prescribe.

"Band 7 in the ward can prescribe it. I mean we can to a degree, but we have a list of what we can prescribe and what we can't prescribe." *(Participant.11)*

Some midwives could thus prescribe antibiotics to a certain extent, although in cases of sepsis they aimed to find a member of the medical staff to prescribe them. Patient review by the medical staff was important at this stage and could shape the treatment pathway.

"We can do a certain amount of antibiotics … But we could certainly, we can give them, we can make up antibiotics, we can prescribe certain ones, but in that case you would probably get the medical staff, because you would obviously be wanting them to know that someone's unwell." *(Participant.8)*

4.3.2.2.2 The verbal prescription of antibiotics

The flexibility of approach in the maternity ward apparently allowed IV antibiotics to be prescribed through verbal instruction. Where the midwives were not able to call a member of the medical staff to the ward, verbal prescription was a way of ensuring that antibiotic treatment was commenced within the required one-hour window.

"IV antibiotics I would be a bit… because it's not prescribed I'd be a bit doubtful about doing that, but I could certainly maybe take a verbal instruction to do that if it's needed." *(Participant.9)*

This approach of verbal instruction to prescribe antibiotics was very well integrated between medical staff and midwives. Medical staff would approve the administration of antibiotics off site to allow midwives to administer a dose within the one-hour window.

"Occasionally [they'll] say, 'Yeah, give her that and I'll prescribe it when I get there." *(Participant.13)*

This supportive teamwork approach was seen to be capable of driving the patient safely through the process of care. While it was not always possible to have a member of medical staff present in the ward whenever needed, the midwives showed their ability to act on this matter by receiving a verbal instruction to administer the antibiotic in a telephone call with a member of the medical staff in theatre. This would allow the process to start, while another midwife or auxiliary would take the drug Kardex to the medical staff in theatre for the written prescription to be signed.

"If we think someone is really bad and we cannot get a doctor, they will verbally allow us to do it and let someone run to theatre, because there are quite often two doctors in theatre. Someone runs the Kardex over to the theatre to prescribe it for us." *(Participant.10)*

4.3.2.2.3 The initiation of gentamicin therapy

The response to the initial antibiotic therapy can vary among patients. It was observed that when a woman did not respond well to the therapy, gentamicin was added to the treatment regimen.

"If their blood results are not improving on the co-amoxiclav they might add in another antibiotic. Quite often gentamicin seems to be the next one that gets added in." *(Participant.9)*

The therapeutic drug monitoring that is required with gentamicin is essential to ensure patient safety and the efficacy of the antibiotic. Midwives acknowledged their awareness of this need and their belief in the process of monitoring gentamicin level, as one of their responsibilities was to monitor it and modify the antibiotic if the level was not satisfactory.

"If she needs gentamicin levels done or anything like that to make sure that her blood level of antibiotic is adequate to combat the infection, we will do those and we'll make sure that we get the result to make sure that her levels are adequate." *(Participant.7)*

4.3.2.2.4 Rapid identification and management

Participants noted the possibility that the suspected sepsis patient might not be septic and that the initiation of the Sepsis Six care bundle could be unnecessary. The patient's true condition might be quickly settled by a negative culture or swab and unremarkable inflammatory markers.

"There's definitely cases where women perhaps get antibiotics where they maybe don't need them and you discover that and they had two down the line. Nothing grows in the culture, nothing on their swabs. They're quite well." *(Participant.9)*

The concern that the one-hour window might be missed and the treatment of a woman with sepsis be delayed led to quick action in commencing antibiotic treatment. There was an awareness that this could lead to a longer stay in hospital and increase the cost burden, but because sepsis is a critical diagnosis, the practice seems to have been to err on the side of

overusing antibiotics to prevent the deterioration of patients and to avoid the risk of treatment being started too late.

> *"You don't want to miss the opportunity of giving someone antibiotics that might improve their outcome, but then there is the other patient that made you think as well we should not be giving people too much antibiotics. That causes its own problems … gives them longer stays in hospital ... makes them think they are unwell. But that's what you have to, act on the side of caution, because sepsis is such a serious thing usually for women around that time. It is just you don't want to miss your chance to keep them well."* *(Participant.9)*

The women in the postnatal ward were seen as not requiring the elements of care listed in the bundle. They were "self-caring", their observations were stable, they were mobile and not catheterised, and were able to care for their babies.

> *"They're not catheterized. They are self-caring. They are not unwell, they don't have a high temperature or a raised pulse. Their observations are all stable. They're doing everything they have to for their baby, so they're just here for a treatment they require because their blood levels are elevated, so there is a concern that there are infections, but they're actually physically quite well."* *(Participant.4)*

Treating patients in maternity for a suspected sepsis by commencing an IV antibiotic seems to have been very common as a precaution.

> *"Treating patients as query sepsis is very common."* *(Participant.4)*

Once a woman had been commenced on the Sepsis Six protocol, a decision which may have been based on an abnormality observed during labour, the protocol would continue to be followed after she had been transferred to the postnatal ward.

"When they're starting down that route then it usually continues when they come up here." *(Participant.4)*

Failure to take account of the changes in a woman's physiology during labour can lead to a wrong diagnosis of sepsis. Women were commenced on the Sepsis Six protocol following a raised temperature or pulse throughout labour and these treatments were extended to include the baby.

"Somebody who commences Sepsis Six for maternal temperature in labour while their body is doing a lot of work, I expect their temperature to be raised. So I think there's far too many women who are commenced on Sepsis Six but they don't have to be, and a lot of babies get antibiotic cover as well." *(Participant.4)*

4.3.2.3 Antibiotic de-escalation

4.3.2.3.1 The role of the multidisciplinary team

The role of flagging any updates in patients' health condition was noticeably fulfilled by the midwives, who collated the findings and provided an evidence-based summary of each patient's wellbeing. This process allowed healthcare providers to work as a team, with the midwives providing all the information and the decisions on patients' treatment pathways being left to the medical staff. These decisions were driven by both the culture results and the information provided by the midwife.

"If we felt that she's well, and now she's clinically well … Then if the blood result showed that there is nothing growing, there is no infection, the doctor will make the decision based on that, or if it's coming back saying, 'This bug on this swab is resistant to them'." *(Participant.12)*

Patients differed in their response to the antibiotic therapy and these variations had the potential to affect the action taken. The medical staff would assess each patient and their assessment would drive their decisions on the de-escalation of antibiotic therapy.

> *"Depending on how the patient's responding to the treatment and whether things have changed, then it will be up to the medical staff to decide whether to de-escalate the antibiotics."* *(Participant.3)*

The midwives were observed to be involved in the process of de-escalation to oral antibiotics by emphasising facts that supported their opinion, based on the patient's condition and the stability of her observation.

> *"If the patient is improving, so I'll be at the ward round and I'll be saying, 'She's getting better. Do we still needs IVs? Can we change it to oral?' "*
>
> *(Participant.3)*

Positive microbiology reports also provided information on any pathogen detected in a sample and its resistance and sensitivity to various antibiotics, allowing midwives to detect any problem in the current therapy. This empowered them in discussions with medical staff about changing the therapy and de-escalating to a narrow spectrum antibiotic or to a more suitable one.

> *"If I got a result from the microbiologist I'd be flagging that up and saying, you know, 'We've got this result. Do we need to change these now?'."*
>
> *(Participant.3)*

The initiation of a daily review of sepsis patients provided a scale of improvement and enhancement in the women's health. This could lead the process of de-escalation following the registrar's assessment or of providing another member of medical staff to review and assess the patient on behalf of the registrar.

> *"Everybody who's on IV antibiotics is daily reviewed here for the registrar."* *(Participant.4)*

Following the taking of cultures and swabs, the medical and microbiology staff would decide jointly on the patient's treatment, including the antibiotic agent, dose and duration of therapy.

> *"They* [the medical staff] *usually hear from microbiology rather than us and get the decision to them as to what to be on and how long for and what the best plan of action is."* *(Participant.6)*

Microbiology reports on sepsis patients were usually communicated directly to the doctor by the microbiology lab and the midwife would not be involved in this conversation. This does not mean that midwives did not communicate with the microbiologists, as they were involved in cases with positive urine specimens; nevertheless, they were not involved in sepsis cases.

> *"Somebody with a positive mid specimen of urine, you may got a phone call to say, you know, 'This patient should be on this antibiotic', but when it comes to somebody that's septic, it's always doctor to microbiologist. Midwives are not involved in that conversion usually. I will say I haven't been."* *(Participant.4)*

Communication with microbiologists occurred in two ways, as they would also contact the ward when they had a positive culture result for a patient, in order to discuss their concerns and the treatment plan.

> *"Sometimes they do, if they have something that they have grown in their cultures that they feel it needs specific antibiotics or it is a little bit unusual, then they'll call us and tell us."* *(Participant.3)*

Communicating the result to the ward after analysis of a sample was fundamental to processing the patient's care. Some wards were able to receive blood results within an hour, due to their high alert level.

> *"To review the result, we're lucky in that. We'll quite often get the blood results back within an hour. We'll be looking for those to come back, so we can determine what follow-up treatment was needed."* *(Participant.3)*

De-escalation from intravenous to oral antibiotics is a medical decision. Women would sometimes not be de-escalated to an oral antibiotic, because the course of intravenous therapy she had already received seemed sufficient. This might be decided in a discussion between doctor and microbiologist.

> *"Sometimes they make the decision themselves to change to an oral tablet or to discontinue or whatever, or they will telephone microbiology and have a discussion."* *(Participant.9)*

Midwives felt that they had no role in making decisions about the de-escalation of antibiotic therapy and they very seldom tended to be involved, as the medical staff took this role.

> *"Not really on the decision making of it, I would not say. No, one of the medical staff."* *(Participant.9)*

4.3.2.3.2 Criteria for deciding on antibiotic de-escalation

There was no protocol to fix the duration of the intravenous antibiotic therapy, which instead was determined by considering each patient's clinical condition. There was a baseline agreement of an initial 24 hours of IV antibiotic, which midwives believed could then be extended in response to inflammatory markers such as CRP and WCC, or to abnormalities in observation such as pyrexia. In such cases, a prolongation of IV therapy was considered until the patient was ready for the switch to oral administration.

> *"I don't know if there is a set protocol, but usually they want them to have at least 24 hours of the IV antibiotics … then it just depends … what all the bloods are doing, how high their CRP and their white cell count were, if they're on the way down … how the patient's observations have been, like if they settled really quickly, but if she's still over with peaking temperature or… CRP was really high, they might want them to carry on a bit longer."* *(Participant.13)*

Following the completion of the 24 hours of IV antibiotic, there were some patients for whom the antibiotic therapy would be discontinued, rather than de-escalated to oral therapy. Their condition would continue to be monitored by observation for a further 24 hours, after which the blood tests would be repeated to determine how their inflammatory markers had responded without the effect of the antibiotic.

> *"Some girls are discontinued after the 24 hours, but they would not be discontinued and discharged. They would be discontinued, monitored, and bloods repeated 24 hours later to make sure their CRP was continuing to fall without the antibiotic."* *(Participant.12)*

In another group of women, when normality was observed in their inflammatory markers, culture results and observation, their IV antibiotic therapy would be de-escalated to oral therapy.

> *"If her observations are all fine, her cultures are negative, her bloods are improving, then occasionally they will change them onto oral antibiotics."*
>
> *(Participant.13)*

The process of following up the improvement of sepsis patients does not seem to have been straightforward in cases where their inflammatory markers remained elevated above the normal range. The follow-up treatment pathway seemed to begin with gentamicin

discontinuation, followed by de-escalation from IV to oral administration of co-amoxiclav. This could be initiated as the result of an observed improvement in the patient's condition and laboratory values.

> *"They usually wait for them to fall. They don't wait for them to fall within normal level. Sometimes they're still elevated if they're… They usually stop the gentamicin first if they are on both, leave them on the co-amoxiclav again, and then if it continues to fall they will, once it's within, but not always within normal range, they will stop the co-amoxiclav and usually give them oral."* *(Participant.4)*

The choice of treatment agent adhered to the local guidelines, co-amoxiclav being prescribed for patients not allergic to penicillin. This could then be amended to a different antibiotic based on positive culture results and information obtained from the microbiology report, whereas when there was a negative result, the co-amoxiclav therapy would be continued.

> *"If they want the antibiotic to continue then usually it's IV co-amoxiclav they're on, [then] that's what [they continue on] if they change them to oral, unless as I say … we've done a swab and something comes back and it's sensitive to whatever."* *(Participant.13)*

When a patient's microbiology report was negative, the decision on whether to discontinue antibiotic therapy or to move to oral co-amoxiclav, for instance, would be taken either directly by the medical staff or based on a discussion with the microbiologist.

> *"Sometimes they [the medical staff] make the decision themselves to change it to oral tablets or to discontinue or whatever, or they will telephone microbiology and have a discussion."* *(Participant.9)*

Given the lack of direct evidence inherent in a negative culture result being reported, the medical staff would monitor the patient's situation and use their clinical judgment to decide whether to switch to an oral antibiotic or to discharge her with no antibiotic.

> *"Some of it might be, I won't say personal preference, but it's clinical judgment that could vary depending on the doctor's point of view."*
>
> *(Participant.9)*

Where a patient had scored zero on the MEOWS chart for 48 hours, when her observations had normalised and when she felt that she was recovering, then oral therapy could be commenced. In other words, IV antibiotic therapy might be prolonged for some women until they had been stable for a period of two days.

> *"I've known the consultant quite often will say, 'When did this lady last have pyrexia?' I would say, 'She has not been pyrexial for 48 hours', or 24 or whatever, and you might use that, you know, based on the MEOWS being zero for 24 or 48 hours or whatever, and you know, and the woman's feeling better, and that might be the thing that made them say, 'We can change to oral tablets in that case'."* *(Participant.9)*

Factors other than observation and laboratory values would sometimes need to be considered. For example, if a woman could not tolerate oral therapy because she had a vomiting condition, then she would remain on IV therapy and not be de-escalated to oral therapy until her vomiting had improved.

> *"Depends on how quick they transfer over to oral antibiotics and obviously if they can tolerate oral. Some patients, if they're vomiting then they can't tolerate oral, so they have to remain on IV antibiotics a bit longer."*
>
> *(Participant.2)*

The patient's condition would either improve or deteriorate following the initiation of broad spectrum IV therapy. In cases where it deteriorated, there would be a decision to change the antibiotic therapy. It was not clear whether there was a specific period of time for which the medical staff would observe the patient and wait for the initial therapy to take effect, or whether they would make a quick judgement immediately it became evident that there was no clinical or laboratory improvement.

> *"So just basically, if they're not responding, you know, to the treatment, you know, if their condition continues to deteriorate then they change."*
>
> *(Participant.8)*

Conversely, if there was an observed improvement in the patient's condition, the decision would be taken to continue with the initial treatment.

> *"If they're getting better on the antibiotics they're on, then most of the time they just stay on them."* *(Participant.8)*

The confirmed cases of sepsis required 48 hours of IV antibiotic therapy, after which the patient would be de-escalated to oral therapy for a duration of between five and seven days.

> *"If it's been a definite sepsis then they would give an IV antibiotic usually for 48 hours and then into oral antibiotics for five to seven days after that."* *(Participant.8)*

4.3.3 Communication within the multidisciplinary team

There are many arguments concerning genuine sepsis, workload, patient transfer and ward support. The management pathway of genuine cases of maternal sepsis seems to work in practice thanks to multidisciplinary team support.

> *"On the night shift we had two genuine Sepsis Six people, and two genuine [cases] who were a woman with antenatal urinary sepsis and one*

was a postnatal day 16, it was a wound sepsis, and they were ill, and labour ward knew that we had them so they sent somebody to help with the other patient that we had and a member of staff. So we do all work as a team. We work well." *(Participant.10)*

There is a communication configuration between medical staff and midwives, although it was not clear in which direction the communication and support were assumed to operate. In the case of recently qualified midwives who lack experience, medical staff will drive the decision and provide the support.

"Medical staff are there to support us." *(Participant.5)*

On the other hand, years of experience and exposure to different cases during prolonged practice can shape a midwife's confidence and drive her decisions. Midwives will participate in making care decisions by clearly stating their views.

"Sometimes it is just politer to just say 'This is what I would think, but it is totally up to you'." *(Participant.1)*

Others agreed that the clinical experience of healthcare providers can emphasise the importance of caring for the patient. A rich discussion between midwives and the medical team could enlighten the pathway of patient care when consensus is reached.

"We work as a team and we sit and discuss it with them. We disagree with the doctor, the doctor disagrees with us, but we kind of come to a mutual agreement." *(Participant.10)*

Among all these scenarios of teamwork and communication between medical staff and midwives, the Sepsis Six sticker has the additional benefit of saving time and paperwork by summarising the steps of care and providing a tick list and a space for time. Midwives, when commencing the bundle for a patient, can tick the box and write in the time, so that when

the medical staff arrive in the ward they will be able to see from the sticker what care was delivered and when.

> *"So if you do have a very ill patient and you've got a sticker and all you need to write is the time, medical staff can come behind you and they can see exactly what you've done and they can pick up and continue it."*
>
> *(Participant.12)*

Nonetheless, being able to speak with medical staff to confirm and review a case of care by phone can be beneficial for an experienced midwife. Midwives are capable of prescribing an antibiotic after confirming this with medical staff and having the care initiated.

> *"We can just have a conversion with them if they're in theatre and say 'I've got this girl, this is what she presented', and we can actually go ahead and get the antibiotic. We can prescribe the antibiotic ourselves."*
>
> *(Participant.8)*

Accountability for reviewing the results of laboratory tests and cultures is shared by medical staff and midwives. However, in a case where the midwife is present when the results are returned and notices from the resistance or sensitivity that the patient is on the wrong antibiotic, it becomes her responsibility to notify medical staff and have the therapy changed.

> *"If cultures come back and she is on the wrong antibiotic we'll notify the medical staff to change it straight away."* *(Participant.7)*

These communications are necessary for inflammatory markers in sepsis women, while any elevation in CRP or WCC that is observed while a woman is under antibiotic treatment constitutes a serious reason for review that requires medical staff to intervene.

> *"We'll phone and say 'Look, she's had another CRP and it's actually gone up'."* *(Participant.7)*

Communication between medical staff and midwives is usually by pager, ensuring rapid response on weekdays. Having a member of the medical staff assigned to the ward will tend to cut waiting time, which can be very long during nightshifts and at weekends.

> *"If you … have somebody … allocated for the ward, so they are the one on that pager, so if you page them and speak to them, they will come right away."* *(Participant.4)*

4.3.3.1 Ward level communication

4.3.3.1.1 Support related communication

Support was said to be delivered quickly in cases of severely ill women. Some midwives noticed a rapid response of medical staff when they had a sick patient.

> *"If you have someone who's sick they will be quite quick in general."* *(Participant.5)*

However, other midwives reported that the level of support and help needed for sepsis women was not always satisfactorily delivered, making them feel more confident in establishing a crash call through 2222 rather than waiting for the medical staff to respond to a pager.

> *"Yes, when you phone the four twos you've got a whole team here before you know it, so it's sorted."* *(Participant.4)*

The supportive environment provided by senior medical and midwifery staff, in addition to the support of their peers, could increase the level of confidence and assurance of any staff member looking after an ill patient. There would always be people available to help and support whenever needed.

"From senior midwives, from medical staff ….. As you can see in the ward there are a lot of us about. There is never anybody too far away to give you help." *(Participant.12)*

It is sometimes fundamental to seek help from the senior medical staff when assessing a sick patient, especially if midwives have limited experience with these patients.

"They should have involvement from quite a senior medical staff member, so maybe getting those. Getting access to them…" *(Participant.5)*

Others were more confident in the competence and ability of the junior medical staff to assess sepsis patients, believing that if an assurance were needed, the junior medic would already have spoken to the registrar to confirm their decision.

"Junior medical staff are more than competent of dealing with it, because they would go to the registrar … so I have no qualms as to that. No, if that's what they say and that's the rule of thumb." *(Participant.11)*

An important factor is the responsibility for informing members of staff who have been absent (e.g. for their annual leave) when significant changes have occurred. It is essential for there to be a communication book and a notice board to ensure that new information remains visible and accessible, so that staff returning to the ward can easily update themselves.

"We do have a communication board and a communication book, so quite often if you've been on holiday and something is introduced, like for instance Sepsis Six, it goes onto the board and it usually stays up there for a good few weeks until the next thing moves on." *(Participant.13)*

The morning safety brief with the ward staff has been used to ensure a satisfactory level of awareness of any updates or new guidelines. The leading role of the senior midwife has been observed to influence the level of awareness among midwives.

> *"I think usually [senior midwife's name] is good at – every morning she has a safety brief so she is quite good at kind of saying, 'Right, does everybody know about this and that? Pass that on to the next [shift]'. So she tries to make sure everybody is covered, because I suppose there could be the odd time when somebody just does happen not be here when people are doing the updates, but we usually use this communication and she does, as I say, go over things if there is anything new for a wee while."*
>
> *(Participant.13)*

The existence of a folder assigned to sepsis paperwork was useful and made it easier for the midwives to check any information and to access the Sepsis Six stickers. Their awareness of having an online protocol that they can access when needed has resulted from the level of alertness in the ward.

> *"Yeah, we've got a folder, and we've got a supply of … the stickers in it. I'm sure there's a protocol online as well, so that whoever can't find anything here, then you can always go online and get it."* *(Participant.13)*

The steps taken to ensure that the morning shift was well informed, including the safety brief and communication board, would be much less valuable if the staff did not pass on all of the relevant details to the nightshift staff at the 8 o'clock handover.

> *"They will or would hopefully pass on the new information to their colleagues at 8 o'clock at night."* *(Participant.7)*

Senior midwives in charge of the ward were able to handle the safety brief between the wards. This was done through her presence in the ward area each morning, making herself aware of each patient's condition, followed by in-depth discussion about each patient's situation and deciding to escalate to senior medical staff if required.

"I talk to midwifes and I give them direction as to well you better do this for that lady or find out if her bloods needed done again, or she had a CRP done yesterday what's the result of it. So we talk about the ongoing planning of care and management even before the medics come, so we are ahead of the game." *(Participant.7)*

This communication extended its role in the day to another safety brief at 1500 hrs while this one is with the presence of medical staff and is not limited to only midwives. This allows a discussion of cases where the patient's status does not improve.

"We have it again at 3 o'clock at the afternoon to see how things are going everywhere, are we meeting our targets! Have we got our ladies down to labour ward, has labour ward got problems, have some wards got problems so on, and we have medical staff present at 3 o'clock"

(Participant.7)

This is not limited to the ward area only, with the discussion happening between the midwives of the same ward. It has been reported that there is a *"unit safety brief"* which allows senior charge midwives to gather and discuss patients' conditions and follow up with any changes or updates in their clinical situation.

"We also have the unit safety brief, where I go [senior charge midwifes for antenatal and postnatal maternity ward] and so does the senior charge midwife from labour ward, the birthing suite, the outpatients"

(Participant.7)

4.3.3.1.2 Criteria for referring to medical staff

There was heavy reliance on patients' MEOWS score to indicate their illness level. One red score would initiate a trigger, requiring medical review.

"So if they have a red score, you need a doctor to review, a [member of] medical staff to come instantly and you need to be continuing their observation regularly." *(Participant.12)*

Other said that they would start triggering a risk if a patient had a yellow score on her MEOWS, which would involve medical staff if not resolved after 30 minutes.

"But if they're scoring yellow and it's not resolved after … 30 minutes when we recheck it, if it's still scoring, so we'll highlight it and get their doctor to see." *(Participant.6)*

Alternatively, the way the patient feels could trigger an immediate referral to medical staff when combined with an abnormality in her MEOWS chart.

"I suppose if I went to see someone and their observation was telling me that they may be septic and that they might not feel very well, I would probably – the first thing I would do would be to page medical staff to ask them to come and review." *(Participant.9)*

The continuity of referring and involving medical staff in the care of sepsis patients was found to be extended to include the follow-up phase of the therapy. This emphasises the midwife's important role as being in a better position to monitor the patient's condition than the medical staff, who only review patients in the postnatal ward after being contacted by midwives.

"No, we have good communication, and we can say to them, you know, 'This lady's observations have been absolutely stable, there is no sign of infection, her bleeding, you know everything, her wound, whatever she has looks fine. Could you review her?'." *(Participant.4)*

4.3.3.1.3 Escalating the referral to medical staff

The allocation of resources is important in cases of critical care including sepsis. While medical staff are in theatre it may be possible to speak with them by phone, but it must be appreciated that their presence in the ward will not be possible. It is thus fundamental to learn how to escalate the case and have another member of the medical staff available in the ward within the one-hour window.

> *"If we need them to prescribe something urgent then we do kind of go above and get a consultant in. Medics are quite good at coming, but if there is [an] emergency going on in labour ward then that takes priority over this if they're both in theatre."* *(Participant.10)*

While getting hold of the obstetric team seemed very challenging at weekends and during nightshifts, midwives realised that the involvement of gynaecology staff in these cases could escalate the process of care for women with sepsis.

> *"Depending on what else they're doing in theatre, for instance, they can't always come straight away, then you've got other options because there are other doctors working in gynaecology and things like that if they are really desperate."* *(Participant.9)*

Despite the good communication with various levels of medical staff, there would be some days when the hospital would be overwhelmed with demanding work and it would be a challenge to find a medical staff member quite quickly.

> *"There are always days that are just really difficult."* *(Participant.9)*

4.3.3.1.4 Patient's admission unit

The location of the patient was said to determine the level of care considered by the medical staff. Priority was always given to labour ward patients, then to triage. Senior and junior

medical staff were present in these wards whenever needed, while patients admitted to postnatal/antenatal wards received less attention.

> *"Usually they are really quick, especially down in the labour ward. They are very quick."* *(Participant.6)*

Midwives believed that transferring a patient from the ward to the labour ward could often solve the problem of the unavailability of medical staff in the ward area, as the patient would be subject to one-to-one monitoring and have a high chance of being reviewed by a member of the medical staff.

> *"You can't always get somebody when you need them, in which case we just have to keep monitoring them more [regularly] to make sure things are not getting any worse, or get them transferred to the labour ward, where they're getting more intensive monitoring."* *(Participant.13)*

4.3.3.1.5 Role of practitioner/ward in patient transfer

A written transfer sheet using the Situation-Background-Assessment-Recommendation (SBAR) approach is a document used in labour wards to summarise the patient's condition for staff in the postnatal ward upon transfer.

> *"When a patient comes up from labour ward, you get a verbal handover, and you get a written yellow sheet! The SBAR sheet, that tells you everything on it"* *(Participant.4)*

However there is no patient transfer sheet for patients moving from postnatal/antenatal wards to the labour wards.

> *"Do we have a sheet? We've got one that they've use in labour ward when they're bringing the patient to us postnatally. But I don't think there is one actually for going the other way because that is … less frequent"* *(Participant.9)*

This will also require the ward coordinator, hospital coordinator and medical staff to be involved in this decision.

> *"If it's a transfer because she is unwell either the coordinator, the hospital coordinator and clinical staff."* *(Participant.11)*

Advance knowledge of the ill patients admitted to postnatal/antenatal wards was reported to help the process of handover by easing communication, as previous knowledge of the situation and care given to these patients could be taken into account.

> *"They would know if we had someone on the ward that was ill … so that if we did have to transfer them then they already sort of know about the patient."* *(Participant.2)*

4.3.3.2 Tools of communication

There is a communication board in the ward that carries a summary of each patient's condition, where practitioners usually write important information in red. This board is on the wall of the doctors' room, which means that the information is handled within the healthcare team only.

> *"We do have like obviously on the name board if there is anything, if somebody's on the Sepsis Six we would put in important information on that on red as well just to highlight the fact just in case you've had been on that somebody's forget to say all the important information should be on that as well so that you're covering hopefully everything."* *(Participant.13)*

4.3.3.2.1 The patient's immediate discharge letter

Patients' discharge medication should be checked by the midwife prior to dispensing. This most frequently happens by reviewing the drug Kardex to ensure that the IDL medication list is appropriate.

"We've got obviously the drug Kardex, we've got to check if they're going home on any medication … we've got immediate discharge letter from the doctors … then two of us got to check that they're giving her the right medication away home with them." *(Participant.13)*

Nonetheless, when checking patients' medication, midwives believe that the patient drug Kardex is the proper place to confirm the patient's medication.

"I'd like it in the Kardex more than anything else, because that's the prescribing one, so I would rather it was written on that." *(Participant.4)*

With that being the situation, some doctors do not endorse their decision by prescribing the duration of therapy in the drug Kardex. This means that medical staff have to come to the ward and review the patient's case to write the discharge plan for the medication.

"The doctors write on the Kardex if they're good doctors, how many days they want them to have it. Sometimes they write it in the case notes, sometimes they don't write it anywhere." *(Participant.4)*

Discharging the women after the initial treatment for sepsis is a senior medical staff decision. If a junior member of the medical staff has to discharge these patients, then a senior medical practitioner must be contacted and consulted prior to the discharge decision.

"It is not junior medial staff who discharge these ladies. It's a registrar or consultant." *(Participant.7)*

The discharge process does not mean that patient is disconnected from the hospital. The contact information and telephone line are given to patients prior to discharge ensuring that they are able to phone and speak with the staff if required.

"The patients are all given the triage number and we're 24/7 they can contact us if they have any concerns" *(Participant.8)*

4.3.3.2.2 The SBAR approach

The SBAR communication tool has been used widely in maternity. It has the potential to highlight that the patient is "commenced on Sepsis Six protocol" and provides a good short history of the patient to highlight care needs. The recommendation part of the SBAR allows the healthcare providers to know what's expected from them in the coming days.

> *"We use a thing called SBAR, and you write what the situation is what is the patient background is you taking into consideration the delivery, whatever their background is, and in the background bit you would say … commenced on Sepsis Six protocol, then your assessment of them now: 'now clinically well'. "* *(Participant.12)*

The bulk of information has to be communicated between and within the multidisciplinary team, emphasising the need to have an SBAR sticker in place to summarise the patient's information (The SBAR sticker was on a pilot trial during the study period).

> *"I think the SBAR stickers when they come [into practice] will be helpful for remembering everything; there is a lot of information sometimes."*
>
> *(Participant.3)*

The presence in the ward of a woman with suspected sepsis requires the calling of medical staff to review the patient. While midwives referred in their responses to taking an SBAR approach, this seems to have been interpreted as informing the medical staff of the patient's situation, background and action taken only.

> *"Just give them the background … so do an SBAR. Situation, background and the action that we've taken."* *(Participant.11)*

It has been noticed that passing on the information required during transfer using an SBAR is not sufficient unless the receiver signs to confirm that this information has been passed on.

"You sign to say that I've passed this information on, and they've sign to say they received this information." *(Participant.10)*

The SBAR is an acknowledged way of transferring patient information particularly between theatre and other areas within the hospital.

"We do an SBAR with all our transfers between our theatre department and until recovery area and up to the ward." *(Participant.8)*

The recommendation part of the SBAR handover was very well understood by the midwives. They believed that they were expected to write information regarding recommended medications, including the duration of antibiotic therapy, as well as information regarding observations and any other recommendations related to the patient's condition.

"…continues on antibiotic and whatever you're dealing with, and then do your recommendation and that's where you will put 'continue on IV antibiotic for 48 hours', 'continue on oral antibiotic 7 days', '4 hourly observations', whatever you continue" *(Participant.12)*

This handover approach can also include highlighting the need for further blood tests and review following the transfer of care, and what's required for the patient at the point of handover.

"I would let them know if bloods were to be repeated, if I knew! You know if I knew the bloods are to be repeated and when! Then I would say: 'She is due to have her blood repeated in the morning or this evening or whatever it was'. " *(Participant.9)*

The SBAR handover approach is not always a written handover; there is a verbal only SBAR handover that was reported mainly by midwives in the postnatal/antenatal wards. However, with a verbal handover, a good documentation in the patient note will allow midwives to

look through the notes while doing the handover verbally, which enhances the accuracy of the handover.

> *"That's probably more of a verbal handover I would say! But I suppose you would be writing on your notes as you were doing all these things you will give your verbal handover face to face… with the midwife taking over their care"* *(Participant.9)*

4.3.3.2.3 Documentation of patient care

The location of documenting the patient's story varied between sites and within the hospital. Documentation of patient care was made in the patient's clinical notes, but this was not always the case, as in some wards the care was written in the patient's handheld notes, where the *"women will hold their own notes"* following their discharge.

> *"Everything documented no matter what, and most of the time with patients that are septic or have had [sepsis], you do write in the handheld for the girls to look back on"* *(Participant.1)*

The woman's vital signs including temperature, heart rate, respiratory rate and blood pressure are documented in the MEOWS chart. This along with the handheld clinical notes provide a complete background about the patient including what has been considered and what's expected.

> *"We have a MEOWS chart and the handheld notes would say how you found the patient, what you did when you're concerned about them, and it will just be chronologically what happened."* *(Participant.4)*

There is different recording chart for a woman's maternal observation when they've been admitted to labour ward; this is called a partogram.

"In labour ward you're using your partogram mainly, rather than your MEOWS trigger" *(Participant.6)*

The partogram does not provide a score for the patient, and does not have the colour code like the one in the MEOWS chart. Midwives refer to the MEOWS chart every time they need to calculate a patient's score.

"There is no [scoring system] in the partogram, but we do have a MEOWS chart that we could refer to if we were not sure" *(Participant.6)*

Although there are two different charts that have been used, midwives have a preference for the MEOWS chart as it is clearer for them to have a look and act on the patient score. The partogram provides an idea about the deterioration and changes over time but does not give a score or a colour code.

"I think the MEOWS chart gives you a clearer picture with the scoring, you can still look at a partogram and see a deterioration or a change over time, which gives you a good idea, but the MEOWS chart definitely is clearer you can't ignore it, you get your scoring and then you have to act"

(Participant.6)

The patient's medical notes are divided into sections (i.e. antenatal, natal and postnatal), but if the patient has been admitted to a labour ward (i.e. HDU) postnatally, the labour ward staff will always write their documentation of care in the natal section.

"When they're re-admitted to the labour ward they continue to use their own paperwork, even if they're no longer in natal, it is postnatal, they still write it there! So it takes a bit of finding sometimes." *(Participant.4)*

The patient's medical notes are also divided into sections regarding healthcare practitioners. Medical staff will document the patient's care on green paper, while midwives will use white.

"Medial staff write in a different place to where the midwife writes … but they are colour coded usually if people used them, so midwives write in white and the doctors write on the green sheets! So yeah that helps a wee bit. Depends on whose entry you're looking for" *(Participant.4)*

4.4 Discussion

Any bundle that is implemented in order to improve practice has a single aim or multiple aims, usually expressed as a list of the outcomes of interest following the objective of the bundle, as reported widely in the literature (Bull *et al*., 2011; Giles *et al*., 2015; Kuan *et al*., 2013). The aim of implementing the SSCB is to deliver six elements of care to the patient within one hour of sepsis being suspected (Daniels *et al*., 2010). Its aim was never to assess patients' needs and evaluate the care before giving it to any patient, yet this emerges from our findings as an area of considerable confusion. Respondents fell into two groups regarding their practice: some would deliver the six care elements to each patient without questioning their applicability, while others would assess the patient and evaluate her needs. The literature recommends that when failure to achieve the aim of a care bundle is detected; efforts should be made to reiterate the aim, obtain updates on the progress of implementation and provide feedback to the people who are supposed to use the bundle. Further work should be done to identify the reasons for the failure (Bull *et al*., 2011). An Australian study of a bundle designed to reduce surgical site infection identified the need to improve staff education, as a deficit in education had interfered with the implementation of the bundle, although deeper analysis indicated the root cause as heavy turnover among education staff (Bull *et al*., 2011). In the current evaluation of SSCB, the data collected from midwives indicates an inadequate strategy concerning two phases of education: the formal introduction and education prior to the initiation of the bundle in maternity wards and the provision of follow-up meetings and visits to enhance this initial education. The literature identifies the fundamental role of education in the implementation of care bundles. Teaching on a small scale and the consideration of formal education have been highlighted as

important steps in the implementation of the surviving sepsis campaign bundle in Singapore, where a study has found that barriers to implementation include time shortage, staffing issues, equipment and training needs and poor communication and collaboration among medical staff (Kuan *et al*., 2013).

The implementation of the SSCB in six Scottish hospitals was evaluated in an ethnographic study based on 300 hours of observation and interviews with 43 members of staff including pharmacists, nurses, physicians, consultants and managers (Tarrant *et al*., 2016). The main focus of the implementation strategy was to educate employees about the SSCB and the diagnosis and management of sepsis (Tarrant *et al*., 2016). This was observed in the present study in only one site, as the staff showed better awareness compared to the other two sites, which was achieved by reminding and prompting staff in safety briefs and ward rounds. In addition, posters were displayed in their wards, along with a supply of the Sepsis Six sticker for use in patients' medical notes and of the Sepsis Six pack, constituting all that is needed to deliver the six elements of care. Other strategies reported in the literature are motivating and rewarding staff when the bundle had been delivered within one hour and facilitating implementation by making the necessary resources and equipment easily accessible. Despite these initiatives, delivering the bundle within an hour was still a complex task (Tarrant *et al*., 2016). The use of a behavioural science approach indicated that the lack of audit, feedback, training and communication were barriers to Sepsis Six implementation (Roberts *et al*., 2017). These barriers were also found in the present study, as no audit was considered prior to this work and no feedback was provided either. Lack of training was mainly observed among midwives working in postnatal/antenatal wards. A challenge was observed in monitoring patients who were awaiting transfer to a ward area, as this period varied between patients based on their recovery (Bull *et al*., 2011). The present study also found that monitoring patients was challenging, with respondents identifying workload as a barrier to doing so in postnatal wards. It has been observed that all aspects of the implementation process need to be considered and that education alone will not ensure its success.

Nonetheless, the introduction of bundle updates and progress reports in staff meetings has been shown to enhance the delivery of the bundle and improve outcomes (Bull *et al*., 2011). This strategy was integrated into one maternity site and its performance is worth learning from, as it was shown to improve the delivery of sepsis management and SSCB in ill women. This was mainly achieved by a senior midwife lead, who organized and managed the wards, ensuring that staff reached an acceptable level of awareness and knowledge.

Many studies have emphasised the fundamental benefits of staff education. It has been reported that the implementation of education strategies has the potential to reduce catheter-associated urinary tract infection when associated with surveillance and feedback, while the use of audit with feedback of the results was found to reduce the duration of catheterisation in post-operative patients (Giles *et al*., 2015). It is reported that 15-25% of inpatients experienced an indwelling urinary catheter during their hospital stay and that this intervention was not justified in up to 50% of cases (Giles *et al*., 2015). A systematic review of seven clinical studies found that implementation of Surviving Sepsis guidelines failed to enhance the delivery of care to sepsis patients. Instead, patients with suspected sepsis were over-treated when they were actually well and needed no therapy (Turi and Von Ah, 2013). The challenge of diagnosing sepsis in maternity plays an important role, as many therapies were initiated for suspected rather than confirmed sepsis. This was the main challenge identified in this study. The literature reports that accurate diagnosis is thus the main barrier to implementing care bundles, while the second most significant is staffing, which includes staff knowledge and training received as well as the provision of staff resources to successfully implement the care bundle (Turi and Von Ah, 2013).

The implementation of a care bundle follows a strategy and is based on evidence. In a systematic review of 47 studies of the implementation of 49 care bundles within ICU settings, Borgert *et al*. (2015) categorise the main implementation strategies as education, reminders and audit/feedback. Education, in its various formats of education materials, meetings, visits

and others, comprised about 88% of the implementation strategies and was reported in studies of 43 bundles (Borgert *et al*., 2015). Reminders were reported for 71% of bundles, but only one of these was a sepsis bundle. The third main implementation strategy, audit and feedback, was reported in studies of 31 bundles. Focusing on studies of sepsis care bundle implementation, education was the most commonly reported strategy, in 89% of the studies (8/9), followed in four studies by mass media, including the use of posters (Borgert *et al*., 2015). It is notable that the audit and feedback strategy was not reported to have been used in the setting of maternity wards. A study in England reports that the SSCB has been evaluated prior to its implementation in three hospital settings: accident and emergency departments, renal units and medical departments (Steinmo *et al*., 2015). No formal evaluation of auditing and feedback has been conducted with respect to SSCB implementation in maternity wards. This questions the applicability and feasibility of implementing the care bundle in these settings.

There is a need for comprehensive management of the use of antibiotics and for urgent work towards effective antimicrobial stewardship. Effort should be concentrated on optimising the so-called 4 Ds of drug, dose, de-escalation and duration (Pulia *et al*., 2017). Very limited literature has been published on the role of midwives in AMS. An online survey of acute care hospitals in Los Angeles County found limited involvement of bedside nurses in AMS. Instead, it was expected that antibiotic orders and administration of therapy would be commenced by nurse practitioners (Cadavid *et al*., 2017). The authors identify potential for improving AMS by having nurses question antibiotic orders before acting on them. It is fundamentally important to target these groups of practitioners for education and awareness to ensure a full understanding of the concepts and their roles (Cadavid *et al*., 2017). Both nurses and midwives are in a position to have a good impact on antimicrobial stewardship if the required education and awareness are delivered. Their position as a communication hub between patients and physicians, when used efficiently, should empower the concept of AMS (Cadavid *et al*., 2017). It was noticed in the present study that

midwives had a limited role in deciding on antibiotic prescription and de-escalation, with some participants relying on the decisions of medical staff or following their orders without questioning them. The roles of midwives and nurses put them in very close contact with patients. This active role is ideal for evaluating antibiotic therapy based on the patient's condition and clinical situation (Manning *et al*., 2016). In the present study, labour ward midwives who had long experience were able to develop a positive role in the de-escalation to oral therapy and antibiotic escalation when required. Through this close contact with patients, they would present the case to the medical staff in the ward round, emphasising that a patient's vital signs were now stable, that laboratory values were starting to fall and that the patient's condition was improving. This basic communication could trigger the IV-to-oral switch. Such experienced midwives would also contact medical staff when blood culture results were available, with sensitivity and resistance patterns, to aid in the decision of changing the antibiotic to whatever the pathogen was sensitive to. This indicates that both length of experience and confidence to take decisions are fundamental and should be enhanced in this group of practitioners. This could be achieved by rotating midwives between wards, which would allow postnatal/antenatal midwives to work in triage and labour wards, to gain broader experience in dealing with these groups of patients. Confidence could be built by allowing them to make decisions under supervision at first, which is ideal in labour and triage wards, then with continuity they would gain more confidence and would be able to take decisions alone in communicating with the medical staff.

"Nurses [and midwives] are antibiotic first responders, central communicators, coordinators of care, as well as 24-hour monitors of patient status, safety and response to antibiotic therapy" (Olans *et al*., 2016). There is a reported need to enhance nurses' awareness and knowledge of AMS (Monsees *et al*., 2017).There are limited publications on AMS involving midwives and nurses, according to an evaluation of work appearing in specialised journals, which identified only 11 such studies published in nursing journals, in contrast to 900 in medical, microbiology and pharmacy journals (Monsees *et al*., 2017). Midwives' roles in AMS

have been reported in only one journal (Charani *et al*., 2013), while one report has been published by the Scottish Antimicrobial Prescribing Group and NHS Education for Scotland (SAPG and NHS Education, 2014). There is a fundamental and traditional reliance on infectious disease physicians or pharmacists to drive AMS. But these professionals have limited involvement in many wards and settings including long-term caring facilities and community settings. Therefore, it has become necessary to provide nurses and midwives with education to enhance their knowledge of AMS (Monsees *et al*., 2017).

In a study of antimicrobial prescribing, Charani and colleagues interviewed a number of healthcare providers, only one of whom was a midwife. They describe the "prescribing etiquette" as non-interference with the prescription decisions of colleagues, or with the noncompliance policy of the antibiotic prescription (Charani *et al*., 2013). Senior doctors believe in their own ability to judge their patients and in the complete appropriateness of their decisions on prescribing antibiotics for treatment or prophylactic options. They rely on their years of clinical experience and this will drive them to overrule policies, as reported by nurses throughout their regular practice when they notice that an action by these doctors does not adhere to the policies. Communication within the multidisciplinary team to discuss this policy will be ignored and will not reverse the doctors' actions and judgement (Charani *et al*., 2013). It is essential for the success of any AMS programme to involve the multidisciplinary team in this process (Olans *et al*., 2016). During the data collection, researcher NA noticed that medical staff changed antibiotics prescribed by colleagues when they felt that a prescription was not appropriate. In one case, a patient was escalated to IV therapy following a discussion with the microbiologist. It was felt that decisions to change prescriptions made by colleagues should be supported by a microbiologist or by guidelines when the changes were to antibiotic doses or route of adminstration.

Medical hierarchy has a negative impact on antibiotic de-escalation, according to a qualitative study which gathered data from medical staff using semi-structured interviews

(Broom *et al*., 2016a). Junior medical staff do not feel confident and comfortable in de-escalating IV antibiotics to the oral route. The absence of senior medical staff from the daily review delays the process of switching from IV to PO. Thus, unnecessarily prolonged IV therapy results from decisions being taken by senior doctors who are not present every day in the ward (Broom *et al*., 2016a). Another reason is a false belief among both patients and clinicians that IV antibiotics are more potent and effective than oral ones. Confidence in prescribing PO antibiotics may be achieved with experience, when the clinician observes that there have been no adverse outcomes from doing so (Broom *et al*., 2016a).

It is essential to obtain a culture before any dose of antibiotic is given to a patient. This has the potential to enhance the chance of identifying the pathogen (Rojo, 2006). There is a reported decrease in the yield taken from blood cultures when antibiotics are administered before obtaining a culture. This could result in inconclusive findings due to the absence of microbial growth following exposure to antibiotic treatment (Rojo, 2006). The administering of an antibiotic has the potential to restrict the growth of the colonised pathogen and reduce the ability to detect it in order to tailor the treatment pathway. The sepsis guidelines emphasise the fundamental need to obtain the culture before starting antibiotic therapy; then, while the specimen is being processed for pathogens, tests of sensitivity and resistance to the empiric antibiotics should be initiated (Rojo, 2006). Cultures have to be collected by medical staff and midwives are not allowed to do this, but as the present study observed, antibiotics are sometimes prescribed remotely, to allow the midwife to administer the first dose when medical staff are not able to be present in the ward. Thereafter, there is a strong reliance on medical review and any culture that is taken after the administration of antibiotic doses. This behaviour seriously challenges the process of managing sepsis and adds confusion to the management of the patient's situation.

A qualitative investigation was conducted to assess the reasons for not following microbiology advice on antibiotic choice. It has been reported that junior medical staff found

themselves caught between infectious disease (ID) specialists, clinical microbiologists (CM) and their superiors on the medical team (Broom *et al*., 2016b). Although ID or CM approval is required for some antibiotic treatments, the influence of senior medical staff is likely to outweigh other considerations and determine the treatment decision. Junior medical staff resort to communicating with mid-level doctors to contact senior medical staff regarding changes to prescriptions. Alternatively, to avoid conflict, they sometimes postpone a decision until a different consultant arrives in the ward (Broom *et al*., 2016b). One justification for ignoring microbiologists' advice is the claim that laboratory-based medicine is different from bedside medicine and that medical staff are more aware than microbiologists of what is the appropriate treatment for their patients. Decisions on antibiotic prescribing are reported to be driven by years of experience and skills development, rather than being based on clinical guidelines. These reported data show that medical practice was driven by the opinions of practitioners and that this determines the making of antibiotic decisions despite the availability of microbiology advice (Broom *et al*., 2016b). The present study found that microbiologists had a role in the choice of antibiotic and in deciding antibiotic de-escalation, and that their impact was noticeable in genuine cases of sepsis. During the period of about 48 hours while the culture was being analysed and the results awaited, a concern for follow-up and reporting to the medical staff was noticed by researcher NA, as it was documented in patients' medical notes. This included recommending therapy and advising on the pathogen detected.

A survey of 30 physicians in two American acute hospital settings found that antibiotic treatment was prescribed as a precaution, to avoid any undetected infection from being untreated. Precaution was the main reason for the overuse and prescribing of antibiotics in maternal sepsis, as the risk of deterioration and missing a timely opportunity to treat was always a concern. The absence of familiarisation with overnight patients drove the decision to prescribe antibiotics if a decline was observed in their condition, on the assumption that the daytime healthcare team would de-escalate treatment if no infection was found (Livorsi

et al., 2015). Physicians were motivated to overprescribe by fear of litigation for any delay in initiating antibiotic treatment. Participants were aware of the global problem of antibiotic resistance and recognised the need to reduce the use of broad spectrum antibiotics, but they also tried not to go too narrow and miss the chance of treating a potential infection. The stigma of missing an infection by delaying the prescribing of antibiotic therapy influenced physicians in their reluctance to decide not to treat, because they reported experiencing pressure in the form of criticism of a physician who did not prescribe antibiotics to a stable patient overnight, whereas no such stigma was reported when patients developed antibiotic resistance or *Clostridium difficile* infection from the overuse of antibiotics (Livorsi *et al*., 2015). The findings of this study confirm that antibiotic therapy was prescribed as a "precaution" to prevent patients from deteriorating. It was also found that the management of critically ill patients was challenging during night shifts because limited medical staff were present in the ward. Therefore, decisions and/or and follow-up would be postponed until the morning ward round. Participants were found to be very well aware of the existence of antimicrobial resistance, but since very few cases actually occur in the current setting, this problem is not very well understood. This poor understanding was demonstrated by participants' stated willingness to put every woman on IV antibiotic therapy if this would save one life. The potential risks of overusing antibiotics and the associated global risk of antimicrobial resistance must be more strongly emphasised by the current health board and among midwives and other healthcare practitioners.

Another study interviewed pharmacists and physicians participating in the AMSP to investigate the factors behind its implementation (Pakyz *et al*., 2014). It identified the importance of communication in the preauthorisation period, when the antibiotic prescription was passed to the antimicrobial team for approval. Findings suggest that the information was usually well communicated. The AMSP team including the pharmacist explained the recommendation very clearly. This was found to facilitate AMSP implementation, as the team acted as a facilitator of the service, not as an antibiotic police

force (Pakyz *et al*., 2014). The communication worked better when conducted face to face, although AMSP implementation was also positively affected by the use of newsletters to disseminate AMSP strategies and by being part of the P&T committee. Other factors reported to facilitate AMSP implementation were education, evidence-based practice and recommendations, real-time data and guideline implementation. While some participants also reported that the support of non-AMSP pharmacists enhanced implementation, one AMSP pharmacist disagreed, believing that such pharmacists can constitute a barrier and had been observed to offer resistance when a suggestion was provided. Thus, a non-AMSP pharmacist was seen as an "enemy on the team" (Pakyz *et al*., 2014). The literature indicates that efficient work within the AMS team is very promising and that enhancing collaboration with the antimicrobial team in maternity wards would have positive consequences. It has to be appreciated that the current practice lacks the presence of a clinical pharmacist at two sites and this has been found to be associated with a number of drug dosing problems and with a lack of pharmaceutical care plans, which would make the involvement of the antimicrobial team very valuable. Non-AMS pharmacists were also found to enhance the implementation of AMS concepts, as observed at the only site that had clinical pharmacists in its maternity wards. Although it is challenging for other reasons to identify sepsis and follow up these patients, this work is further complicated by the absence of pharmacists in these wards.

Various barriers to achieving effective communication within the multidisciplinary team have been reported. A qualitative analysis was conducted with medical and nursing students undergoing inter-professional communication skills sessions. The findings identified factors including lack of clarity and understanding, related to the level of confidence and experience (Keller *et al*., 2013). It is important to acknowledge that the study was part of an education session and that the subjects had no experience of real-life practice. The workload of individual professionals has the potential to influence the quality of their communication.

The setting of the ward and the hospital environment has also been shown to affect nurses' and physicians' communication negatively (Flicek, 2012).

Wu and colleagues evaluated smartphone communication between nurses and physicians in a mixed-method study, which found that nurses sent an average of 22.3 emails per day, while physicians reported reading 21.9 emails and sending 6.9 per day. Smartphones were found to be more efficient than pagers because their use eliminated the need for the nurse to be available when the doctor responded by telephone and because less time was wasted in trying to locate the physician (Wu *et al*., 2011). However, efficiency was reduced in cases where multiple emails passed between the parties, making the issue more complex when it could have been simplified by a voice call. Building relationships between professionals was also reported to be made more difficult by the integration of the technology into their patterns of communication. The need for an urgent response by the physician was not satisfied by the use of smartphone technology. Nurses reported unsatisfactory levels of response which led them to repeat requests, thus increasing their workload (Wu *et al*., 2011). While methods of communication were not evaluated in this study, it was understood from having to communicate with the clinical pharmacist (JG) and with personnel at other sites that healthcare professionals in this board use email for nonurgent communication, relying on pagers, face-to-face meetings and phone calls for clinically important communication.

The literature indicates that the use of electronic medical record (EMR) systems is intended to improve communication within hospitals, but a pre-post study found less frequent face-to-face communication between nurses and physicians, while communication with patients in the inpatient setting was hindered (Taylor *et al*., 2014a). There was also less agreement on the patient's plan of care following EMR implementation, related to a reduction in the quality of communication. Face-to-face communication was found to be preferable in that it enhanced the delivery of care, although the study did not explore the reasons for this. The use of computerised physician order entry (CPOE) was associated with a decrease in the

quality of communication among healthcare professionals, but it was found that this negative effect was resolved after 12 months of CPOE use (Taylor *et al*., 2014a). Throughout the period of data collection for this study, the patients' medical records were all on paper, so CPOE was not applicable. Since then, the maternity sites have introduced electronic medical records. This development was not investigated as part of this study, but it is assumed that the shift to electronic records will allow the development of a very rich database of medical records and will improve clinical studies and audit. It is understandable that as with any new technology there are some obstacles, which should not be allowed to hinder this change. The literature indicates the need for a period of 12 months to resolve negative effects on communication (Taylor *et al*., 2014a), but it might also be worth exploring the positive effects on the healthcare system of the introduction of EMRs. These are not intended to supersede traditional methods of communication among healthcare providers, but to replace paper medical notes, which could improve the documentation of patient care, for example by the inclusion of mandatory fields to avoid the omission of essential data. Further evaluation of both documentation and communication is worth exploring in future research.

4.5 Limitations

This study was limited to the experience of a single health board and possibly reflects the practice of healthcare professionals within this setting. A wider evaluation and assessment of different maternity units is worth exploring. This study also acknowledges a limitation in the recruitment process, as the participants in some wards were selected by senior staff. This element of selection by their superiors led some midwives to identify the researcher NA with the hospital administration and they were therefore reluctant to talk openly, apparently not wishing to be seen as speaking out against their colleagues. In most cases this was resolved within ten minutes, but it did affect the start of a few interviews. Finally, conducting the interviews in the ward setting constitutes another limitation, as each participant was taken from her ward and another midwife allocated to look after her patients while the interview took place.

4.6 Conclusion

This study has identified three main categories of barriers to implementing the SSCB in maternity wards and these are supported by the literature. The first was the absence of implementation strategies in the pre-implementation phase; the second was the difficulty of diagnosing sepsis, especially in the obstetric population, which results in patients being over-treated and the care bundle being commenced unnecessarily; and the third was the need for evaluation and feedback to identify all other barriers that affect the implementation and monitoring of the bundle, including the workload in maternity wards. It is recommended that the strategies for implementation of the SSCB be reviewed in light of the needs of the obstetric population and the physiological changes affecting these women. An audit should be conducted to evaluate the care of sepsis patients and to identify any opportunity for improvement. Finally, the availability of the care bundle should be ensured for all wards that are required to implement it and the stock should be updated whenever required.

There is a reported overuse of precautionary antibiotic therapy, as the practice is to continue to treat a woman with a full course even when her cultures are negative and all observations are stable. The AMSP team has at present a limited role in maternity and the participation of midwives in the process is limited. They largely believe that they are giving care to patients who are well and able to care for themselves, because they are treating many women for suspected rather than confirmed infections, limiting their ability to contribute to a successful AMSP in maternity wards. Steps should be taken to empower midwives to identify unnecessary therapy and the opportunity for antimicrobial de-escalation. The position of midwives in delivering direct care to patients and their awareness of patients' medical history and wellbeing give them the opportunity to make a valuable contribution to an AMSP. There is a limited literature on midwives' role in AMSPs, but it is very well appreciated that resources should be allocated to support a plan of AMSP implementation in maternity wards. This would be expected to have the desirable results of reducing unnecessary antibiotic therapy and enhancing antibiotic de- escalation, for example through the activation of review

and communication with microbiologists that would drive IV-to-oral switching, de-escalation to a narrow-spectrum agent or antibiotic cessation.

Effective communication within the multidisciplinary team is fundamental and cannot occur in the absence of standardised documentation and communication modules. The initiation of communication should follow a clear pathway, with collaboration among the team of healthcare providers to triage the urgency of patients' needs. In addition, a standardised documentation of patient care would deliver better care following patient transfer from one ward to another within the hospital. A communication map to facilitate both documentation, i.e. written communication methods, and agreement within the team would facilitate the delivery of better care and enhance the outcome of patients who experience sepsis in maternity wards. The SBAR approach to communication started within the maternity wards but was not widely integrated into every aspect of patient communication. If this were developed further and expanded to form a standardized approach to communication, promising patient outcomes should be achieved.

5 Chapter 5: General Discussion

5.1 Future work and further explanation of some methodologies

The evaluation of current clinical practice is a methodological challenge; therefore, a baseline assessment to understand what was happening within maternity practice was conducted, as reported in Chapters 2 and 3, followed by a further qualitative evaluation (Chapter 4). Those findings indicate a lack of sufficient antimicrobial stewardship strategy within the maternity units under investigation. This was mainly because sepsis diagnosis was extremely challenging, which adds to the complexity of its management, particularly in women in labour, where local hospital guidelines have weak indices to identify sepsis. Furthermore, the SIRS parameters have not been modified to accommodate the physiological changes associated with labour. It was also found that the use of the Sepsis Six care bundle sticker is limited and that the initiation of some antibiotic therapy seems to be common in women who have not been commenced on the SSCB. The qualitative investigation identified the absence of implementation strategies in the pre-implementation phase of the SSCB. This includes the absence of formal education and pre-evaluation of the bundle in the maternity population prior to its use.

5.1.1 Quality improvement

The publication in 1999 of a report by the US Institute of Medicine on medical errors, entitled *To Err is Human*, initiated debate about the quality of care in health settings. Since then, quality management has increasingly been seen as an essential strategy in healthcare (Khoury and Amin, 2017). Quality improvement (QI) has been defined as "the combined and unceasing efforts of healthcare professionals, patients and their families, researchers, payers, planners and educators – to make the changes that will lead to better patient outcome (health), better system performance (care) and better professional development" (Batalden and Davidoff, 2007). Among the numerous methodologies of QI are Plan-Do-Study-

Act (PDSA), Six Sigma, Lean, Model for Improvement, root cause analysis and process mapping (Khoury and Amin, 2017; Fereday, 2015).

PDSA, also called plan-do-check-act or the Deming circle (Khoury and Amin, 2017), is one of twelve quality improvement methodologies which aims to test potential improvement on a small scale before wider implementation, by means of a cycle of activities designed to ensure the safety and efficacy of the quality improvement (Fereday, 2015). This approach is associated with a significant improvement in patient outcome (Taylor *et al*., 2014b) and allows improvement to occur in a continuous cycle, by the identification and implementation of the required processes (Khoury and Amin, 2017). The first stage, "plan", involves the identification of the improvement targeted by the changes. Followed by "do", which means testing the changes by applying them on a small scale. Next, the "study" stage assesses and evaluates the efficacy of the changes that have been implemented, then at the "act" stage the changes are adopted more widely if assessed as successful; if not, then further evaluation is needed, so a new cycle is initiated (Taylor *et al*., 2014b).

These four steps constitute an experimental process whereby a hypothesis is formed and tested. Its application on a small scale provides flexibility and in the healthcare context allows lessons to be learned and acted upon with a minimum of risk exposure for patients and a minimum use of resources, while providing sound evidence to drive the necessary change (Taylor *et al*., 2014b). The cycle is repeated until the desired outcome is achieved; to determine when this has occurred, the use of 'run charts' is recommended at the study stage (Khoury and Amin, 2017). A run chart is a method of displaying data graphically by plotting the data points of the outcome over a period of time. Alternatively, control charts draw attention to the average values and to any variation in the process. Although control charts still serve to evaluate the outcome of the process over time, their secondary focus is to draw further attention to variation (Khoury and Amin, 2017).

Six Sigma focuses on reducing the variation within processes, which explains the use of control charts in displaying the data (Khoury and Amin, 2017). This method when applied in was found to be successful in reducing *MRSA* infection by 51% in a period of 12 months and reducing discharge time in a tertiary hospitals of 386 beds in Beirut, Lebanon from 2.2 to 1.7 hours over a period of 10 months (El-Eid *et al*., 2015; Khoury and Amin, 2017). Lean methodology aims to reduce waste and enhance efficiency in healthcare. It has proved successful in improving the overall A&E triage waiting time and the subgroup triage categories (Kelly *et al*., 2007; Khoury and Amin, 2017). Lean methodology uses process mapping to identify inefficiencies in healthcare and to improve the quality of care (Fereday, 2015).

The 'model for improvement' approach consists of two phases, as shown in Figure 5-1. The first is to identify the required changes and define the measures of improvement by asking three questions, which are: "What we are trying to accomplish?", "How will we know that a change is an improvement?" and "What changes can we make that will result in improvement?" The second phase is the PDSA cycle as described above (Fereday, 2015).

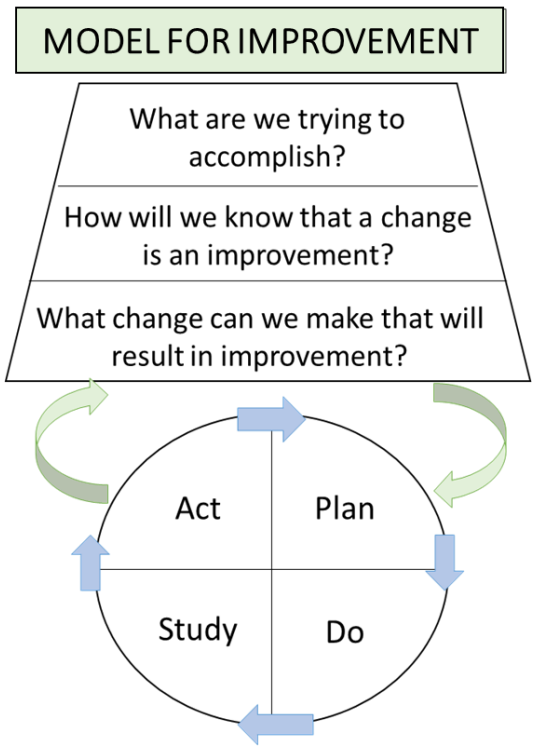

Figure 5-1: The model for improvement method of quality improvement

5.1.2 Clinical practice guidelines

There has been a rapid increase in the number of clinical practice guidelines (CPGs) being produced in the last three decades. CPGs are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances" (Alonso-Coello *et al*., 2010). Their use is an evidence-based approach that aims to bridge the gap between research and practice; the evidence should be of high quality to enhance patient outcomes (Alonso-Coello *et al*., 2010). CPGs provide standardized treatment plans for patients with specific clinical conditions and help healthcare providers to identify best practice by following the evidence-based recommendations arising from the guidelines (Jun *et al*., 2016). The process of developing a CPG begins with a systematic review of the available literature, then an analysis of the findings, highlighting possible risks and benefits associated with the recommended treatment (Jun *et al*., 2016). There is evidence that CPGs improve the quality of care, minimize variation in practice and enhance health outcomes for patients (Kissoon, 2014). Recognising the fundamental need to appraise all CPGs, researchers in 13 countries collaborated to design the Appraisal Guidelines for Research and Evaluation (AGREE) to evaluate guideline quality. Since its development, validation and publication in 2003, the AGREE instrument has been translated into many languages, used widely and given formal endorsement by the WHO (Alonso-Coello *et al*., 2010). A systematic review using the AGREE tool to evaluate 626 CPGs published in 42 articles between 1980 and 2007 found that most achieved only moderate or low AGREE scores. The authors of the review recommend that to enhance the quality of CPGs, their developers should invest in stronger methodology to develop those guidelines (Alonso-Coello *et al*., 2010).

A second problem identified as affecting CPGs is poor adherence to their use: an evaluation found that only 24% of the guidelines were followed in ICU settings, while even the relatively simple hand hygiene guidelines achieved only 40% adherence (Jun *et al*., 2016). The close

contact of patients with nurses or midwives gives these professionals an advantage in using the CPGs in their settings (Jun *et al*., 2016). Sepsis guidelines emphasise early diagnosis and aggressive treatment (Kissoon, 2014). Despite agreement on the impact of their implementation, there are some reported barriers to adherence to these guidelines, including the difficulty of recognising sepsis as a disease, poor awareness of local sepsis guidelines and the fact that physicians may disagree with the CPG recommendations. Furthermore, it may be difficult to implement guidelines that recommend laboratory tests or other types of monitoring when the necessary resources are unavailable (Kissoon, 2015). The result is that adherence to sepsis guidelines is reported to be poor, amounting to only 24-52% for the resuscitation bundle and as little as 10-25% for the management bundle (Kissoon, 2014). Healthcare practitioners' behaviour and uncertainty about the evidence-based guidelines also limit the influence of CPGs on sepsis practice (Kissoon, 2015). Finally, environmental factors such as limited resources and time may affect the adoption of sepsis guidelines (Kissoon, 2014).

5.1.3 Behaviour Change Wheel

The process of changing people's behaviour requires an understanding of the factors influencing them to behave as they do. This is fundamental when implementing a change in practice or introducing a new practice, because successful implementation will depend on modifying the behaviour of practitioners to accommodate the desired changes (Atkins *et al*., 2017). This applies to the implementation of evidence-based practice in the healthcare domain, where behaviour change interventions (BCIs) are essential to drive effectiveness in practice. BCIs are defined as "coordinated sets of activities designed to change specified behaviour patterns" (Michie *et al*., 2011). NICE guidelines and Cochrane reviews provide the evidence base necessary for the implementation of best practice in healthcare settings. Interventions may be ineffective without such evidence (Michie *et al*., 2011). The translation of scientific and technological research into practice, if not considered carefully, has the

potential to impact healthcare outcomes negatively. It is essential to enhance this translation process through the management of behaviour change, which will allow policy to be developed and interventions to be designed on a solid base of practicality (Michie *et al*., 2011). The COM-B behaviour system developed by Michie *et al*. has three main components apart from behaviour itself. These are Capability, Opportunity and Motivation all influence behaviour; both opportunity and capability influence motivation; and behaviours can change capability, opportunity and motivation (Michie *et al*., 2011).

Capability is defined as *"the individual's psychological and physical capacity to engage in the activity concerned"*; opportunity is "*all the factors that lie outside the individual that make the behaviour possible or prompt it*" and motivation is "*all those brain processes that energise and direct behaviours, not just goals and conscious decision-making*" (Michie *et al*., 2011). These three components of the COM-B system can be subdivided into six as follows: capability can be either physical or psychological, opportunities are physical (environmental) and social (cultural), and motivation comprises both reflective and automatic processes. Based on this information, there are nine intervention functions and seven policy categories, as listed in Table 5.1 (Michie *et al*., 2011).

Table 5.1: Definitions of interventions & policies in the behaviour change wheel

Intervention	Definition
Education	Increasing knowledge or understanding
Persuasion	Using communication to induce positive or negative feelings or stimulate action
Incentivisation	Creating expectation of reward
Coercion	Creating expectation of punishment or cost
Training	Imparting skills
Restriction	Using rules to reduce the opportunity to engage in the target behaviour (or to increase the target behaviour by reducing the opportunity to engage in competing behaviours)
Environmental restructuring	Changing the physical or social context
Modelling	Providing an example for people to aspire to or imitate
Enablement	Increasing means/reducing barriers to increase capability or opportunity

Policies	Definition
Communication/marketing	Using print, electronic, telephonic or broadcast media
Guidelines	Creating documents that recommend or mandate practice. This includes all changes to service provision
Fiscal	Using the tax system to reduce or increase the financial cost
Regulation	Establishing rules or principles of behaviour or practice
Legislation	Making or changing laws
Environmental/ social planning	Designing and/or controlling the physical or social environment
Service provision	Delivering a service

5.1.4 Theoretical Domains Framework

The theoretical domains framework (TDF) was initially integrated into implementation research to determine the factors that influence healthcare behaviour when evidence-based recommendations are implemented. TDF acts as a theoretical lens through which to examine the environmental, cognitive, affective and social influences on behaviour (Atkins *et al*., 2017). It was validated by an independent group of behaviour experts, whose work produced TDF (v2), a framework of 14 domains covering 84 theoretical constructs (Atkins *et al*., 2017). Table 5.2 gives the definitions of the 14 domains and lists their respective constructs. The domains are: knowledge, skills, social/professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory attention and decision processes, environmental context and resources, social influences, emotions and behavioural regulation.

Table 5.2: Definitions and constructs of the 14 domains of the TDF

Domain name	Definition	Constructs
Knowledge	An awareness of the existence of something	Knowledge (including knowledge of condition/scientific rationale) Procedural knowledge Knowledge of task environment
Skills	An ability or proficiency acquired through practice	Skills Skills development Competence Ability Interpersonal skills Practice Skill assessment
Social/ professional role and identity	A coherent set of behaviours and personal qualities displayed by an individual in a social or work setting	Professional identity Professional role Social identity Identity Professional boundaries Professional confidence Group identity Leadership Organisational commitment
Beliefs about capabilities	Acceptance of the truth, reality or validity of an ability, talent or facility that a person can put to constructive use	Self-confidence Perceived competence Self-efficacy Perceived behavioural control Beliefs Self-esteem Empowerment Professional confidence
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Optimism Pessimism Unrealistic optimism Identity
Beliefs about consequences	Acceptance of the truth, reality, or validity of outcomes of a behaviour in a given situation	Beliefs Outcome expectancies Characteristics of outcome expectancies Anticipated regret Consequents
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Rewards (proximal/distal, valued/not valued, probable/improbable) Incentives Punishment Consequents Reinforcement Contingencies Sanctions
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way	Stability of intentions Stages of change model Trans-theoretical model and stages of change

Domain name	Definition	Constructs
Goals	Mental representations of outcomes or end states that an individual wants to achieve	Goals (distal/proximal) Goal priority Goal/target setting Goals (autonomous/controlled) Action planning Implementation intention
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives	Memory Attention Attention control Decision making Cognitive overload/tiredness
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour	Environmental stressors Resources/material resources Organisational culture/climate Salient events/critical incidents Person × environment interaction Barriers and facilitators
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours	Social pressure Social norms Group conformity Social comparisons Group norms Social support Power Intergroup conflict Alienation Group identity Modelling
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	Fear Anxiety Affect Stress Depression Positive/negative affect Burn-out
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions	Self-monitoring Breaking habit Action planning

Source: adapted from (Atkins et al., 2017).

An initiative to match the COM-B system to the 14 domains of the TDF found that the TDF would fit very well within the BCW (Cane *et al*., 2012), as illustrated in Figure 5-2. This has

been validated and certain TDF domains were matched to the COM-B system as presented in Table 5.3 (Cane *et al*., 2012).

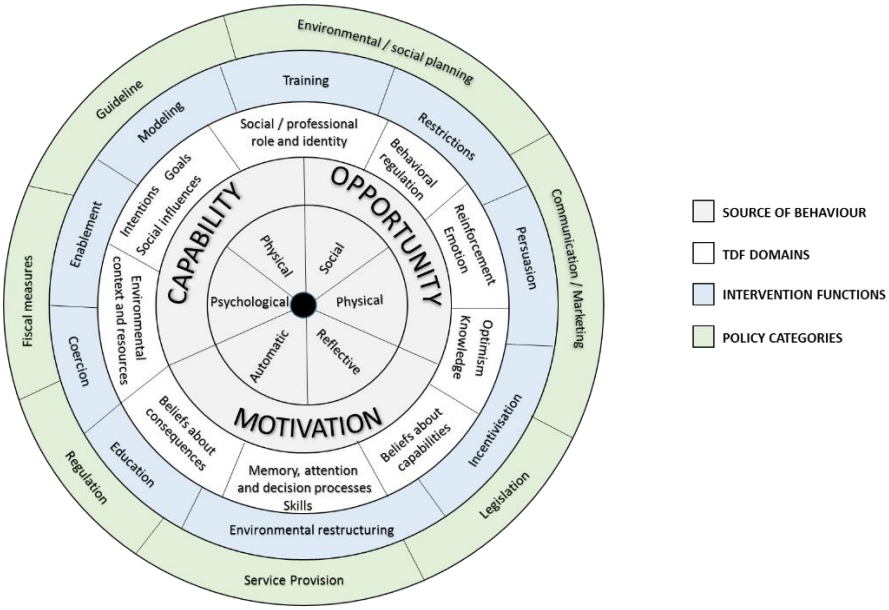

Figure 5-2: The behaviour change wheel and the theoretical domains frameworks

Table 5.3: The mapping of the TDF domains to the COM-B system

COM-B component		**TDF domain**
Capability	Psychological	Knowledge Skills Memory, attention and decision processes Behavioural regulation
	Physical	Skills
Opportunity	Social	Social influence
	Physical	Environmental context and resources
Motivation	Reflective	Social/professional role & identity Beliefs about capabilities Optimism Beliefs about consequences Intentions Goals
	Automatic	Social/professional role & identity Optimism Reinforcement Emotion

5.1.5 Recommendations

The recommendations for changes are divided into two parts, concerning the SSCB sticker and aspects of communication to enhance antimicrobial stewardship. First, the SSCB should be redesigned to emphasise the triggers for sepsis and to highlight “suspected sepsis” as a main aspect of diagnosis, rather than limiting it to two abnormal SIRS criteria. The Sepsis Six care bundle would still have the same six elements, but prior to the introduction of the new bundle it is recommended that an implementation approach be decided. This could be achieved by educating all maternity staff to enhance awareness, by distributing posters and leaflets, by providing continuous updates and by facilitating the discussion of different cases of sepsis. The present study found that in one maternity unit where the senior midwife was involved in the implementation of the SSCB, the staff were very well educated and aware of this care bundle; therefore their practice (assessed both qualitatively and quantitatively) reflected better adoption and understanding of the SSCB and the management of sepsis compared to the other two settings. In the healthcare environment, learning from practices in similar settings should be better accepted, compared to applying evidence-based practices from the literature. As all three sites are within one health board it would be worth sharing any successful experience with other settings. The supply of stickers was found to be an issue, as these were not available in a number of wards. It was therefore intended to recommend ensuring a continuous supply of stickers to all wards, but this is no longer applicable, as electronic medical records are now in place.

As for antibiotic prescriptions, a review should be considered after 48 hours to decide whether therapy is still required or if cessation of therapy is most appropriate. Midwives should be encouraged to question the justification for having patients on antibiotics and establishing a discussion at ward and unit handovers. Following this, it is recommended that the TDF and BCW tools be used to design interventions to improve the adoption of both the SSCB and antimicrobial stewardship in maternity wards.

5.2 Conclusion

At the starting point of this work, there were many gaps in knowledge of the process of managing sepsis in maternity wards. The picture was complicated by recent changes in the definition of sepsis worldwide and in the application or adoption of sepsis management practices in maternity settings. The adoption of the SSCB by the NHSGGC health board, a year before the start of this PhD work, was the trigger for observing how this care bundle had been integrated into the board's practice. A further motivation for the study was the concern of a specialised clinical pharmacist (JG) that the introduction of the bundle had led to many women being commenced on the associated protocol, with consequences for a large number of babies. As explained in Chapter 2, these consequences are the associated risk of antimicrobial resistance and the development of other complications for babies later in childhood.

A review of the literature revealed limitations in the number and quality of publications that addressed the adoption of the SSCB in obstetric settings. There was, however, a measure of agreement in the literature that the individual components of the bundle had been poorly implemented in UK maternity wards. This review prompted the design and test of a data collection form to evaluate the use of the SSCB and management of sepsis in NHSGGC maternity wards. The pilot study (limited to PRM, as explained in Chapter 2) found that the SSCB sticker had not been used for every woman who had been treated for sepsis and for whom the Sepsis Six protocol had been commenced. It was clear at that stage that "Sepsis Six protocol" was a written diagnosis or instruction in a woman's medical notes which served to justify the prescribing of antibiotic therapy and the associated blood tests, rather than necessarily indicating the delivery of all six of the elements of care within the bundle.

It was then deemed necessary to slightly extend the range of observational data collected, to include the results of all laboratory investigations conducted during each woman's admission, all of the MEOWS observations until the patient was stabilized, all of the

antibiotics prescribed to inpatients and in IDLs, microbiology reports on pathogens and their sensitivity and/or resistance, and others detailed in Chapter 2. Some of these data that were collected have not been used in this PhD study and were of no value in establishing the findings, but this flexibility allowed me to gather other data that I was later able to relate to the application of the SSCB protocol. As these data were not based on hospital standards or protocols that healthcare providers should follow, the results were neither comparable nor subject to judgement; the sole aim was to observe what occurred throughout the treatment journey of women with sepsis, from diagnosis to discharge.

I found that 3% of women in maternity wards received antibiotic treatment for suspected sepsis. This was a higher rate than those reported in the published literature, which referred to confirmed diagnoses based on culture results. When assessing justification, I found that in only 14 cases (15.7%) was there a positive blood culture result. If I had considered only these cases, the findings would have been of much less value, because they would merely have confirmed the findings reported in the literature, without adding to knowledge concerning the use of antibiotics in those with negative culture results and suspected sepsis. Being a pharmacist by background and appreciating the concept of antimicrobial stewardship allowed me to look at the adoption of the Sepsis Six protocol from a unique angle. The observation that practitioners had complied with the SSCB sticker in only a third of the cases prompted an exploratory study of the reasons for such a poor level of compliance, using the qualitative approach set out in Chapter 4. On the other hand, healthcare providers' attitudes and behaviour in antibiotic prescription following a non-sepsis diagnosis indicated an overall good standard of practice, as explained in Chapter 3.

The difficulty of diagnosing sepsis, because of the lack of a test of sufficient specificity and sensitivity on which to base such a diagnosis at the point when sepsis is suspected, is a matter of great concern. Physical assessment in cases of UTI or SSI is relatively straightforward, relying on pain, redness, tenderness or draining, while in sepsis-related systemic

inflammation, the signs and symptoms are non-specific. This presents substantial challenges for practitioners, who will require considerable medical experience and access to patient history before deciding to commence a patient on antibiotic therapy.

One suggestion, discussed in Chapter 2, is that rather than relying on any single parameter, a number of indices should be used in combination to aid the diagnosis of sepsis. Alternatively, three recommendations can be made to mitigate the difficulty of diagnosis and to help in limiting the overuse in maternity wards of antibiotics for suspected sepsis, taking account of the available resources and protocols currently in force in the health board. First, a diagnosis of sepsis should be confirmed by a senior member of the medical staff before any care is delivered. Second, a woman who is septic should not be treated with IV antibiotics in postnatal/antenatal ward setting and should be transferred to these wards only if her vital signs are stable and if she is on oral antibiotics. Third, blood culture results should be communicated promptly, with negative results being returned within 24 hours, which would allow further assessment of the patient by senior medical staff, thus minimizing the prolongation of unnecessary antibiotic therapy. If sepsis is suspected during labour, requiring the baby to be commenced on antibiotic therapy, then it is recommended that the baby's vital signs be monitored by the use of the NEWS chart and that relevant blood test and culture results be obtained before antibiotics are used in response to a suspicion of sepsis in the mother based on a single risk factor.

The advantage of following the observational arm of the study by qualitative interviews was that it facilitated the understanding of healthcare providers' behaviours and beliefs, thus helping to explain why certain observed events had occurred. The available literature focuses on the behaviour change wheel and the use of the TDF to improve the adoption of the SSCB. It considers cases where the SSCB sticker is available rather than those where treatment has been commenced. It does not address the introduction of the SSCB to maternity wards, but one explanation of compliance failure has always been poor education. Therefore, when

designing the interview questions I focused on the need to listen to midwives and to elicit in-depth accounts of their thoughts and beliefs, rather than asking them to explain why they had failed to comply with the protocol. This required an in-depth interview design where I would use a set of bullet points to guide me as researcher in keeping to the topic of interest, while allowing each interviewee to determine the precise direction that the interview would take.

The data reveal that the implementation of the SSCB sticker was empowered within HDU and ITU settings, but not completely integrated within postnatal and antenatal wards. The initiation of sepsis management occurred mostly at ward level, after which the patient would either be transferred to a higher care setting (i.e. HDU or ITU) or remain in the ward. The fact that midwives rotate among the different wards emphasises the need for training of postnatal/antenatal midwives, as this will mean that those who have been trained will use the knowledge acquired on how to treat septic women in the HDU or other high-risk settings. This will allow the hospital to have a large number of well-trained midwives who can be transferred to any ward as required. In addition, since adoption of the SSCB protocol was based on its use in adult medical, A&E and renal units, without evaluation in the maternity population prior to its implementation, it was helpful to have done this briefly as part of the interview study.

Since suspected sepsis could be just a non-life threatening infection or abnormal physiological functions following childbirth, oxygen and a catheter may seem unnecessary for those patients. It was noticed that these two elements of care were the subject of most discussion about the applicability of the bundle. Referring to the pathophysiology of sepsis explained in Chapter 1, organ failure including respiratory distress and acute renal failure could develop from sepsis in cases of severe sepsis and septic shock. Therefore, patients who had been treated with an antibiotic but not commenced on the whole SSCB protocol probably had an infection or some physiological changes and were not septic. Communication within

the MDT is very important to enhance sepsis management and empower antimicrobial stewardship. The diagnosis of sepsis is very challenging; therefore, many patients will be commenced on antibiotic therapy until all clinical values and relevant assessment are available to inform a definitive judgment. Between 24 and 48 hours, microbiologists will be analysing the culture, midwives will be monitoring vital signs and withdrawing blood samples for routine monitoring (including CRP and WCC) and physicians will assess the physical condition of the patients. At this point, a review of the initial diagnosis is necessary to minimize unnecessary treatment and allocate the required resources to sepsis patients.

A degree of confusion was observed in this study when some patients received the whole Sepsis Six bundle while others were commenced on some elements only. This confusion arose from the difficulty of diagnosis and the reluctance to reverse a positive diagnosis when there was evidence for doing so. Resolving this will be possible only if the whole team works together with the support of the leads and directors to drive the assessment and management of sepsis to different stages of post diagnosis in order to initiate the decision to undo the diagnosis or to continue with the sepsis management protocol.

This study has provided evidence in favour of the new definition of sepsis as sepsis-related organ failure requiring attention and medical care. If this concept were adopted in maternity wards it would make more sense to treat women at risk of organ failure with the complete SSCB protocol, providing support to the respiratory and urinary tract systems, meaning that these women would require close monitoring and should not be treated on a normal ward setting but in an HDU or ITU until stabilized. Conversely, cases treated in the ward setting would be those not requiring the SSCB protocol, which could be treated as infections rather than sepsis, requiring no catheterization or oxygen supply. This would reduce both the exposure of babies to antibiotics and the amount of unnecessary care delivered as part of the SSCB. If this policy were adopted, antibiotics could be used at a similar rate as was observed in the work described in Chapter 2, but as reported in Chapter 4, midwives tended

to see sepsis as “a big thing”, driving them towards overuse of antibiotics in an attempt to err on the side of caution to be ‘safe’. This is a behavioural issue; simplifying the diagnosis of sepsis to base it only on two abnormal SIRS criteria will cause far too many women to be commenced on the protocol in the false belief that this is necessary to prevent or treat sepsis.

To summarise the findings of this thesis, it is acknowledged that the diagnosis of sepsis in maternity patients is very challenging. The prescribing of antibiotics at the point of suspecting sepsis is not a matter of choice; indeed, the findings support the initiation of antibiotic therapy in women with suspected sepsis within an hour of diagnosis. This would be followed by a senior member of the medial team confirming the diagnosis within 24 to 48 hours of initiation of therapy and this decision would be supported by active communication with a microbiologist and by the clinical observations reported by midwives and made by medical staff during ward rounds. Where the secondary diagnosis (24 to 48 hours after the initial one) reveals that a patient is septic, then it is deemed unnecessary to activate the whole Sepsis Six bundle, as parts of the care bundle have already been delivered (i.e. antibiotic and blood test), but if transfer to an HDU or ITU was considered, then oxygen, IV fluid and catheter if needed will be commenced, while those with a secondary diagnosis of infection will remain on the postnatal or antenatal ward until stabilised, then be discharged. Finally, if the patient is found to have neither an infection nor sepsis, then cessation of antibiotic therapy is fundamental.

These conclusions were not discussed during the interviews with medical staff or microbiologists, nor have they emerged from them, which is one of the limitations of this study. It is therefore recommended that a focus group including senior medical staff, microbiologists and midwives be convened to examine and assess their views on the validity and applicability of these proposals. Furthermore, strong collaboration and agreement within the team is fundamental to carry this research forward.

Another limitation is that data on the SSCB were collected and analysed only in respect of those patients who had the sticker. It would have been better to extend collection of data on the SSCB to those who did not have the sticker. The narrow scope of the study and the limited time available at the point of data collection made it difficult to do this, but if the dataset had been broadened in this way, it would perhaps have enriched the discussion and thereby produced some explanation of the practice in the absence of the sticker. This is quite important, as electronic medical records have been in use since November 2017 and the sticker is no longer an option. The integration of the bundle within the electronic system has not been studied and this should be investigated as a priority if a further audit of the SSCB is considered.

The findings of this study, including my experiences and recommendations, will be shared with the staff of NHSGGC maternity wards and I trust that improved collaboration within multidisciplinary teams will lead to improvements in practice. The action meeting I attended showed evidence of a willingness to improve practice and the only limitation that I have identified is the need for adequate resources of time and people in order to evaluate, observe and audit practice in the wards. Therefore, collaboration between researchers at the university and healthcare providers on the wards is required to resolve this issue and to ensure that the process runs more smoothly. The next step would be to share the findings within the wider population of maternity units across the UK and research papers are being written for submission to relevant specialist journals to assist in the dissemination of the research findings. There is the potential for considerable benefits, whether the application of the recommendations to different settings has some negative outcomes, which would encourage more quality improvement, or whether the outcomes are positive, allowing the proposed reforms to be extended worldwide, or perhaps a mix of both.

6 References

ACOSTA, C. D., KNIGHT, M., LEE, H. C., KURINCZUK, J. J., GOULD, J. B. & LYNDON, A. 2013. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PloS one, 8, e67175.

ACOSTA, C. D., KURINCZUK, J. J., LUCAS, D. N., TUFFNELL, D. J., SELLERS, S., KNIGHT, M. & ON BEHALF OF THE UNITED KINGDOM OBSTETRIC SURVEILLANCE, S. 2014. Severe Maternal Sepsis in the UK, 2011–2012: A National Case-Control Study. PLoS Medicine, 11, e1001672.

ACOSTA, C., BHATTACHARYA, S., TUFFNELL, D., KURINCZUK, J. & KNIGHT, M. 2012. Maternal sepsis: a Scottish population-based case–control study. BJOG: An International Journal of Obstetrics & Gynaecology, 119, 474-483.

AGGARWAL, R., DEUTSCH, L., HARRISON, S., STAPLETON, C., STANLEY, S. & WRIGHT, A. 2015. 'sepsis six'-adaptation of a trust innovation in maternity. BJOG: An International Journal of Obstetrics and Gynaecology, 122, 233.

ALBRIGHT, C. M., ALI, T. N., LOPES, V., ROUSE, D. J. & ANDERSON, B. L. 2014. The Sepsis in Obstetrics Score: a model to identify risk of morbidity from sepsis in pregnancy. American journal of obstetrics and gynecology, 211, 39. e1-39. e8.

ALONSO-COELLO, P., IRFAN, A., SOLÀ, I., GICH, I., DELGADO-NOGUERA, M., RIGAU, D., TORT, S., BONFILL, X., BURGERS, J. & SCHUNEMANN, H. 2010. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Quality & Safety in Health Care, 19, e58-e58.

ALTMAN, D. G. 1990. Practical statistics for medical research, CRC press.

ARULKUMARAN, N. & SINGER, M. 2013. Puerperal sepsis. Best Practice & Research Clinical Obstetrics & Gynaecology, 27, 893-902.

ATKINS, L., FRANCIS, J., ISLAM, R., O'CONNOR, D., PATEY, A., IVERS, N., FOY, R., DUNCAN, E. M., COLQUHOUN, H. & GRIMSHAW, J. M. 2017. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implementation Science, 12, 77.

BAMFO, J. E. 2013. Managing the risks of sepsis in pregnancy. Best practice & research Clinical obstetrics & gynaecology, 27, 583-595.

BANFIELD, P. & SISTER, C. R. I. P. 2015. The early detection of maternal deterioration in pregnancy. The health foundation inspiring improvement [online]. Available: http://patientsafety.health.org.uk/sites/default/files/resources/4.early_detection_of_maternal_deterioration_1_.pdf [Accessed 29.03.2018].

BARCAITE, E., BARTUSEVICIUS, A., TAMELIENE, R., MALECKIENE, L., VITKAUSKIENE, A. & NADISAUSKIENE, R. 2012. Group B streptococcus and Escherichia coli colonization in pregnant women and neonates in Lithuania. International Journal of Gynecology & Obstetrics, 117**,** 69-73.

BARLAM, T. F., COSGROVE, S. E., ABBO, L. M., MACDOUGALL, C., SCHUETZ, A. N., SEPTIMUS, E. J., SRINIVASAN, A., DELLIT, T. H., FALCK-YTTER, Y. T. & FISHMAN, N. O. 2016. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clinical Infectious Diseases, 62, e51-e77.

BAROCHIA, A. V., CUI, X., VITBERG, D., SUFFREDINI, A. F., O'GRADY, N. P., BANKS, S. M., MINNECI, P., KERN, S. J., DANNER, R. L. & NATANSON, C. 2010. Bundled care for septic shock: an analysis of clinical trials. Critical care medicine, 38, 668.

BATALDEN, P. B. & DAVIDOFF, F. 2007. What is "quality improvement" and how can it transform healthcare? Quality & Safety in Health Care, 16**,** 2-3.

BAUER, M. E., LORENZ, R. P., BAUER, S. T., RAO, K. & ANDERSON, F. 2015. Maternal Deaths Due to Sepsis in the State of Michigan, 1999-2006. Obstetrics and gynecology, 126, 747-752.

BEIGI, R. H., BUNGE, K., SONG, Y. & LEE, B. Y. 2009. Epidemiologic and economic effect of methicillin-resistant Staphylococcus aureus in obstetrics. Obstetrics & Gynecology, 113**,** 983-991.

BENJAMIN, D. K., GARGES, H. & STEINBACH, W. J. Candida bloodstream infection in neonates. Seminars in perinatology, 2003. Elsevier, 375-383.

BENNETT, V. 2016. Antimicrobial stewardship: The critical role of nurses and midwives by Karen Shaw [Online]. Available: https://vivbennett.blog.gov.uk/2016/11/14/antimicrobial-stewardship-the-critical-role-of-nurses-and-midwives-by-karen-shaw/ [Accessed 12.10 2017].

BERG, B. R., HOUSEMAN, J. L., LEBAR, W. D. & NEWTON, D. W. 2014. Antimicrobial susceptibilities of group B streptococcus isolates from prenatal screening samples. Journal of clinical microbiology, 52**,** 3499-3500.

BERNATZ, J. T., SAFDAR, N., HETZEL, S. & ANDERSON, P. A. 2017. Antibiotic Overuse is a Major Risk Factor for Clostridium difficile Infection in Surgical Patients. Infection Control & Hospital Epidemiology, 38, 1254-1257.

BLACKBURN, R., VERLANDER, N., HEATH, P. & MULLER-PEBODY, B. 2014. The changing antibiotic susceptibility of bloodstream infections in the first month of life: informing antibiotic policies for early-and late-onset neonatal sepsis. Epidemiology & Infection, 142, 803-811.

BLAIR, J. M., WEBBER, M. A., BAYLAY, A. J., OGBOLU, D. O. & PIDDOCK, L. J. 2015. Molecular mechanisms of antibiotic resistance. Nature Reviews Microbiology, 13**,** 42.

BOCKSTAEL, K. & AERSCHOT, A. 2009. Antimicrobial resistance in bacteria. Open Medicine, 4, 141-155.

BONET, M., PILEGGI, V. N., RIJKEN, M. J., COOMARASAMY, A., LISSAUER, D., SOUZA, J. P. & GÜLMEZOGLU, A. M. 2017. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reproductive Health, 14, 67.

BORGERT, M. J., GOOSSENS, A. & DONGELMANS, D. A. 2015. What are effective strategies for the implementation of care bundles on ICUs: a systematic review. Implementation Science, 10, 119.

BOWLING, A. 2014. Research methods in health: investigating health and health services, McGraw-Hill Education (UK).

BRITTEN, N. 1995. Qualitative research: qualitative interviews in medical research. British Medical Journal, 311, 251-253.

BROOM, J., BROOM, A., ADAMS, K. & PLAGE, S. 2016a. What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice. Journal of Antimicrobial Chemotherapy, 71, 2295-2299.

BROOM, J., BROOM, A., PLAGE, S., ADAMS, K. & POST, J. 2016b. Barriers to uptake of antimicrobial advice in a UK hospital: a qualitative study. Journal of Hospital Infection, 93, 418-422.

BROWN, K., VALENTA, K., FISMAN, D., SIMOR, A. & DANEMAN, N. 2015. Hospital ward antibiotic prescribing and the risks of Clostridium difficile infection. JAMA internal medicine, 175, 626-633.

BRYMAN, A. 2015. Social research methods, Oxford university press.

BULL, A., WILSON, J., WORTH, L., STUART, R., GILLESPIE, E., WAXMAN, B., SHEARER, W. & RICHARDS, M. 2011. A bundle of care to reduce colorectal surgical infections: an Australian experience. Journal of Hospital Infection, 78, 297-301.

CADAVID, C. D., SAKAMOTO, S. D., TERASHITA, D. M. & SCHWARTZ, B. 2017. Bedside Registered Nurse Roles in Antimicrobial Stewardship: A Survey of Acute-Care Hospitals in Los Angeles County. Infection Control & Hospital Epidemiology, 38, 1263-1265.

CANE, J., O'CONNOR, D. & MICHIE, S. 2012. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implementation Science, 7, 37.

CAO, F., CHEN, C., WANG, M., LIAO, H., WANG, M., HUA, S., HUANG, B., XIONG, Y., ZHANG, J. & XU, Y. 2018. Updated meta-analysis of controlled observational studies: proton-pump inhibitors and risk of Clostridium difficile infection. Journal of Hospital Infection, 98, 4-13.

CARLE, C., ALEXANDER, P., COLUMB, M. & JOHAL, J. 2013. Design and internal validation of an obstetric early warning score: secondary analysis of the Intensive Care National Audit and Research Centre Case Mix Programme database. Anaesthesia, 68, 354-367.

CHANDRAHARAN, E. & KRISHNA, A. 2017. Diagnosis and management of postpartum haemorrhage. British Medical Journal, 358**,** j3875.

CHANDY, S. J., NAIK, G. S., BALAJI, V., JEYASEELAN, V., THOMAS, K. & LUNDBORG, C. S. 2014. High cost burden and health consequences of antibiotic resistance: the price to pay. The Journal of Infection in Developing Countries, 8, 1096-1102.

CHARANI, E., CASTRO-SANCHEZ, E., SEVDALIS, N., KYRATSIS, Y., DRUMRIGHT, L., SHAH, N. & HOLMES, A. 2013. Understanding the determinants of antimicrobial prescribing within hospitals: the role of "prescribing etiquette". Clinical Infectious Diseases, 57, 188-196.

CIARKOWSKI, S.L. AND STALBURG, C.M., 2010. Medication safety in obstetrics and gynecology. Clinical obstetrics and gynecology, *53*(3), pp.482-499.

CLARK, K., CURRY, T. & BYFIELDT, N. 2015. The effect of a care bundle on nursing staff when caring for the dying. International journal of palliative nursing, 21, 392-398.

CLIFFORD, V., HEFFERNAN, H. M., GRIMWOOD, K. & GARLAND, S. 2011. Variation in erythromycin and clindamycin resistance patterns between New Zealand and Australian group B streptococcus isolates. Australian and New Zealand Journal of Obstetrics and Gynaecology, 51**,** 328-332.

COOKE, F. J. & HOLMES, A. H. 2007. The missing care bundle: antibiotic prescribing in hospitals. International journal of antimicrobial agents, 30, 25-29.

CORDIOLI, R. L., CORDIOLI, E., NEGRINI, R. & SILVA, E. 2013. Sepsis and pregnancy: do we know how to treat this situation? Revista Brasileira de terapia intensiva, 25, 334-344.

COSGROVE, S. E., HERMSEN, E. D., RYBAK, M. J., FILE, T. M., PARKER, S. K. & BARLAM, T. F. 2014. Guidance for the knowledge and skills required for antimicrobial stewardship leaders. Infection Control & Hospital Epidemiology, 35, 1444-1451.

COTTEN, C. M. 2016. Adverse consequences of neonatal antibiotic exposure. Current opinion in pediatrics, 28, 141-149.

COVVEY, J., GRANT, J. & MULLEN, A. 2015. Development of an obstetrics triage tool for clinical pharmacists. Journal of clinical pharmacy and therapeutics, 40, 539-544.

CRESWELL, J. W. & CLARK, V. L. P. 2007. Designing and conducting mixed methods research.

CRESWELL, J. W. & POTH, C. N. 2017. Qualitative inquiry and research design: Choosing among five approaches, Sage publications.

CUNNINGTON, A. J. 2015. The importance of pathogen load. PLoS pathogens, 11, e1004563.

DANIELS, R., NUTBEAM, T., MCNAMARA, G. & GALVIN, C. 2010. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emergency Medicine Journal. 2010.095067.

DAVEY, P., BROWN, E., CHARANI, E., FENELON, L., GOULD, I. M., HOLMES, A., RAMSAY, C. R., WIFFEN, P. J. & WILCOX, M. 2013. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews, 4.

DAVEY, P., SNEDDON, J. & NATHWANI, D. 2010. Overview of strategies for overcoming the challenge of antimicrobial resistance. Expert review of clinical pharmacology, 3, 667-686.

DAVIES, S. & GIBBENS, N. 2013. UK five year antimicrobial resistance strategy 2013 to 2018. London: Department of Health [online]. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf [Accessed 29.03.2018].

DE JONG, K. 2016. Deriving implementation strategies for outcome monitoring feedback from theory, research and practice. Administration and Policy in Mental Health and Mental Health Services Research, 43, 292-296.

DE TEJADA, B. M. 2014. Antibiotic use and misuse during pregnancy and delivery: benefits and risks. International journal of environmental research and public health, 11**,** 7993-8009.

DELLINGER, R. P., LEVY, M. M., RHODES, A., ANNANE, D., GERLACH, H., OPAL, S. M., SEVRANSKY, J. E., SPRUNG, C. L., DOUGLAS, I. S. & JAESCHKE, R. 2013. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive care medicine, 39, 165-228.

DESHPANDE, A., PASUPULETI, V., THOTA, P., PANT, C., ROLSTON, D. D., SFERRA, T. J., HERNANDEZ, A. V. & DONSKEY, C. J. 2013. Community-associated Clostridium difficile

infection and antibiotics: a meta-analysis. Journal of Antimicrobial Chemotherapy, 68, 1951-1961.

EDWARDS, S. E., GROBMAN, W. A., LAPPEN, J. R., WINTER, C., FOX, R., LENGUERRAND, E. & DRAYCOTT, T. 2015. Modified obstetric early warning scoring systems (MOEWS): validating the diagnostic performance for severe sepsis in women with chorioamnionitis. American Journal of Obstetrics & Gynecology, 212**,** 536. e1-536. e8.

EDWARDS, S., BLOTKAMP, A., YELLAND, A., WINTER, C., DARLEY, E., DRAYCOTT, T. & FOX, R. 2013. RCOG criteria for sepsis in pregnancy, labour and the puerperium - how do they perform in practice? BJOG-an International Journal of Obstetrics and Gynaecology.

EL-EID, G. R., KADDOUM, R., TAMIM, H. & HITTI, E. A. 2015. Improving hospital discharge time: a successful implementation of Six Sigma methodology. Medicine (Baltimore), 94**,** e633.

ERKAYA, S., ENGIN-USTUN, Y. & AKTULAY, A. 2014. Mode of delivery does not effect C - reactive protein and perritin levels. Acta Medica Mediterranea, 30, 477-479.

ESAIASSEN, E., FJALSTAD, J. W., JUVET, L. K., VAN DEN ANKER, J. N. & KLINGENBERG, C. 2017. Antibiotic exposure in neonates and early adverse outcomes: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy, 72, 1858-1870.

EYADA, T., KHATTAB, S., BADRAWI, H. MAGHALLAWY, A., EL SHIMY, N., 1994 C-reactive protein in pregnancy, labor, in the post partum period and in premature rupture of membranes [Online]. The Department of Clinical Pathology and Gynecology & Obstetrics, Facility of Medicine, Cairo University. Available: http://applications.emro.who.int/imemrf/med_j_cairo_univ_1994_62_2_351_356.pdf [accessed 16.03.2018]

FEREDAY, S. 2015. A guide to quality improvement methods. London: Healthcare Quality Improvement Partnership [online]. Available: https://nhfd.co.uk/20/hipfracturer.nsf/b83841ab51769e1d802581a4005978ed/205c2976b502ffc2802581ee0053a23f/$FILE/HQIP%20guide%20to%20QI%202017.pdf [Accessed 29.03.2018]

FJALSTAD, J. W., STENSVOLD, H. J., BERGSENG, H., SIMONSEN, G. S., SALVESEN, B., RØNNESTAD, A. E. & KLINGENBERG, C. 2016. Early-onset sepsis and antibiotic exposure in term infants: a nationwide population-based study in Norway. The Pediatric infectious disease journal, 35, 1-6.

FLICEK, C. L. 2012. Communication: A dynamic between nurses and physicians. Medsurg Nursing, 21, 385.

FOUNOU, R. C., FOUNOU, L. L. & ESSACK, S. Y. 2017. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PloS one, 12, e0189621.

FRANCIS, C., MUMFORD, M., STRAND, M. L., MOORE, E. S. & STRAND, E. A. 2013. Timing of prophylactic antibiotic at cesarean section: a double-blinded, randomized trial. Journal of perinatology, 33**,** 759-62.

FRANCIS, J., MOROSAN, M., WHELAN, E. & MORRIS, E. 2015. Audit of obstetric sepsis bundle in a tertiary referral obstetric hospital. Bjog: An International Journal of Obstetrics and Gynaecology, 122, 200.

FRÈRE, J.-M. & PAGE, M. G. 2014. Penicillin-binding proteins: evergreen drug targets. Current opinion in pharmacology, 18**,** 112-119.

FRONTIER ECONOMICS. 2014. Exploring the costs of unsafe care in the NHS. London: Frontier Economics [online]. Available: https://www.frontier-

economics.com/documents/2014/10/exploring-the-costs-of-unsafe-care-in-the-nhs-frontier-report-2-2-2-2.pdf [Accessed 03.04.2018].

FULBROOK, P. & MOONEY, S. 2003. Care bundles in critical care: a practical approach to evidence-based practice. Nursing in critical care, 8, 249-255.

GALVÃO, A., BRAGA, A. C., GONÇALVES, D. R., GUIMARÃES, J. M. & BRAGA, J. 2016. Sepsis during pregnancy or the postpartum period. Journal of Obstetrics and Gynaecology, 36, 735-743.

GAO, F., MELODY, T., DANIELS, D. F., GILES, S. & FOX, S. 2005. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. Critical care, 9, R764.

GAREY, K. W., JIANG, Z.-D., YADAV, Y., MULLINS, B., WONG, K. & DUPONT, H. L. 2008. Peripartum Clostridium difficile infection: case series and review of the literature. American Journal of Obstetrics & Gynecology, 199, 332-337.

GARLAND, S. M., COTTRILL, E., MARKOWSKI, L., PEARCE, C., CLIFFORD, V., NDISANG, D., KELLY, N. & DALEY, A. J. 2011. Antimicrobial resistance in group B streptococcus: the Australian experience. Journal of medical microbiology, 60**,** 230-235.

GE, L. 2007. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer–2003-2005. The seventh report on confidential enquiries into maternal deaths in the United Kingdom. London, CEMACH [online]. Available: http://www.publichealth.hscni.net/sites/default/files/Saving%20Mothers%27%20Lives%202003-05%20.pdf [Accessed 29.03.2018].

GELBRAND, H., MILLER-PETRIE, M., PANT, S., GANDRA, S., LEVINSON, J., BARTER, D., WHITE, A., LAXMINARAYAN, R., GANGULY, N. & KARIUKI, S. 2015. The State of the World's Antibiotics. Center for Disease Dynamics, Economics & Policy: Washington, D.C. [online].

Available: https://cddep.org/wp-content/uploads/2017/06/swa_edits_9.16.pdf [Accessed 14.07.2018].

GILES, M., WATTS, W., O'BRIEN, A., BERENGER, S., PAUL, M., MCNEIL, K. & BANTAWA, K. 2015. Does our bundle stack up! Innovative nurse-led changes for preventing catheter-associated urinary tract infection (CAUTI). Healthcare infection, 20, 62-71.

GOFF, D. A., KARAM, G. H. & HAINES, S. T. 2017. Impact of a national antimicrobial stewardship mentoring program: Insights and lessons learned. American Journal of Health-System Pharmacy, 160379.

GOMEZ-ARANGO, L. F., BARRETT, H. L., MCINTYRE, H. D., CALLAWAY, L. K., MORRISON, M. & NITERT, M. D. 2017. Antibiotic treatment at delivery shapes the initial oral microbiome in neonates. Scientific Reports, 7, 43481.

GOOSSENS, H., FERECH, M., VANDER STICHELE, R., ELSEVIERS, M. & GROUP, E. P. 2005. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. The Lancet, 365**,** 579-587.

GRAY, J., PATWARDHAN, S. & MARTIN, W. 2010. Meticillin-resistant Staphylococcus aureus screening in obstetrics: a review. Journal of Hospital Infection, 75**,** 89-92.

GREEN, J. & THOROGOOD, N. 2013. Qualitative methods for health research, Sage.

GRIGORYAN, L., HAAIJER-RUSKAMP, F. M., BURGERHOF, J. G., MECHTLER, R., DESCHEPPER, R., TAMBIC-ANDRASEVIC, A., ANDRAJATI, R., MONNET, D. L., CUNNEY, R. & DI MATTEO, A. 2006. Self-medication with antimicrobial drugs in Europe. Emerging infectious diseases, 12, 452.

GUINN, D. A., ABEL, D. E. & TOMLINSON, M. W. 2007. Early goal directed therapy for sepsis during pregnancy. Obstetrics and gynecology clinics of North America, 34, 459-479.

HAENNI, M., SARAS, E. & MADEC, J.-Y. 2010. Demonstration of a shift towards penicillin resistance in the Streptococcus uberis population. Journal of medical microbiology, 59**,** 993-995.

HAWKEY, P. 2008. The growing burden of antimicrobial resistance. Journal of antimicrobial chemotherapy, 62**,** i1-i9.

HEALTH PROTECTION SCOTLAND AND INFORMATION SERVICES DIVISION. 2015. Report on Antimicrobial Use and Resistance in Humans in 2014. Scotland: Health Protection Scotland and Information Services Division [online]. Available: http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2015-10-06/2015-10-06-SAPG-2014-Report.pdf [Accessed 29.03.2018].

HIENSCH, R., POERAN, J., SAUNDERS-HAO, P., ADAMS, V., POWELL, C. A., GLASSER, A., MAZUMDAR, M. & PATEL, G. 2017. Impact of an electronic sepsis initiative on antibiotic use and health care facility–onset Clostridium difficile infection rates. American journal of infection control, 45, 1091-1100.

HISAMUDDIN, E., HISAM, A., WAHID, S. & RAZA, G. 2015. Validity of C-reactive protein (CRP) for diagnosis of neonatal sepsis. Pakistan journal of medical sciences, 31, 527.

HOFER, N., ZACHARIAS, E., MÜLLER, W. & RESCH, B. 2012. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology, 102**,** 25-36.

HOLMES, A. H., MOORE, L. S., SUNDSFJORD, A., STEINBAKK, M., REGMI, S., KARKEY, A., GUERIN, P. J. & PIDDOCK, L. J. 2016. Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet, 387**,** 176-187.

HORNER, D. L. & BELLAMY, M. C. 2012. Care bundles in intensive care. Continuing Education in Anaesthesia, Critical Care & Pain, 12, 199-202.

HOWIE, R., PALANIAPPAN, N., POUND, C., BARWICK, A. & LOVE, C. 2015. Sepsis 6 in maternity patients: from testing to successful implementation using quality improvement methodology. BJOG-an International Journal of Obstetrics and Gynaecology.

HUGHES, D. 2014. Selection and evolution of resistance to antimicrobial drugs. IUBMB life, 66**,** 521-529.

ISAACS, R., WEE, M., BICK, D., BEAKE, S., SHEPPARD, Z., THOMAS, S., HUNDLEY, V., SMITH, G. B., TEIJLINGEN, E. & THOMAS, P. 2014. A national survey of obstetric early warning systems in the United Kingdom: five years on. Anaesthesia, 69, 687-692.

ISMAIL, A. Q. T. & LAHIRI, S. 2013. Management of prelabour rupture of membranes (PROM) at term. Journal of perinatal medicine, 41**,** 647-649.

JACOB, S. T., BANURA, P., BAETEN, J. M., MOORE, C. C., MEYA, D., NAKIYINGI, L., BURKE, R., HORTON, C. L., IGA, B. & WALD, A. 2012. The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study. Critical care medicine, 40, 2050.

JOHNSTON, M. J., KING, D., ARORA, S., COOPER, K., PANDA, N. A., GOSLING, R., SINGH, K., SANDERS, B., COX, B. & DARZI, A. 2014. Requirements of a new communication technology for handover and the escalation of patient care: a multi-stakeholder analysis. Journal of evaluation in clinical practice, 20, 486-497.

JONGE, L., BOS, H. J., LANGEN, I. M., JONG-VAN DEN BERG, L. T. & BAKKER, M. K. 2014. Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study. Pharmacoepidemiology and drug safety, 23**,** 60-68.

JUN, J., KOVNER, C. T. & STIMPFEL, A. W. 2016. Barriers and facilitators of nurses' use of clinical practice guidelines: An integrative review. International journal of nursing studies, 60, 54-68.

KANG, H. E. & PARK, D. W. 2016. Lactate as a Biomarker for Sepsis Prognosis? Infection & chemotherapy, 48, 252-253.

KARDAS, P., DEVINE, S., GOLEMBESKY, A. & ROBERTS, C. 2005. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. International journal of antimicrobial agents, 26, 106-113.

KAYA, A., KARATEKIN, G., UZUNHASAN, I. & HATıPOĞLU, S. 2009. The influence of mode of delivery on the levels of high-sensitivity C-reactive protein determined in umbilical cord blood. International Journal of Medicine and Medical Sciences, 1**,** 115-118.

KELLER, K. B., EGGENBERGER, T. L., BELKOWITZ, J., SARSEKEYEVA, M. & ZITO, A. R. 2013. Implementing successful interprofessional communication opportunities in health care education: a qualitative analysis. International journal of medical education, 4, 253.

KELLY, A. M., BRYANT, M., COX, L. & JOLLEY, D. 2007. Improving emergency department efficiency by patient streaming to outcomes-based teams. Australian Health Review, 31**,** 16-21.

KENYON, S., TAYLOR, D. & TARNOW-MORDI, W. 2001. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. The Lancet, 357**,** 979-988.

KESKI-NISULA, L., KIRKINEN, P., OLLIKAINEN, M. & SAARIKOSKI, S. 1997. C-reactive protein in uncomplicated parturients delivered by cesarean section. Acta Obstetricia et Gynecologica Scandinavica, 76**,** 862-7.

KHOURY, L. & AMIN, A. 2017. What Hospitalists Need to Know About Quality Improvement. Current Emergency and Hospital Medicine Reports, 5, 109-113.

KIBE, S., ADAMS, K. & BARLOW, G. 2011. Diagnostic and prognostic biomarkers of sepsis in critical care. Journal of antimicrobial chemotherapy, 66, ii33-ii40.

KING, J. E. 2007. Standardized Coefficients in Logistic Regression. The annual meeting of the Southwest Educational Research Association. San Antonio, Texas [online]. Available: http://www.ccitonline.org/jking/homepage/standardized_paper.doc [Accessed 29.03.2018].

KISSOON, N. 2014. Sepsis guideline implementation: benefits, pitfalls and possible solutions. Critical Care, 18, 207.

KISSOON, N. 2015. Sepsis guidelines: Suggestions to improve adherence. Journal of Infection, 71, S36-S41.

KLEINBAUM, D. G. & KLEIN, M. 2010. Logistic regression a self-learning text, Springer; Statistics for Biology and Health.

KNOWLES, S., O'SULLIVAN, N., MEENAN, A., HANNIFFY, R. & ROBSON, M. 2015. Maternal sepsis incidence, aetiology and outcome for mother and fetus: a prospective study. BJOG: An International Journal of Obstetrics & Gynaecology, 122, 663-671.

KOVACS, G. & BRIGGS, P. 2015. Lectures in Obstetrics, Gynaecology and Women's Health, Springer.

KRANZ, J., SCHMIDT, S., LEBERT, C., SCHNEIDEWIND, L., SCHMIEMANN, G. & WAGENLEHNER, F. 2017. Uncomplicated Bacterial Community-acquired Urinary Tract Infection in Adults: Epidemiology, Diagnosis, Treatment, and Prevention. Deutsches Aerzteblatt International, 114.

KUAN, W.-S., MAHADEVAN, M., TAN, J.-H., GUO, J. & IBRAHIM, I. 2013. Feasibility of introduction and implementation of the Surviving Sepsis Campaign bundle in a Singapore emergency department. European Journal of Emergency Medicine, 20, 344-349.

KUHN, P., DHEU, C., BOLENDER, C., CHOGNOT, D., KELLER, L., DEMIL, H., DONATO, L., LANGER, B., MESSER, J. & ASTRUC, D. 2010. Incidence and distribution of pathogens in

early-onset neonatal sepsis in the era of antenatal antibiotics. Paediatric and perinatal epidemiology, 24, 479-487.

KUPERMAN, A. A. & KOREN, O. 2016. Antibiotic use during pregnancy: how bad is it? BMC medicine, 14**,** 91.

LAWES, T., LOPEZ-LOZANO, J.-M., NEBOT, C. A., MACARTNEY, G., SUBBARAO-SHARMA, R., WARES, K. D., SINCLAIR, C. & GOULD, I. M. 2017. Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of Clostridium difficile infections in a region of Scotland: a non-linear time-series analysis. The Lancet Infectious Diseases, 17, 194-206.

LEE, C.-C., LEE, N.-Y., CHEN, P.-L., HONG, M.-Y., CHAN, T.-Y., CHI, C.-H. & KO, W.-C. 2015. Impact of antimicrobial strategies on clinical outcomes of adults with septic shock and community-onset Enterobacteriaceae bacteremia: de-escalation is beneficial. Diagnostic microbiology and infectious disease, 82, 158-164.

LEEKHA, S., TERRELL, C. L. & EDSON, R. S. 2011. General principles of antimicrobial therapy. Mayo Clinic Proceedings. Elsevier, 156-167.

LETH, R. A., ULDBJERG, N., NORGAARD, M., MOLLER, J. K. & THOMSEN, R. W. 2011. Obesity, diabetes, and the risk of infections diagnosed in hospital and post-discharge infections after cesarean section: a prospective cohort study. Acta Obstetricia et Gynecologica Scandinavica, 90**,** 501-9.

LI, D., QI, R., YANG, M., ZHANG, Y. & YU, T. 2011. Bacterial community characteristics under long-term antibiotic selection pressures. Water research, 45**,** 6063-6073.

LIABSUETRAKUL, T., CHOOBUN, T., PEEYANANJARASSRI, K. & ISLAM, Q. M. 2014. Antibiotic prophylaxis for operative vaginal delivery. The Cochrane Library.

LIANG, S. Y. & KUMAR, A. 2015. Empiric antimicrobial therapy in severe sepsis and septic shock: optimizing pathogen clearance. Current Infectious Disease Reports, 17, 493.

LIPSITCH, M. & SAMORE, M. H. 2002. Antimicrobial use and antimicrobial resistance: a population perspective. Emerging infectious diseases, 8, 347.

LIU, R., LIN, L. & WANG, D. 2016. Antimicrobial prophylaxis in caesarean section delivery. Experimental and therapeutic medicine, 12**,** 961-964.

LIVORSI, D., COMER, A., MATTHIAS, M. S., PERENCEVICH, E. N. & BAIR, M. J. 2015. Factors influencing antibiotic-prescribing decisions among inpatient physicians: a qualitative investigation. Infection control & hospital epidemiology, 36, 1065-1072.

LUCAS, D., ROBINSON, P. & NEL, M. 2012. Sepsis in obstetrics and the role of the anaesthetist. International journal of obstetric anesthesia, 21, 56-67.

LYIMO, F. M., MASSINDE, A. N., KIDENYA, B. R., KONJE, E. T. & MSHANA, S. E. 2013. Single dose of gentamicin in combination with metronidazole versus multiple doses for prevention of post-caesarean infection at Bugando Medical Centre in Mwanza, Tanzania: a randomized, equivalence, controlled trial. BMC Pregnancy Childbirth, 13**,** 123.

MACDOUGALL, C. & POLK, R. E. 2005. Antimicrobial stewardship programs in health care systems. Clinical microbiology reviews, 18, 638-656.

MAGUIRE, P. J., O'HIGGINS, A. C., POWER, K. A., DALY, N., MCKEATING, A. & TURNER, M. J. 2015. Maternal bacteremia and the Irish maternity early warning system. International Journal of Gynecology & Obstetrics, 129, 142-145.

MANN, C. 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency medicine journal, 20, 54-60.

MANNING, M. L., PFEIFFER, J. & LARSON, E. L. 2016. Combating antibiotic resistance: The role of nursing in antibiotic stewardship. American journal of infection control, 44, 1454-1457.

MARTíN, G. R., PRIETO, J. P., DE CABO, J. V., LUS, L. G., BARBERÁN, J., LANDA, J. M. G. & FERNÁNDEZ, C. 2004. Plasma fibronectin as a marker of sepsis. International journal of infectious diseases, 8**,** 236-243.

MARTIN, R., MAKINO, H., YAVUZ, A. C., BEN-AMOR, K., ROELOFS, M., ISHIKAWA, E., KUBOTA, H., SWINKELS, S., SAKAI, T. & OISHI, K. 2016. Early-life events, including mode of delivery and type of feeding, siblings and gender, shape the developing gut microbiota. PLoS One, 11, e0158498.

MARWICK, C. & DAVEY, P. 2009. Care bundles: the holy grail of infectious risk management in hospital?. Current opinion in infectious diseases, 22, 364-369.

MASON, K. L. & ARONOFF, D. M. 2012. Postpartum group A Streptococcus sepsis and maternal immunology. American Journal of Reproductive Immunology, 67, 91-100.

MCNEILL, G., DIXON, M. & JENKINS, P. 2008. Can acute medicine units in the UK comply with the Surviving Sepsis Campaign's six-hour care bundle? Clinical medicine, 8, 163-165.

MD REZAL, R. S., HASSALI, M. A., ALRASHEEDY, A. A., SALEEM, F., MD YUSOF, F. A. & GODMAN, B. 2015. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. Expert review of anti-infective therapy, 13, 665-680.

MICHIE, S., VAN STRALEN, M. M. & WEST, R. 2011. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implementation science, 6, 42.

MINDERHOUD, T., SPRUYT, C., HUISMAN, S., OSKAM, E., SCHUIT, S. & LEVIN, M. 2017. Microbiological outcomes and antibiotic overuse in Emergency Department patients with suspected sepsis. The Netherlands journal of medicine, 75, 196.

MOGES, F., ESHETIE, S., YESHITELA, B. & ABATE, E. 2017. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC pediatrics, 17, 137.

MONSEES, E., GOLDMAN, J. & POPEJOY, L. 2017. Staff nurses as antimicrobial stewards: An integrative literature review. American Journal of Infection Control, 45, 917-922.

MORGENTHALER, N. G. & KOSTRZEWA, M. 2015. Rapid Identification of Pathogens in Positive Blood Culture of Patients with Sepsis: Review and Meta-Analysis of the Performance of the Sepsityper Kit. International journal of microbiology , 827416.

MORSE, J. M. 2016. Mixed method design: Principles and procedures, Routledge.

MOULTON, L. J., MUNOZ, J. L., LACHIEWICZ, M., LIU, X. & GOJE, O. 2017. Surgical site infection after cesarean delivery: incidence and risk factors at a US academic institution. The Journal of Maternal-Fetal & Neonatal Medicine**,** 1-8.

MUSHTAQ, A., AWALI, R. A., CHANDRAMOHAN, S., KRISHNA, A., BIEDRON, C., JEGEDE, O. & CHOPRA, T. 2017. Implementing an antibiotic stewardship program at a long-term acute care hospital in Detroit, Michigan. American journal of infection control, 45, e157-e160.

NAPOLITANO, F., IZZO, M. T., DI GIUSEPPE, G. & ANGELILLO, I. F. 2013. Public knowledge, attitudes, and experience regarding the use of antibiotics in Italy. PloS one, 8, e84177.

NATHWANI, D. & SNEDDON, J. 2015. Practical guide to antimicrobial stewardship in hospitals [online]. Available: http://bsac.org.uk/wp-content/uploads/2013/07/Stewardship-Booklet-Practical-Guide-to-Antimicrobial-Stewardship-in-Hospitals.pdf [Accessed 26.03.2018].

NATHWANI, D., SNEDDON, J., MALCOLM, W., WIUFF, C., PATTON, A., HURDING, S., EASTAWAY, A., SEATON, R.A., WATSON, E., GILLIES, E. & DAVEY, P., 2011. Scottish antimicrobial prescribing group (SAPG): development and impact of the Scottish

national antimicrobial stewardship programme. International Journal of Antimicrobial Agents, 38(1), pp.16-26.

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE. 2014. Sepsis Management; National Clinical Guideline No. 6 [Online]. National Clinical Effectiveness Committee. Available: http://hse.ie/eng/about/Who/clinical/natclinprog/sepsis/sepsis6.pdf [Accessed 23 May 2017].

NATIONAL COLLABORATING CENTRE FOR WOMEN'S AND CHILDREN'S HEALTH (UK). 2012. Antibiotics for Early-Onset Neonatal Infection: Antibiotics for the Prevention and Treatment of Early-Onset Neonatal Infection. London [online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK116612/ [Accessed 29.03.2018].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2011. Caesarean section clinical guideline (CG132). National Institute for Health and Clinical Excellence [online]. Available: https://www.nice.org.uk/guidance/cg132/resources/caesarean-section-pdf-35109507009733 [Accessed 03.04.2018].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2012. Neonatal infection (early onset): antibiotics for prevention and treatment (CG149). National Institute for Health and Clinical Excellence [Online]. Available: https://www.nice.org.uk/guidance/cg149/resources/neonatal-infection-early-onset-antibiotics-for-prevention-and-treatment-pdf-35109579233221 [Accessed 06.02 2018].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2014. Neonatal infection: quality standard (QS75) [online]. National Institute for Health and Care Excellence. Available: https://www.nice.org.uk/guidance/qs75/resources/neonatal-infection-pdf-2098849787845 [Accessed 09.03.2018].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2015a. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15)

[Online]. National Institute for Health and Care Excellence. Available: https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-pdf-1837273110469 [Accessed 06.02 2018].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2015b. Preterm labour and birth (NG25) [Online]. National Institute for Health and Care Excellence. Available: https://www.nice.org.uk/guidance/ng25 [Accessed 26.03 2018].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2016. Sepsis: recognition, diagnosis and early management (NG51) [Online]. National Institute for Health and Care Excellence. Available: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-management-pdf-1837508256709 [Accessed 06.02 2018].

NHS GREATER GLASGOW & CLYDE. 2015a. Obstetric Guidelines: Antibiotic Policy for Obstetric Patients [Online]. Greater Glasgow & Clyde. Available: http://www.ggcprescribing.org.uk/blog/guideline-news-february-2015/ [Accessed 30.01 2018].

NHS GREATER GLASGOW & CLYDE. 2015b. Greater Glasgow & Clyde Obstetric Guidelines: Maternal Sepsis. NHS Greater Glasgow & Clyde. Available: http://www.staffnet.ggc.scot.nhs.uk/Info%20Centre/PoliciesProcedures/GGCClinicalGuidelines/GGC%20Clinical%20Guidelines%20Electronic%20Resource%20Direct/Maternal%20Sepsis,%20Obstetrics.pdf [Accessed 30.01 2018].

NHS GREATER GLASGOW & CLYDE. 2017. IV-Oral Antibiotic Switch Therapy (IVOST) Guideline [Online]. NHS Greater Glasgow & Clyde Area Drug and Therapeutics Committee. Available: http://app.ggcprescribing.org.uk/guidelines/infections/iv-oral-antibiotic-switch-therapy-ivost-guideline/ [Accessed 01.05 2017].

NHS NATIONAL SERVICE SCOTLAND & INFORMATION SERVICES DIVISION. 2017. Births in Scottish Hospitals- Year ending 31 March 2017 [Online]. NHS National Service Scotland, Information Services Division. Available: http://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/2017-11-28/2017-11-28-Births-Report.pdf [Accessed 06.02 2018].

NHS NATIONAL SERVICE SCOTLAND & INFORMATION SERVICES DIVISION. 2016. Births in Scottish Hospitals- Year ending 31 March 2016. NHS National Service Scotland, Information Services Division [online]. Available: https://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/2016-11-29/2016-11-29-Births-Report.pdf [Accessed 29.03.2018].

O'Neill, J., 2016. Tackling drug-resistant infections globally: Final report and recommendations. HM Government and Welcome Trust: UK [online]. Available: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [Accessed 09.07.2018].

OLANS, R. N., OLANS, R. D. & DEMARIA, J. A. 2016. The Critical Role of the Staff Nurse in Antimicrobial Stewardship—Unrecognized, but Already There. Clinical Infectious Diseases, 62, 84-89.

O'LEARY, K. J., LIEBOVITZ, D. M., WU, R. C., RAVI, K., KNOTEN, C. A., SUN, M., WALKER, A. M. & REDDY, M. C. 2017. hospital-based Clinicians' Use of Technology for Patient Care-related Communication: A National Survey. Journal Of Hospital Medicine, 12, 530-535.

OLSEN, P., WILLIAMSON, M., TRAYNOR, V. & GEORGIOU, C. 2018. The impact of oral probiotics on vaginal Group B Streptococcal colonisation rates in pregnant women: A pilot randomised control study. Women and Birth, 31, 31-37.

OSHIMA, T., WU, L., LI, M., FUKUI, H., WATARI, J. & MIWA, H. 2018. Magnitude and direction of the association between Clostridium difficile infection and proton pump inhibitors in

adults and pediatric patients: a systematic review and meta-analysis. Journal of gastroenterology, 53, 84-94.

PAKYZ, A. L., MOCZYGEMBA, L. R., VANDERWIELEN, L. M., EDMOND, M. B., STEVENS, M. P. & KUZEL, A. J. 2014. Facilitators and barriers to implementing antimicrobial stewardship strategies: results from a qualitative study. American journal of infection control, 42, S257-S263.

PATEL, S. J. & SAIMAN, L. 2012. Principles and strategies of antimicrobial stewardship in the neonatal intensive care unit. Seminars in perinatology. Elsevier, 431-436.

PATRAS, K. A. & NIZET, V. 2018. Group B Streptococcal Maternal Colonization and Neonatal Disease: Molecular Mechanisms and Preventative Approaches. Frontiers in Pediatrics, 6.

PAUL, M., DICKSTEIN, Y. & RAZ-PASTEUR, A. 2016. Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. Clinical Microbiology and Infection, 22, 960-967.

PERNIA, S. & DEMAAGD, G. 2016. The new pregnancy and lactation labeling rule. Pharmacy and Therapeutics, 41**,** 713.

PERRONE, S., LOTTI, F., LONGINI, M., ROSSETTI, A., BINDI, I., BAZZINI, F., BELVISI, E., SARNACCHIARO, P., SCAPELLATO, C. & BUONOCORE, G. 2017. Creactive protein in healthy term newborns during the first 48 hours of life. Archives of Disease in Childhood-Fetal and Neonatal Edition, fetalneonatal-2016-312506.

PETRIE, A. & SABIN, C. 2013. Medical statistics at a glance, John Wiley & Sons.

PIERRAKOS, C. & VINCENT, J.-L. 2010. Sepsis biomarkers: a review. Critical care, 14, R15.

PLACHOURAS, D. & HOPKINS, S. 2017. Antimicrobial stewardship: we know it works; time to make sure it is in place everywhere. The Cochrane database of systematic reviews, 2, ED000119.

POLLACK, L. A. & SRINIVASAN, A. 2014. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clinical Infectious Diseases, 59, S97-S100.

POPE, C., VAN ROYEN, P. & BAKER, R. 2002. Qualitative methods in research on healthcare quality. Quality and Safety in Health Care, 11, 148-152.

POPOVICI, I., MORITA, P. P., DORAN, D., LAPINSKY, S., MORRA, D., SHIER, A., WU, R. & CAFAZZO, J. A. 2015. Technological aspects of hospital communication challenges: an observational study. International Journal for Quality in Health Care, 27, 183-188.

POWELL, B. J., BEIDAS, R. S., LEWIS, C. C., AARONS, G. A., MCMILLEN, J. C., PROCTOR, E. K. & MANDELL, D. S. 2017. Methods to improve the selection and tailoring of implementation strategies. The journal of behavioral health services & research, 44, 177-194.

POWELL, B. J., WALTZ, T. J., CHINMAN, M. J., DAMSCHRODER, L. J., SMITH, J. L., MATTHIEU, M. M., PROCTOR, E. K. & KIRCHNER, J. E. 2015. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implementation Science, 10, 21.

PROCTOR, E. K., POWELL, B. J. & MCMILLEN, J. C. 2013. Implementation strategies: recommendations for specifying and reporting. Implementation Science, 8, 139.

PUBLIC HEALTH ENGLAND. 2014. UK Standards for Microbiology Investigations. London: Public Health England [online]. Available: https://www.gov.uk/guidance/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories [accessed 29.03.2018].

PUBLIC HEALTH ENGLAND. 2015. Start smart then focus: antimicrobial stewardship toolkit for English hospitals [Online]. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF [Accessed 06.02 2018].

PUBLIC HEALTH ENGLAND. 2017a. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). London: Public Health England [Online]. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/656611/ESPAUR_report_2017.pdf [Accessed 06.02 2018].

PUBLIC HEALTH ENGLAND. 2017b. Management and treatment of common infections Antibiotic guidance for primary care: for consultation and local adaptation. London: Public Health England [online]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/664740/Managing_common_infections_guidance_for_consultation_and_adaptation.pdf [Accessed 11.07.2018].

PULIA, M. S., REDWOOD, R. & SHARP, B. 2017. Antimicrobial Stewardship in the Management of Sepsis. Emergency Medicine Clinics of North America, 35, 199-217.

RATNASEKERA, L., WAHBA, J., FOO, L., BROWN, R., JONES, B. & AKMAL, S. C. 2014. A retrospective audit of the management of sepsis in labour at Queen Charlotte's and Chelsea hospital, London. BJOG-an International Journal of Obstetrics and Gynaecology.

RESAR, R., GRIFFIN, F. A., HARADEN, C. & NOLAN, T. W. 2012. Using Care Bundles to Improve Health Care Quality. IHI Innovation Series white paper. Cambridge, Massachusetts: Institute for Healthcare Improvement [Online]. Available: http://www.ihi.org/resources/Pages/IHIWhitePapers/UsingCareBundles.aspx [Accessed 29.03.2018].

RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMSTON, R. 2013. Qualitative research practice: A guide for social science students and researchers, Sage.

RIVERS, E., NGUYEN, B., HAVSTAD, S., RESSLER, J., MUZZIN, A., KNOBLICH, B., PETERSON, E. & TOMLANOVICH, M. 2001. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New England Journal of Medicine, 345, 1368-1377.

ROBERTS, N., HOOPER, G., LORENCATTO, F., STORR, W. & SPIVEY, M. 2017. Barriers and facilitators towards implementing the Sepsis Six care bundle (BLISS-1): a mixed methods investigation using the theoretical domains framework. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 25, 96.

RODRIGUES, A. T., ROQUE, F., FALCÃO, A., FIGUEIRAS, A. & HERDEIRO, M. T. 2013. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. International journal of antimicrobial agents, 41, 203-212.

ROJO, M. 2006. Collect before you treat: obtaining cultures before antibiotic treatment. Drug and Therapy. Shands at The University of Florida [online]. Available: http://professionals.ufhealth.org/files/2011/11/1006-drugs-therapy-bulletin.pdf [Accessed 29.03.18].

RONNESTAD, A., ABRAHAMSEN, T. G., MEDBO, S., REIGSTAD, H., LOSSIUS, K., KAARESEN, P. I., ENGELUND, I. E., IRGENS, L. M. & MARKESTAD, T. 2005. Septicemia in the first week of life in a Norwegian national cohort of extremely premature infants. Pediatrics, 115, e262-8.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS. 2012a. Bacterial Sepsis in Pregnancy. Green-top Guideline No. 64a [Online]. Royal College of Obstetricians & Gynaecologists [online]. Available: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_64a.pdf [Accessed 06.02 2018].

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS. 2012b. The Prevention of Early-onset Neonatal Group B Streptococcal Disease; Green–top Guideline No. 36. Royal College of Obstetricians and Gynaecologists [online]. Available: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg36/ [Accessed 29.03.2018].

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS. 2017. The Prevention of Early-onset Neonatal Group B Streptococcal Disease. Green–top Guideline No. 36 [Online]. Royal College of Obstetricians and Gynaecologists. Available: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.14821 [Accessed 20.03 2018].

RUIZ-GIARDÍN, J. M., MARTIN-DÍAZ, R. M., JAQUETI-AROCA, J., GARCIA-ARATA, I., SAN MARTÍN-LÓPEZ, J. V. & BUITRAGO, M. S.-S. 2015. Diagnosis of bacteraemia and growth times. International Journal of Infectious Diseases, 41, 6-10.

SÁEZ-LÓPEZ, E., GUIRAL, E., FERNÁNDEZ-ORTH, D., VILLANUEVA, S., GONCÉ, A., LÓPEZ, M., TEIXIDÓ, I., PERICOT, A., FIGUERAS, F. & PALACIO, M. 2016. Vaginal versus obstetric infection Escherichia coli isolates among pregnant women: antimicrobial resistance and genetic virulence profile. PloS one, 11, e0146531.

SALONGA, S. 2018. Types of transcription explained: verbatim vs. Intelligent vs. Edited transcription [Online]. Available: https://www.globalme.net/blog/verbatim-vs-intelligent-vs-edited-transcription [Accessed 30.10 2017].

SANAMI, M. N., RADFAR, M., SHIRVANI, F., NABAVI, M. & GACHKAR, L. 2015. Candida Colonization in Low Birth Weight and Very Low Birth Weight Infants in a Neonatal Intensive Care Unit. Archives of Pediatric Infectious Diseases, 3.

SCHATZ, M., CHAMBERS, C. & MITCHELL, A. A. 2016. Sizing up the Pregnancy and Lactation Labeling Rule: Understanding Challenges and Opportunities [Online]. Clinical Drug

Information. Available: http://www.wolterskluwercdi.com/white-papers/pregnancy-lactation-labeling/ [Accessed 22.03 2018].

SCHRAG, S. J., FARLEY, M. M., PETIT, S., REINGOLD, A., WESTON, E. J., PONDO, T., JAIN, J. H. & LYNFIELD, R. 2016. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics, 138, 9.

SCOTTISH ANTIMICROBIAL PRESCRIBING GROUP & NHS EDUCATION FOR SCOTLAND. 2014. Exploring the role of nurses and midwives in Antimicrobial stewardship [Online]. Scottish Antimicrobial Prescribing Group and NHS Education for Scotland Available: http://www.nes.scot.nhs.uk/about-us/whats-new/exploring-the-role-of-nurses-and-midwives-in-antimicrobial-stewardship.aspx [Accessed 26.01 2018].

SCOTTISH ANTIMICROBIAL PRESCRIBING GROUP. 2014. Primary Care Prescribing Indicators - Annual Report 2013-2014 [Online]. Scotland: Scottish Antimicrobial Prescribing Group. Available: https://www.scottishmedicines.org.uk/files/sapg/2014-10-14-SAPG-Primary-Care-PI-2013-14-Report.pdf [Accessed 26.01 2018].

SCOTTISH ANTIMICROBIAL PRESCRIBING GROUP. 2018. about us, SAPG representation [online]. Available: https://www.sapg.scot/about-us/ [Accessed 13.07.2018]

SCOTTISH ANTIMICROBIAL PRESCRIBING GROUP.2017. How should antibiotics be dosed in obesity? [Online]. Available: https://www.sapg.scot/media/2918/howshouldantibioticsbedosedinobesity_2016_update.pdf [Accessed 19.07.2018].

SEGAL, S. 2010. Labor epidural analgesia and maternal fever. Anesthesia & Analgesia, 111, 1467-1475.

SEKIKUBO, M., HEDMAN, K., MIREMBE, F. & BRAUNER, A. 2017. Antibiotic Overconsumption in Pregnant Women with Urinary Tract Symptoms in Uganda. Clinical Infectious Diseases, 65, 544-550.

SGRO, M., SHAH, P., CAMPBELL, D., TENUTA, A., SHIVANANDA, S. & LEE, S. 2011. Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008. Journal of Perinatology, 31, 794.

SHALLCROSS, L. J. & DAVIES, D. S. C. 2014. Antibiotic overuse: a key driver of antimicrobial resistance. British Journal of General Practice, 64, 604-605.

SHANKAR-HARI, M., PHILLIPS, G. S., LEVY, M. L., SEYMOUR, C. W., LIU, V. X., DEUTSCHMAN, C. S., ANGUS, D. C., RUBENFELD, G. D. & SINGER, M. 2016. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315, 775-787.

SHARMA, S. K., ROGERS, B. B., ALEXANDER, J. M., MCINTIRE, D. D. & LEVENO, K. J. 2014. A randomized trial of the effects of antibiotic prophylaxis on epidural-related fever in labor. Anesthesia & Analgesia, 118, 604-610.

SHARPE, E. E. & ARENDT, K. W. 2017. Epidural Labor Analgesia and Maternal Fever. Clinical obstetrics and gynecology, 60, 365-374.

SHULKIN, D. 2012. Reinventing the Pharmacy and Therapeutics Committee. Pharmacy and Therapeutics, 37, 623-649.

SINGER, M., DEUTSCHMAN, C. S., SEYMOUR, C. & ET AL. 2016. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA, 315, 801-810.

SINGH, S., MCGLENNAN, A., ENGLAND, A. & SIMONS, R. 2012. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia, 67, 12-18.

SMAILL, F. M. & VAZQUEZ, J. C. 2015. Antibiotics for asymptomatic bacteriuria in pregnancy. The Cochrane Library.

SMITH, R. & COAST, J. 2012. The economic burden of antimicrobial resistance: why it is more serious than current studies suggest. Technical Report. London School of Hygiene & Tropical Medicine, London. Available: http://researchonline.lshtm.ac.uk/639028/ [Accessed 29.03.2018].

SMITH, R. & COAST, J. 2013. The true cost of antimicrobial resistance. BMJ: British Medical Journal [Online]. Available: https://search.proquest.com/docview/1945630086?pq-origsite=gscholar [Accessed 29.03.2018].

SMITH, R. D. & COAST, J. 2002. Antimicrobial resistance: a global response. Bulletin of the World Health Organization, 80, 126-133 [online]. Available: http://www.who.int/bulletin/archives/80(2)126.pdf [Accessed 03.04.2018].

SONG, J. W. & CHUNG, K. C. 2010. Observational Studies: Cohort and Case-Control Studies. Plastic and reconstructive surgery, 126, 2234-2242.

SREEJESH, S. & MOHAPATRA, S. 2013. Mixed Method Research Design: An Application in Consumer-Brand Relationships (CBR), Springer Science & Business Media.

STEER, P. & FLINT, C. 1999. Physiology and management of normal labour. BMJ: British Medical Journal, 318**,** 793-796.

STEINMO, S., FULLER, C., STONE, S. P. & MICHIE, S. 2015. Characterising an implementation intervention in terms of behaviour change techniques and theory: the 'Sepsis Six'clinical care bundle. Implementation Science, 10, 111.

SUN, J., DENG, Z. & YAN, A., 2014. Bacterial multidrug efflux pumps: mechanisms, physiology and pharmacological exploitations. Biochemical and biophysical research communications, 453(2), pp.254-267.

TAMELIENĖ, R., BARČAITĖ, E., STONIENĖ, D., BUINAUSKIENĖ, J., MARKŪNIENĖ, E., KUDREVIČIENĖ, A., VITKAUSKIENĖ, A., JOMANTIENĖ, D. & NADIŠAUSKIENĖ, R. J. 2012.

Escherichia coli colonization in neonates: prevalence, perinatal transmission, antimicrobial susceptibility, and risk factors. Medicina, 48**,** 71-76.

TARRANT, C., O'DONNELL, B., MARTIN, G., BION, J., HUNTER, A. & ROONEY, K. D. 2016. A complex endeavour: an ethnographic study of the implementation of the Sepsis Six clinical care bundle. Implementation Science, 11, 149.

TAYLOR, M. J., MCNICHOLAS, C., NICOLAY, C., DARZI, A., BELL, D. & REED, J. E. 2014b. Systematic review of the application of the plan–do–study–act method to improve quality in healthcare. BMJ Quality & Safety, 23, 290.

TAYLOR, S. P., LEDFORD, R., PALMER, V. & ABEL, E. 2014a. We need to talk: an observational study of the impact of electronic medical record implementation on hospital communication. BMJ Quality & Safety, 23, 584-588.

TENOVER, F. C. 2006. Mechanisms of antimicrobial resistance in bacteria. American journal of infection control, 34, S3-S10.

TILLEKERATNE, L. G., BODINAYAKE, C. K., DABRERA, T., NAGAHAWATTE, A., ARACHCHI, W. K., SOORIYAARACHCHI, A., STEWART, K., WATT, M., ØSTBYE, T. & WOODS, C. W. 2017. Antibiotic overuse for acute respiratory tract infections in Sri Lanka: a qualitative study of outpatients and their physicians. BMC family practice, 18, 37.

TITA, A. T., SZYCHOWSKI, J. M., BOGGESS, K., SAADE, G., LONGO, S., CLARK, E., ESPLIN, S., CLEARY, K., WAPNER, R. & LETSON, K. 2016. Adjunctive azithromycin prophylaxis for cesarean delivery. New England Journal of Medicine, 375**,** 1231-1241.

TOWERS, C. V., YATES, A., ZITE, N., SMITH, C., CHERNICKY, L. & HOWARD, B. 2017. Incidence of fever in labor and risk of neonatal sepsis. American Journal of Obstetrics and Gynecology, 216, 596. e1-596. e5.

TURI, S. K. & VON AH, D. 2013. Implementation of early goal-directed therapy for septic patients in the emergency department: a review of the literature. Journal of Emergency Nursing, 39, 13-19.

TUULI, M. G., LIU, J., STOUT, M. J., MARTIN, S., CAHILL, A. G., ODIBO, A. O., COLDITZ, G. A. & MACONES, G. A. 2016. A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery. New England Journal of Medicine, 374**,** 647-55.

TWYCROSS, A. & SHORTEN, A. 2014. Service evaluation, audit and research: what is the difference? Evidence-based nursing, 17, 65-66.

UK SPESIS TRUST & YORK HEALTH ECONOMICS CONSORTIUM. 2017. Sepsis could cost UK economy up to £15.6 billion each year, new study suggests [online]. Available: https://www.york.ac.uk/news-and-events/news/2017/research/sepsis-economy-report/ [Accessed 28.04.2018].

URQUHART, C. 2012. Grounded theory for qualitative research: A practical guide, Sage.

VAN DILLEN, J., ZWART, J., SCHUTTE, J. & VAN ROOSMALEN, J. 2010. Maternal sepsis: epidemiology, etiology and outcome. Current opinion in infectious diseases, 23, 249-254.

VAN SCHALKWYK, J. & VAN EYK, N. 2010. Antibiotic prophylaxis in obstetric procedures. Journal of obstetrics and gynaecology Canada, 32, 878-892.

VAZQUEZ-LAGO, J. M., LOPEZ-VAZQUEZ, P., LÓPEZ-DURÁN, A., TARACIDO-TRUNK, M. & FIGUEIRAS, A. 2011. Attitudes of primary care physicians to the prescribing of antibiotics and antimicrobial resistance: a qualitative study from Spain. Family practice, 29, 352-360.

VIJAYAN, A. L., VANIMAYA, RAVINDRAN, S., SAIKANT, R., LAKSHMI, S., KARTIK, R. & MANOJ, G. 2017. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. Journal of Intensive Care, 5, 7.

VILLERS, M., GROTEGUT, C., HEINE, P. & SWAMY, G. 2015. 21: Prevalence and risk factors for clostridium difficile infection in obstetric patients. American Journal of Obstetrics and Gynecology, 6, 892-893.

VINCENT, J.-L., MARTIN, G. S. & LEVY, M. M. 2016. qSOFA does not replace SIRS in the definition of sepsis. Critical Care, 20, 210.

WANG, J.-L., CHIN, C.-S., CHANG, M.-C., YI, C.-Y., SHIH, S.-J., HSU, J.-Y. & WU, C.-L. 2009. Key process indicators of mortality in the implementation of protocol-driven therapy for severe sepsis. Journal of the Formosan Medical Association, 108, 778-787.

WARD, N. S. & LEVY, M. M. 2017. Sepsis: Definitions, Pathophysiology and the Challenge of Bedside Management, Humana Press.

WEINDLING, A. 2003. The confidential enquiry into maternal and child health (CEMACH). Archives of Disease in Childhood, 88, 1034-1037.

WEINSTEIN, R. A. & BOYER, K. M. 2016. Antibiotic Prophylaxis for Cesarean Delivery — When Broader Is Better. New England Journal of Medicine, 375**,** 1284-1286.

WEST OF SCOTLAND NEONATAL MANAGED CLINICAL NETWORK. 2017. Neonatal Guideline; Early Onset Sepsis in the Neonate: Prevention and Treatment [Online]. West Of Scotland Neonatal Managed Clinical Network Available: http://www.staffnet.ggc.scot.nhs.uk/Acute/Women%20and%20Childrens%20Services/Neonatology/Greater%20Glasgow%20and%20Clyde%20Guidelines/Documents/WoS_EOS_Neonates.pdf [Accessed 30.01 2018].

WITTAYACHAMNANKUL, B., CHENTANAKIJ, B., SRUAMSIRI, K. & CHATTIPAKORN, N. 2016. The role of central venous oxygen saturation, blood lactate, and central venous-to-arterial carbon dioxide partial pressure difference as a goal and prognosis of sepsis treatment. Journal of critical care, 36, 223-229.

WORLD HEALTH ORGANIZATION. 2009. WHO guidelines for the management of postpartum haemorrhage and retained placenta, World Health Organization [online]. Available: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241598514/en/ [Accessed 29.03.2018].

WORLD HEALTH ORGANIZATION. 2012. WHO recommendations for the prevention and treatment of postpartum haemorrhage, World Health Organization [online]. Available: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/ [Accessed 29.03.2018].

WORLD HEALTH ORGANIZATION. 2015. Global action plan on antimicrobial resistance. World Health Organization [online]. Available: http://www.who.int/antimicrobial-resistance/global-action-plan/en/ [Accessed 29.03.2018].

WORLD HEALTH ORGANIZATION. 2017. Statement on maternal sepsis. World Health Organization online]. Available: http://apps.who.int/iris/bitstream/handle/10665/254608/WHO-RHR-17.02-eng.pdf;jsessionid=C7E530F5E7EBB44700EDDC7D55D2EADD?sequence=1 [Accessed 29.03.2018].

WRIGHT, D. J., BECKETT, D. J. & COOKE, B. 2014. Use of sepsis 6 raises some interesting questions. Emergency Medicine Journal, 31, 948-948.

WU, R., ROSSOS, P., QUAN, S., REEVES, S., LO, V., WONG, B., CHEUNG, M. & MORRA, D. 2011. An evaluation of the use of smartphones to communicate between clinicians: a mixed-methods study. Journal of medical Internet research, 13.

YEALY, D. M., HUANG, D. T., DELANEY, A., KNIGHT, M., RANDOLPH, A. G., DANIELS, R. & NUTBEAM, T. 2015. Recognizing and managing sepsis: what needs to be done? BMC medicine, 13, 98.

ZANATTA, D. A. D. L., ROSSINI, M. D. M. & TRAPANI JÚNIOR, A. 2017. Pyelonephritis in pregnancy: clinical and laboratorial aspects and perinatal results. Revista Brasileira de Ginecologia e Obstetrícia, 39**,** 653-658.

ZHANG, L., LEVY, K., TRUEBA, G., CEVALLOS, W., TROSTLE, J., FOXMAN, B., MARRS, C. F. & EISENBERG, J. N. 2015. Effects of selection pressure and genetic association on the relationship between antibiotic resistance and virulence in Escherichia coli. Antimicrobial agents and chemotherapy, 59**,** 6733-6740.

ZHANG, Z., XU, X. & CHEN, K. 2014. Lactate clearance as a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review study protocol. British Medical Journal open, 4, e004752.

ZWEIG, M. H. & CAMPBELL, G. 1993. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clinical chemistry, 39, 561-577.

Appendix A: A Microsoft Excel Function for Calculating a Standardized Logistic Regression Coefficient as adjusted from (King, 2007).

Cell A1 = Enter the mean predicted probability for the dataset.

Cell A2 = Enter the unstandardized beta weight for X.

Cell A3 = Enter the sample standard deviation for X.

Cell A4: Calculate a standardized coefficient for X by typing:

=(1/(1+EXP(-(LN(A1/(1-A1))+0.5*A2*A3))))-(1/(1+EXP(-(LN(A1/(1-A1))-0.5*A2*A3))))

Repeat for additional predictor variables.

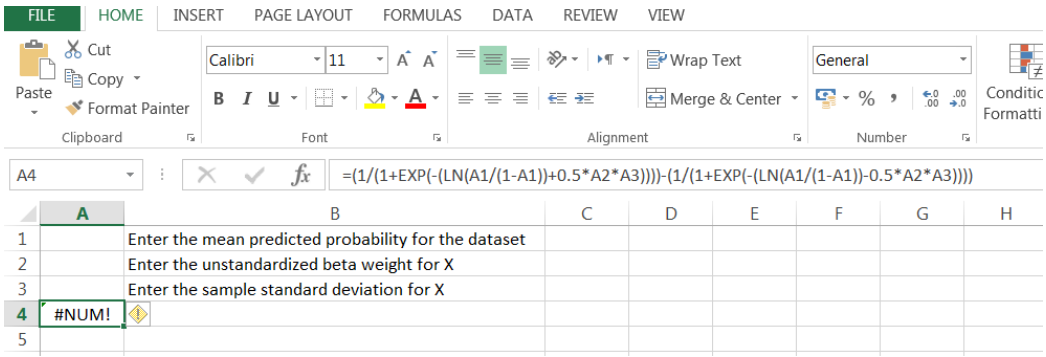

Figure A-1: Print screen of Microsoft Excel function to calculate the standardized logistic regression coefficient

X is the variable (i.e. HR, RR, temperature or WCC). To calculate standardized logistic regression coefficient for all variables, this step must to be repeated for each individual variable.

Appendix B: Reported sensitivity and resistance to antibiotic therapy based on the isolated pathogen from patient's culture

Pathogen	amp/amoxicillin	aztreonam	cephalexin	ciprofloxacin	clarithromycin	clindamycin	co. amoxiclav	flucloxacillin
Enterococcus Faecalis	S							
Group B Streptococcus	S					S		
Staphylococcus aureus					S			S
S.Pyrogenes (GAS)						S		
E coli	S	S		S			S	
E coli	S	S		S			S	
E coli	R	S					S	
E coli		S		S			S	
E coli	R						S	
E coli							S	
Coliform Bacilli	S		S					
Coliform Bacilli	S		S					
Coliform Bacilli	S							
mixed anaerobic organisms								
mixed anaerobic organisms								
mixed anaerobic organisms								
mixed anaerobic organisms								
mixed anaerobic organisms								
mixed anaerobic organisms								
S.Pyrogenes (GAS)								

mixed anaerobic organisms								
mixed anaerobic organisms								
Propionibacterium species								
Micrococcus Luteus / Lylae - Aerobics								
Yeasts								
Group B streptococcus					**R**			
Group B streptococcus					**R**			
Streptococcus Anginosus								
Group B Streptococcus					**S**			
Group B streptococcus					**S**			
Group B streptococcus					**S**			
Group B streptococcus					**S**			
Group B streptococcus					**S**			
S.Pyrogenes (GAS)						**S**		
Group B streptococcus					**R**	**R**		

Pathogen	flucloxacillin	gentamicin	meropenem	metronidazole	nitrofurantoin	penicillin	temocillin	trimethoprim	vancomycin
Enterococcus Faecalis		S							S
Group B Streptococcus						S			
Staphylococcus aureus	S								
S.Pyrogenes (GAS)						S			S
E coli		S							
E coli		S	S				S		
E coli		S					S		
E coli		S							
E coli		S							
E coli		S							
Coliform Bacilli		S			S			R	
Coliform Bacilli		S			S			S	
Coliform Bacilli		S			S			S	
mixed anaerobic organisms				S					
mixed anaerobic organisms				S					
mixed anaerobic organisms				S					
mixed anaerobic organisms				S					
mixed anaerobic organisms				S					
mixed anaerobic organisms				S					
S.Pyrogenes (GAS)				S					
mixed anaerobic organisms				S					
mixed anaerobic organisms				S					

Propionibacterium species									
Micrococcus Luteus / Lylae - Aerobics									
Yeasts									
Group B streptococcus						**S**			
Group B streptococcus						**S**			
Streptococcus Anginosus						**S**			
Group B Streptococcus						**S**			
Group B streptococcus						**S**			
Group B streptococcus						**S**			
Group B streptococcus						**S**			
Group B streptococcus						**S**			
S.Pyrogenes (GAS)						**S**			
Group B streptococcus						**S**			**S**

Appendix C: Additional lab data collected from women

Urea and electrolytes

This evaluation included the assessment of sodium (Na), potassium (K), chlorine (Cl), urea (Ur), creatinine and estimated glomerular filtration rate (eGFR). The lab values were collected from the patients' electronic health records from admission to the hospital until discharge. Values varied between and within the women. Na levels were normal in three-quarters of patients, only 24.7% (n=22) having abnormal levels, while K levels were abnormal in 12.4% (n=11) of women. Cl was above the normal reference range in 22.5% (n=20) and Ur levels were abnormal in 37% (n=33). Creatinine levels were normal in most women, leaving only two patients with abnormal values, while eGFR was abnormal in four patients. The details of the abnormalities for Na, K, Cl and Ur are reported in Table A.1, while eGFR and creatinine levels are reported in Figure A-1.

Table A.1: The abnormality reported within Na, K, Cl and Ur laboratory values

Normal Reference values		Reported levels below the reference range	Reported levels above the reference range
Na	133-146 mmol/L	126-132 mmol/L	-
K	3.5-5.3 mmol/L	2.8-3.4 mmol/L	5.6-6 mmol/L
Cl	95-108 mmol/L	-	109-111 mmol/L
Ur	2.5-7.8 mmol/L	0.8-2.4 mmol/L	7.9-22.9 mmol/L

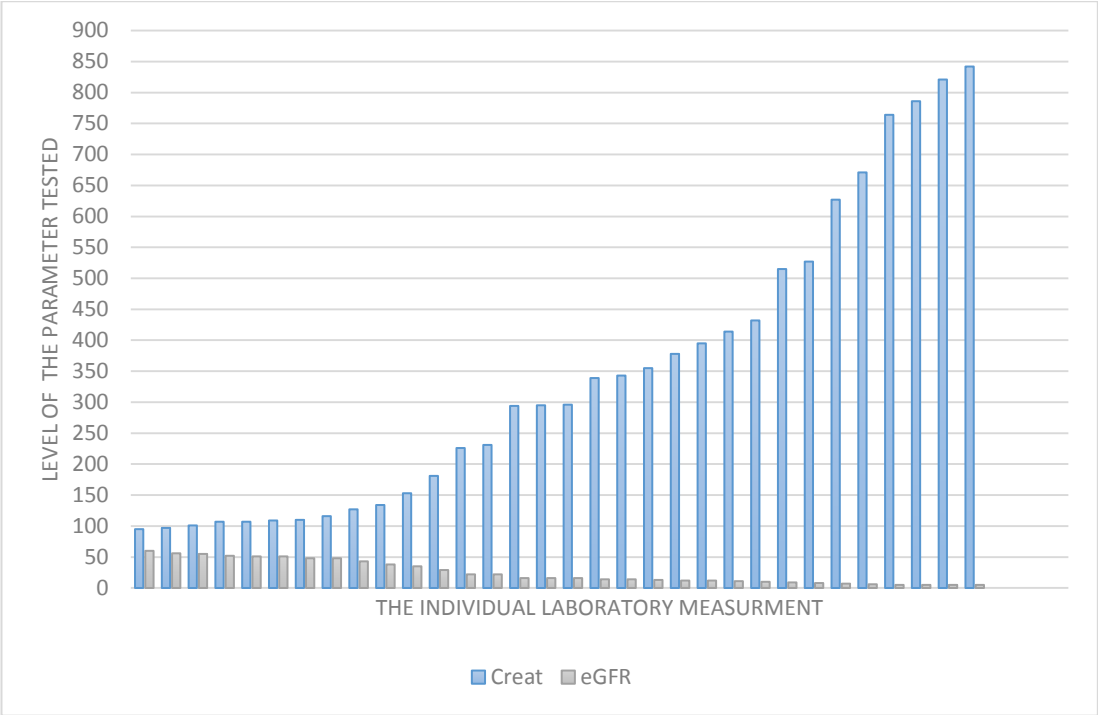

Figure A-1: Abnormalities in eGFR values and/or creatinine level reported in 35 readings of four sick women

Liver function test

Figure A-2 plots ALT and AST readings captured for the 89 women throughout their hospital stay. This excluded one pair of readings above 200 for both ALT and AST, reported as 363 U/L and 416 U/L respectively. The AST and ALT reference ranges for normal function should be < 40 U/L and < 50 U/L respectively. There were only four patients with both AST and ALT abnormalities that were observed in 12 readings from their lab records. Only three patients had elevated ALT and normal AST, whereas seven had elevated AST and normal ALT.

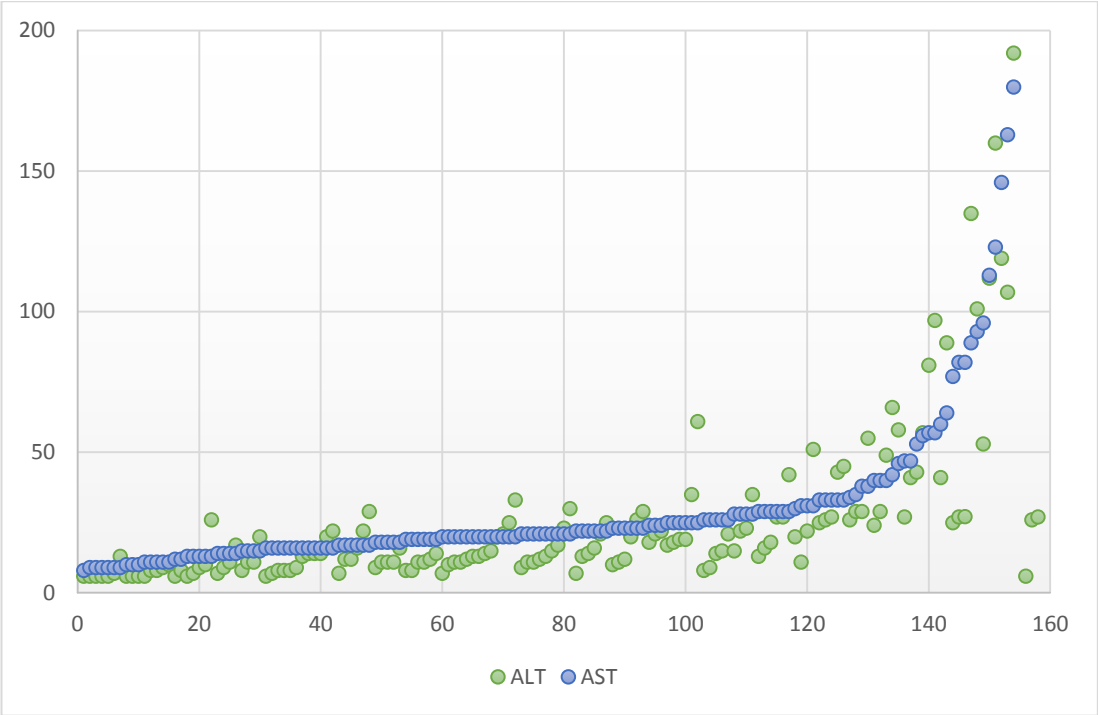

Figure A-2: Levels of ALT and AST in women treated with antibiotic for suspected or confirmed sepsis

The other liver function tests included ALP, total bilirubin and albumin, the results of which are displayed in Table A.2. There were 32 abnormal readings of total bilirubin that were observed in ten women's lab reports and 101 abnormal ALP values that were over 130 U/L, reported in 55 women.

Table A.2: ALP, albumin and total bilirubin

Normal Reference values	Reported levels below the reference range	Reported levels above the reference range
Total bilirubin <20 µmol/L	-	20-415 µmol/L
ALP 30-130 U/L	-	132-455 U/L
Albumin 35-50 g/L	13-34 g/L	87 g/L

Albumin levels were abnormal in all women. One woman had an elevated albumin level of 87 g/L and there was one reading of 35 g/L reported in a patient with other abnormal values. The rest of the results were for low albumin levels below 35 g/L. The distribution of albumin levels below 35 g/L is explicated in Figure A-3.

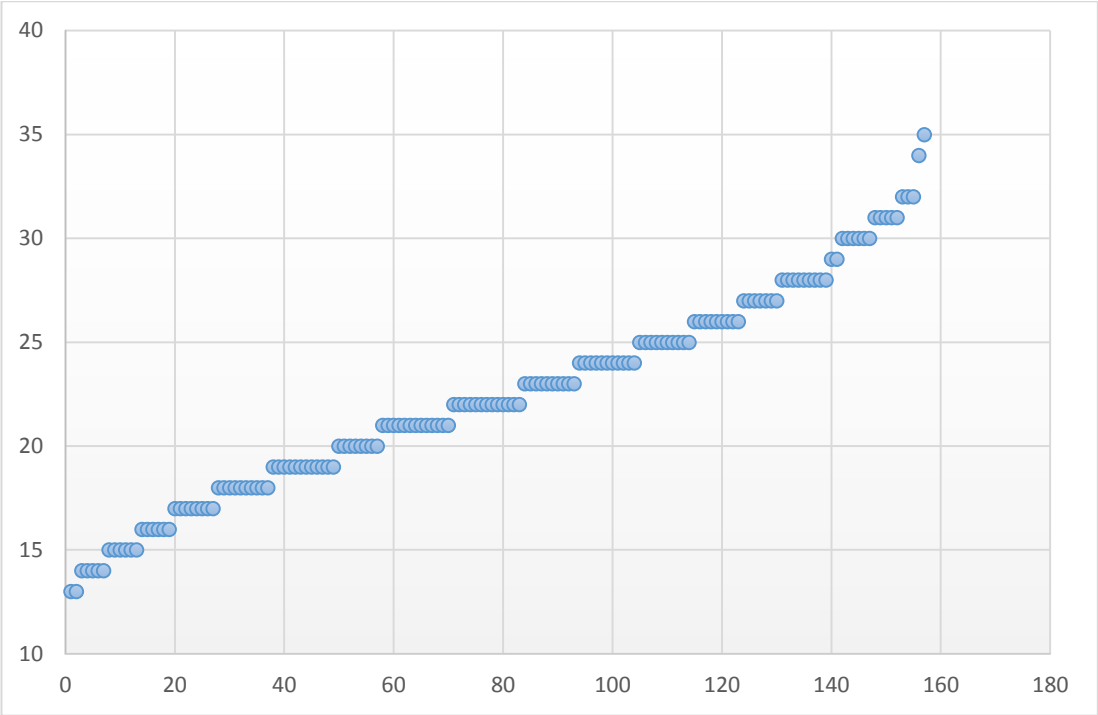

Figure A-3: Albumin level reported as g/L in all women with suspected sepsis

Appendix D: Women data collection sheet

Patient SN: _____

Sepsis Six – Audit

Hospital: PRM □ QEUH □ RAH □

Patient Demographic:

Age:	Allergy:	Pregnancy stage
Weight:	BMI:	Antenatal □ Labour □ Postnatal □
Parity:	Gestation:	If postnatal, number of days after delivery:_____

HPC:

Ways of identifying the patient:

Handover sheet □ Drug kardex □ Medical note □ Pharmacy referral □

Day of admission:

Monday□ Tuesday □ Wednesday □ Thursday □ Friday □ Saturday □ Sunday □

Length of admission (d/h):

Medical conditions:

Chronic medicine:

Summary of related previous admission:

Number of days before current admission:_ _ _

DELIVERY INFORMATION

EBL (ml): Pre-delivery Hb (g/L): Gestation:

Unit of women admission: P/N □ ICU □ HDU □ Labour □

Time of delivery: Day of delivery:

VTE risk assessment: Low □ intermediate □ high □

Enoxaparin does/ duration:

Mode of delivery:

Perineal tear:

1st degree □ 2nd degree □ 3rd degree □ 4th degree □

Outcome after 42 days of delivery: Sepsis □ Sepsis free □

Outcome after 90 days of F/U: Patient survived □ Patient died □

1

Patient SN: _____

Note of abnormal "women" clinical parameter:			
Day	Time	Parameter	Value

Data when SEPSIS SIX delivered	**Day number:**
What are the SIRS? Temp □ HR □ RR □ WCC □ altered mental status □	Time zero:

Sepsis Six Bundle:

1	Oxygen to achieve saturation >94%, ≤98%	Yes □ No□	Time:
2	Blood culture and relevant swabs	Yes □ No□	Time:
3	Take lactate, Fbc, Crp, U+E, Coag, G+S, +/- ABG	Yes □ No□	Time:
4	Antibiotic intravenous	Yes □ No□	Time:
5	IV fluids challenge	Yes □ No□	Time:
6	Note urine output, fluid balance, consider catheter	Yes □ No□	Time:
Care delivered within 1 hour of suspected/diagnosed		Yes □ No□	
The name of the provider of sepsis six was written: Y□ N□		Designation:	

CLINICAL DIAGNOSIS

Antibiotic therapy:					
Drug name	Dose (g)	Route	frequency	N of doses	Started on Day

TDM	Time of dose:			
	Time of sample:			
	Trough/peak:			

Patient SN: _____

MICROBIOLOGY DATA

Result available on Day: _____

Specimen:

Cultural yields:

Growth:

Sensitivity:

Resistance:

Microbiologist comment:

Result available on Day: _____

Specimen:

Cultural yields:

Growth:

Sensitivity:

Resistance:

Microbiologist comment:

Result available on Day: _____

Specimen:

Cultural yields:

Growth:

Sensitivity:

Resistance:

Microbiologist comment:

Patient SN: _____

MEWS Chart

Day							
Time							
T (ºC):							
HR (bpm):							
SBP (mmHg):							
DBP mmHg):							
RR (bpm):							
O_2 sat							
Neuro							
Day							
Time							
T (ºC):							
HR (bpm):							
SBP (mmHg):							
DBP mmHg):							
RR (bpm):							
O_2 sat							
Neuro							

Intravenous fluid information

Day	Name	Volume	Quantity	Time of infusion

Patient's mediation according to drug kardex

Drug name	Dose	Route/ Frequency	Duration

4

Patient SN: _____

Laboratory Parameter

	Day							
Sodium	133-146 mmol/L							
Potassium	3.5-5.3 mmol/L							
Chloride	95-108 mmol/L							
Urea	2.5-7.8 mmol/L							
Creatinine	40-130 mmol/L							
eGFR								
CRP	0-10 mg/L							
WCC	4-11 x 10^{12}/L							
Haemoglobin	115-165 g/L							
Platelet count	150-400 x10^{9}/L							
Total bilirubin	< 20 umol/L							
ALT	< 50 U/L							
AST	< 40 U/L							
ALP	30-130 U/L							
Albumin	35-50 g/L							
Prothrombin time	9-13 S							
PT ratio								
APTT	27-38 S							
APTT ratio	0.8-1.2							
Thrombin time								
TCT ratio								
PH								
$PaCO_2$								
PaO_2								
HCO_3								
Lactate								
Glucose								

Patient SN: _____

Patient's mediation according to IDLs			
Drug name	**Dose**	**Route**	**Duration**

Question to medical healthcare providers:

1.	What clinical parameter **prioritizes** the call of sepsis?	
2.	Therapy escalate / de-escalate? **Changes in antibiotic therapy**	Yes □ / No □
3.	Antibiotic **route** changed throughout the treatment duration	Yes □ / No □
4.	**Discharge** with normal clinical parameter	Yes □ / No □

Appendix E: Babies data collection sheet

Patient SN: _____

Early onset neonatal sepsis– Audit

Hospital: PRM □ QEUH □ RAH □

Mother Demographic:

Age:	Weight:	BMI:
Allergy:	Parity:	Gestation:
EBL (ml)	Hb (g/L)	Unit of admission:
VTE risk assessment:	Enoxaparin dose:	

Ways of identifying the patient:

Handover sheet □ Drug kardex □ Medical note □ Pharmacy referral □

Day of delivery:

Monday□ Tuesday □ Wednesday □ Thursday □ Friday □ Saturday □ Sunday □

Time of delivery: **Mode of delivery:** **Length of hospital Stay:**

Mother medical conditions:

Mother medicine:

BABY'S INFORMATION

Weight (g): Gestation (wk):

Apgar Score:

Unit of baby admission: P/N □ NICU □ SCBU □ HDU □

IV antibiotic prescribed within 72 hours of birth: Yes □ No □

Antibiotic details: (Drug name- dose- duration)

Patient SN: _____

TDM for gent	Time of dose	Time of sample	level	N of doses

Day										
Time										
Temp										
HR										
RR										
CRP										
WCC:										
Platelet:										
Hb:										
H+										
PCO2										
PO2										
HCO3										
BE										
O_2 Sat										
Na										
K										
Glucose										
Lactate										

MICROBIOLOGY DATA

Result available on Day:
Specimen: Urine □ Blood □ wound swab □ Not available/taken □ other □
Cultural yields:
Growth:

Outcome after 90 days of F/U:	Baby survived □	baby died □

Patient SN: _____

Baby's red flag, risk factors and clinical indicators for sepsis

Red flags	Parental antibiotic for mother with confirmed or suspected infection –not IPA	◻
	Suspected/confirmed infection in another baby in multiple pregnancy	◻
	Respiratory distress starting more than 4 hours after birth	◻
	Seizures	◻
	Need for mechanical ventilation in term baby	◻
	Sign of shock	◻
Risk factors	Invasive GBS infection in a previous baby	◻
	Maternal GBS colonisation, bacteriuria or infection in the current pregnancy	◻
	Pre-labour repute of membrane (Spontaneous)	◻
	Preterm birth following spontaneous labour (before 37 weeks gestation)	◻
	Suspected/confirmed rapture of membrane for more than 18 hr in preterm birth	◻
	Intrapartum fever >38 ºC OR confirmed/suspected chorioamnionitis	◻
Clinical Indicators	Altered behaviour or responsiveness	◻
	Altered muscle tone (e.g. floppiness)	◻
	Feeding difficulties	◻
	Feed intolerance	◻
	Abnormal HR	◻
	Sign of respiratory distress	◻
	Jaundice within 24hr of birth	◻
	Sign of neonatal encephalopathy	◻
	Need for cardio-pulmonary resuscitation	◻
	Need for mechanical ventilation in a preterm labour	◻
	Unexplained excessive bleeding, thrombocytopenia or abnormal coagulation	◻
	Oliguria persisting beyond 24 hr after birth	◻
	Persistent fetal circulation	◻
	Altered glucose homeostatic	◻
	Metabolic acidosis	◻
	Hypoxia	◻
	Apnoea	◻
	Local sign of infection (e.g. skin, eye)	◻
	Temp<36ºC or >38ºC	◻

Other factors/comment:

Patient SN: _____

Readmission for both women & baby

Women's data	
Number of days after prev discharge	
Length of stay	
Ward admitted TO	
Reason for readmission	
Inpatient therapy	
IDLs medicine	

Baby's data	
Number of days after prev discharge	
Length of stay	
Ward admitted TO	
Reason for readmission	
Inpatient therapy	
IDLs medicine	

Appendix F: Participants' letter of invitation

STRATHCLYDE INSTITUTE OF PHARMACY & BIOMEDICAL SCIENCES

University of Strathclyde Science

Sepsis Six Care Bundle in NHS Greater Glasgow and Clyde Maternity Wards

Participant's Letter of Invitation

You are invited to participate in this study which is investigating the Sepsis Six Care Bundle. It is concerned with determining practitioners' knowledge of the sepsis six care bundle by exploring their experience and thoughts regarding their use of the sepsis six sticker and you compliance with the care package. This study will help to inform future developments associated with the delivery of care in your ward(s). The aim is to highlight possible barriers and challenges to the development of sepsis management and identify how to better shape care for women who develop sepsis on maternity wards.

Project background

The MBRRACE-UK 2009-2012 report states that sepsis accounted for one quarter of maternal deaths in the UK and Ireland. The Sepsis Six sticker was introduced in 2015 on all NHSGGC maternity wards, to help ensure that all six items of the Sepsis Six care bundle were delivered within one hour of sepsis being suspected. A recent audit was conducted in all NHSGGC maternity wards, and its findings showed poor use of the sepsis six sticker, with only one third of patients having received the bundle as part of their hospital care.

This study aims to assess practitioners' knowledge of the sepsis six care bundle by exploring their experience and thoughts regarding use of the sepsis six sticker.

Who are we recruiting?

Healthcare providers who work in NHSGGC maternity wards and who have knowledge of the sepsis six care bundle. It is not conditional that you have used the sepsis six sticker yourself; a basic knowledge of what the sepsis six care bundle is will be sufficient for you to participate.

If you want to particpant, please read the attached participant's information sheet, and if you require any further information or clarification, please contact the researcher, Nouf Abutheraa (who will conduct the interview) at the Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, nouf.abuhreraa@strath.ac.uk.You can also contact the academic project supervisor, Professor Alex Mullen of the University of Strathclyde a.mullen@strath.ac.uk, or the NHS project supervisor, June Grant of Princess Royal Maternity June.Grant@ggc.scot.nhs.uk.

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Yours faithfully,
Nouf Abutheraa

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Appendix G: Participants' information sheet

STRATHCLYDE INSTITUTE OF PHARMACY & BIOMEDICAL SCIENCES

University of Strathclyde Science

Participants' Information Sheet

Sepsis Six Care Bundle in NHS Greater Glasgow and Clyde Maternity Wards

Project background The Sepsis Six sticker was introduced in 2015 into NHSGGC maternity wards to help ensure that all six items of the Sepsis Six care bundle were delivered within one hour of suspected sepsis. A recent audit conducted in all NHSGGC maternity wards showed low compliance with using the sepsis six sticker. This study is part of a larger study investigating the Sepsis Six Care Bundle and is concerned with determining practitioners' knowledge of the sepsis six care bundle by exploring their experience and thoughts regarding their use of the sepsis six sticker.

Who are we recruiting? Healthcare providers who work in NHSGGC maternity wards and have knowledge of the sepsis six care bundle. It is not crucial that you have used the sepsis six sticker yourself; a basic knowledge of what the sepsis six care bundle is, will be sufficient for you to participate.

What does taking part involve? If you decide to take part, a University of Strathclyde PhD student, Nouf Abutheraa (NA), will conduct a short interview with you to explore your knowledge, thoughts and your clinical practice in this area. The interview will take place in a location that is convenient to you and will last no more than 30 minutes. The interview will be audio recorded and then transcribed for analysis.

Is there is any possible risk? All data obtained from the interview will be anonymised and handled confidentially. Taking part is completely voluntary. If you agree to take part and then change your mind you are free to withdraw from the study without the need to give a reason.

What are the possible benefits? Taking part in this study will help to inform future developments associated with the delivery of care in your ward. It will highlight possible barriers and challenges to the development of sepsis management. The information you provide will be the foundation of developing a quality improvement plan that should provide a better patient experience. The findings may be published and the study will be reported in the researcher's (Nouf Abutheraa's) PhD thesis.

Ethical approval: This study is sponsored by the University of Strathclyde. An ethics application has been granted by the ethics committee.

Further questions: If you require any further information or clarification, please contact the researcher Nouf by email.

Nouf Abutheraa, Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE
Email: nouf.abuhreraa@strath.ac.uk

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Appendix H: Participants' consent form

University of Strathclyde Science

STRATHCLYDE INSTITUTE OF PHARMACY & BIOMEDICAL SCIENCES

Consent Form

Sepsis Six Care Bundle in NHS Greater Glasgow and Clyde Maternity Wards

- I confirm that I have read the participant information sheet and fully understand the information provided ☐
- I confirm that I was given the opportunity to ask questions ☐
- I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving reasons ☐
- I understand that the interview will be audio recorded then transcribed ☐
- I understand that the data obtained from the interview will be anonymised ☐
- I understand that the results may be published ☐
- **I agree to take part in the study and participate in the interview** ☐

_____	__ /__/____	_____
Name of Participant	Date	Signature
_____	__ /__/____	_____
Researcher	Date	Signature

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Appendix I: Interview schedule

University of Strathclyde Science

STRATHCLYDE INSTITUTE OF PHARMACY & BIOMEDICAL SCIENCES

Interview schedule

Q1: What is your occupation? How many years of experience do you have in the NHS in general and in maternity wards?

Q2: Before the Sepsis Six Care bundle, how did you assess your patients for sepsis?

Q3: Before or after the Sepsis Six Care bundle was introduced, how did your ward prepare you (as a staff member) for using this new tool?

Q4: What are your feelings about using the tool now?

Q5: Tell me in your own words what is your understanding of the sepsis six care bundle?

- How can you identify a patient with sepsis in your ward?
- Elaborate on each element in the care bundle
- Elaborate on antibiotic de-escalation

Q6: How do you continue monitoring your patients after initiating the care bundle?

Q7: Many people in your team are involved in delivering the care bundle, but whose responsibility do you think it is to commence the sepsis six care bundle?

Q8: As for handover communication, how do you perform the shift handover and the transfer of care handover?

Q9: So tell me, before a patient leaves your ward on any normal day, what is the procedure that you follow with every patient regarding their medication?

Q10: Are there any other points you want to add?

Thank you for your time and for your valuable participation in this study.

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