CAUSES AND CONSEQUENCES

OF

MATERNAL SEPSIS

IN THE UK

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Thesis submitted in fulfilment of the Degree of Doctor of Philosophy

February 2014

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Abstract

Background: The rate of maternal death from sepsis has increased in several European countries, most notably the UK, where sepsis is now the leading cause of direct maternal death. An increase in maternal mortality also implies an increase in the number of women with severe, life-threatening morbidity. Key information gaps in the understanding of severe maternal sepsis in the UK are: the incidence, main causative organisms, infection sources, and risk factors for severe maternal sepsis.

Methods: Four population-based observational studies were conducted to address these evidence gaps.

Results: The incidence of severe maternal morbidity from sepsis is increasing in the UK, a trend also evident in the USA. The most common sources are respiratory tract, genital tract and urinary tract infection. The predominant organisms causing infection are *E. coli*, group A *streptococcus*, and strong circumstantial evidence of *Streptococcus pneumonia*. Sepsis progresses very rapidly particularly with group A streptococcal infection. Approximately 20% of women with severe sepsis progress to septic shock and 2% of women die.

Risk factors for severe maternal sepsis in the UK with a large effect size are: febrile illness or antibiotics in the 2 weeks prior to onset of severe sepsis (aOR=12.1, 95% CI 8.1-18.0), caesarean section after the onset of labour (aOR= 8.1, 95% CI 4.7-14.0), multiple pregnancy (aOR= 5.8, 95% CI 1.5-21.5), infection with group A *streptococcus* (aOR=4.8 for progression to septic shock, 95% CI 2.2-10.8), pre-labour caesarean section (aOR= 3.8, 95% CI 2.2-6.6), low socioeconomic status (aOR=2.6, 95% CI 1.03-6.7), and operative vaginal delivery (aOR=2.5, 95% CI 1.3-4.7). Risk factors are significantly cumulative.

Conclusions: Infection prior to or after delivery, even if the woman appears to be well, should be a marker for close clinical monitoring. Suspicion of group A *streptococcus* should be regarded as an obstetric emergency and treated ahead of laboratory confirmation.

Table of Contents

Acknowledgements

I would like to express my deepest thanks and appreciation to my supervisors Prof. Marian Knight and Prof. Jenny Kurinczuk. I have learned so much from you and you have been an inspiration and guiding force throughout my DPhil. I am sincerely grateful for the opportunity you have given me to grow as a research scientist and for your support and mentorship along this journey. I feel extremely lucky to have been your student.

Thank you also to the senior staff at the NPEU: Maggie Redshaw, Jen Hollowell, Ron Gray and Maria Quigley – your enthusiasm, encouragement and congeniality have been so appreciated and valued by me. Catching up on a missed talk over tea, giving advice about future career plans, thinking out the box and giving guidance on research techniques, are just some of the things that you have taken the time to do, and that have made my DPhil experience all the richer.

Kate Fitzpatrick, Lizzy Schroeder, Rachel Rowe, Oya Eddama and Claire Carson – where would I be without your wisdom? Thank you for your countless answers to my questions, and your friendship. I am so very glad you have been part of my time at the NPEU.

And to the engine behind my UKOSS work: Melanie Workman and Charlotte McClymont, and the technical whizzes Philippe Peirsegaele and Patsy Spark – a major part of my DPhil would not have happened had it not been for all of your hard work in getting me the data I needed, and for that I cannot thank you enough.

Dagmar Hutt, Lynne Roberts and Jane Forrester-Barker, I am grateful for your words of encouragement and caring attitude when I seemed to have needed it the most.

I would also like to thank the NIHR for funding my studentship without which the undertaking of this DPhil and work accomplished would not have been possible.

And finally, thank you to my husband Alex and my family for their unfailing support and patience - you know what this means to me, and I would not be where I am today if it were not for you.

List of Tables

List of Figures

Introduction

Topic and scope

The research presented in this thesis addresses questions concerning the current causes and consequences of sepsis amongst the maternal population in the UK. Sepsis is a leading cause of maternal mortality worldwide. Until recently in countries with advanced healthcare systems, sepsis in childbirth had been regarded as a disease of the past. Over the last three decades, however, there has been a near tripling in the rate of maternal deaths from sepsis. This is not a relative increase due other causes of maternal mortality decreasing, but an absolute increase. In an era of modern antibiotics, sepsis is now the leading cause of direct maternal death in the UK.

This thesis reports four epidemiological population-based studies designed to elucidate the key determinants of this trend. The first study is a regional population-based study conducted in Scotland; the following two are national-level studies from the UK; and the last is a large population-based study conducted in the USA. In order to frame this research in its historical context, a brief history of sepsis is presented alongside a review of the literature.

Definition of sepsis

Sepsis is a systemic inflammatory reaction characterised by the uncontrolled release of proinflammatory mediators in response to an overwhelming infection of normally sterile tissue. It is an end-stage condition that occurs following infection from a wide range of pathogenic organisms. If untreated, this condition can result in tissue damage, shock and death (Paruk, 2008). Causative organisms are most commonly bacterial, however fungi, viruses and parasites can also precipitate a septic state (Burke, 2009). Maternal sepsis in

this research refers to all-cause sepsis, unless genital-tract sepsis is specified in analyses or discussion.

Rationale for this research

The rate of maternal deaths from severe sepsis has increased in several European countries, most notably the United Kingdom (Kramer et al., 2009; Cantwell et al., 2011). In 2006-08, the UK maternal mortality rate from sepsis was 1.13 per (95% CI 0.77–1.67) 100,000 maternities; a rate not seen since the early 1970s (Cantwell et al., 2011; Acosta & Knight, 2013; Schutte et al., 2010).

There has also been an increase in the incidence and severity of sepsis morbidity in the general European and US populations (Martin et al., 2003; Dombrovskiy et al., 2007; Esper & Martin, 2007; Padkin et al., 2003; Vincent et al., 2006). Underlying this trend is an increasing number of deaths from group A streptococcal infection, most recently accounting for 50% of direct maternal sepsis deaths in the UK. This trend has also been observed in the Netherlands (Schuitemaker et al., 1998). Although the absolute risk of maternal death from sepsis is low, an increase in maternal mortality implies a greater number of women with severe, life-threatening illness who survive.

Pregnant and peripartum women represent a particularly vulnerable population for developing sepsis because the maternal immune system is modulated during these periods (Lucas et al., 2012). In addition, these women often present with symptoms of systemic inflammatory response syndrome (SIRS) as a result of ruptured membranes and changing biochemistry commensurate with labour and delivery, even without the presence of an infection. Since SIRS is the clinical marker of sepsis, a real infection and

the onset of sepsis can be difficult to recognise due to this masking effect. Recognition of an infection and the onset of sepsis can therefore be delayed due to this masking effect, until progression to severe sepsis (Paruk, 2008).

Waterstone and colleagues (Waterstone et al., 2001) conducted a regional study of severe maternal sepsis morbidity in the UK from 1997 to 1998, however there has not been a recent or national level study of morbidity (as opposed to mortality) since then. As a result, there are key information gaps regarding the incidence, main causative organisms, infection sources, and risk factors for severe maternal sepsis in the UK. Sepsis progresses along a spectrum of severity. Therefore an understanding of the risk factors along the continuum of sepsis morbidity from uncomplicated sepsis to severe sepsis at the population level is important for identifying preventive strategies that could be implemented to prevent maternal deaths.

Work carried out by the author

The author (CA) carried out all literature reviews, analyses and associated work described in this thesis unless otherwise specified. The author did not perform data entry or data extraction for the studies described in Chapters 4-7.

Chapter 1

A brief history of maternal sepsis

"…there was never a time when this disease did not exist."
-Nathaniel Hulme, *A Treatise on the Puerperal Fever* (London, 1772)

1.1 Introduction

Like all infectious diseases, the history of 'childbed fever' is a tragic one, rooted in the incomprehension of contagion. Historically, childbed fever referred to puerperal sepsis due to infection, primarily by the organism Group A *streptococcus*, contracted from unsanitary birthing conditions. Until the recent era of antibiotics, puerperal sepsis was the leading cause of maternal mortality worldwide. In eighteenth century England, sepsis accounted for approximately 50% of all maternal deaths (Loudon, 2000). During this time and up until the latter part of the nineteenth century, the concept of germs or how infection was spread was unknown or misunderstood. Hence, there was no form of antisepsis at this time. Births were attended by midwives or accoucheurs*, and it was these clinical professionals who unknowingly acted as vectors of transmission. As obstetrics became a more formal part of medical practice in mid-nineteenth century Europe and America, physicians reluctantly began to accept the contagious nature of puerperal infection. Louis Pasteur and Robert Koch confirmed this several decades later with their development of germ theory. After the advent of penicillin in 1944, severe puerperal sepsis was finally relegated to the rare case study in most obstetricians' careers – that is until recently.

One of the foremost historians of childbed fever, Dr. Irvine Loudon, wrote a comprehensive history of this disease from the eighteenth through to the twentieth centuries in his book, The Tragedy of Childbed Fever (Loudon, 2000). The brief historical account presented here is a synthesis of this comprehensive work as well as other historical sources. Whilst the text of this chapter is entirely original, its structure including the quotations and their placement in the text follows that of Loudon (Loudon,

* Early obstetricians (licensed physicians with some training in midwifery)

2000), since his work is the single authoritative reference on the history of childbed fever in the UK.

1.2 A brief history of maternal sepsis according to Dr. Irvine Loudon and other sources

Puerperal sepsis, and more broadly 'maternal sepsis' which encompasses both antenatal and postnatal sepsis, is one of the oldest referenced medical conditions. The earliest references date as far back as antiquity. It is thought that several ancient Hindu texts from 1500 B.C. make reference to puerperal sepsis (Lindeboom, 1969; Churchill, 1849). In addition, the Hippocratic Corpus (Corpus Hippocraticum), a compendium of medical works attributed to the teachings of Hippocrates and compiled in Alexandria in third century B.C., contains a treatise "On the Diseases of Women", in which puerperal sepsis is attributed to the imbalance of the humours (Loudon, 2000; Gordon, 1975; King, 2004).

During the first millennium and through the medieval era until the Renaissance however, reference to puerperal sepsis in Europe seems to have all but disappeared. This was most likely due to the few written works that were produced during this period. The earliest documented cases of puerperal sepsis in this period were during the Renaissance, undoubtedly because of the fame of those afflicted; Elizabeth of York, mother of King Henry VIII died one week after childbirth in 1491; Madeleine de la Tour d'Auvergne, mother of Queen consort of France Catherine de' Medici died in 1519; Jane Seymour, third wife of King Henry VIII died in 1537; and Catherine Parr, sixth wife of King Henry VIII died in 1548 (after marriage to her second husband); all from puerperal sepsis.

Although insufficient written accounts were made or have survived from before the seventeenth century to make an estimate of the burden of maternal sepsis, it is generally thought that the incidence was relatively rare. This is attributed to the fact that women gave birth at home and were usually attended by another female family member (Radcliffe, 1989; White, 1773). In seventeenth century Europe however, (ironically during the Age of Enlightenment) several determinants of maternal health changed, and so too did rates of childbed fever.

Firstly, seventeenth century Europe saw the burgeoning of hospital establishments, and with it the beginning of 'lying-in' hospitals. Since before the Renaissance, only wealthy families and individuals could afford the care of a medical practitioner, who was privately summoned when services were needed. The poor had no such option, and only in rare circumstances were attended by a trained medical professional. In the seventeenth century hospitals began to be established as philanthropic endeavours specifically to care for the poor. Caring for the poor, however, was not the only element to galvanize this advance[*] in medical practice.

An auxiliary philanthropic motivation for hospitals, and the second major change in the determinants of health during this time was the formalisation of medical education. During the Renaissance several official medical schools or colleges were formed throughout Europe. In England, the College of Physicians was sanctioned under King Henry VIII in 1518 to "grant licenses to those qualified to practice medicine and to punish unqualified practitioners and those engaging in malpractice." (Radcliffe, 1989;

[*] Historians dispute whether or not this was an 'advance'. At the time, hospitals might have done more harm than good in light of sparse legitimate medical knowledge and understanding of disease transmission.

Gordon, 1975) In the late seventeenth century the college received a royal charter and became the sole licensing body for medical books in England. In addition, partly based on methods being implemented at the medical school of Leiden, the college began to institute new standards of learning through regular lectures, ward rounds and systematic examinations (Shorter, 2012; Radcliffe, 1989; Lindeboom, 1969). Formal medical education, therefore, coincided with the growth in hospital establishments as they served as centres for medical teaching and learning.

These newly established hospitals, however, excluded several 'undesirable' patients including those with known contagious diseases such as scabies and smallpox, or those with venereal diseases. Two of the most egregious exclusions were children (with few exceptions) and pregnant women (Loudon, 2000; LaCroix, 2003). In response to the latter exclusion, philanthropists set about establishing 'lying-in' hospitals, which were early maternity hospitals or wards where poor women could go to deliver their babies. In addition to medical care by trained midwives, lying-in hospitals offered shelter, food, and warmth, which was a welcome respite for the hospitals' poverty stricken charges. As with hospitals and the formalisation of medical education, the establishment of lying-in hospitals coincided with the increasing acceptance of midwifery and eventually obstetrics into medical practice.

One of the first schools of midwifery and lying-in wards was established at the Hôtel Dieu Hospital in Paris in 1610 (Figure 1). Although viewed by impoverished women as preferable to giving birth in squalor outside of the hospital, accounts of conditions inside the hospital were appalling. As the only hospital in the city, it was severely overcrowded with often more than 2000 patients occupying its 1200 beds (Loudon, 1986; Meigs,

1854). Most patients shared beds and it was not uncommon to find a live patient occupying a bed with another who had already died (Barnes, 1865; Loudon, 2000; Radcliffe, 1989). At this time obstetricians or accoucheurs were still not recognised in the medical profession. Obstetric surgery was performed by barbers, then called barber-surgeons, and physicians were seen as superior to either barber-surgeons or midwives. When physicians on occasion had to visit the wards, it is said that they held sponges soaked in vinegar or perfume to their noses to block the vile stench of the sick and dying destitute (Loudon, 1986; Loudon, 2000).

It was in these noxious wards, where mortality is estimated to have been one in four to five (Loudon, 2000; Loudon, 1986), that conditions were rife for epidemics of childbed fever. After the establishment of the Hôtel Dieu lying-in ward in Paris, other lying-in wards and hospitals were founded throughout the eighteenth century in many European cities including Berlin, Vienna, Amsterdam, Stockholm, Copenhagen, Dublin and London. The first documented epidemic of childbed fever occurred at the Hôtel Dieu in 1646. Subsequent epidemics followed in Paris and other European cities throughout the eighteenth and nineteenth centuries.

Figure 1. Woodcut of the Hôtel Dieu Hospital in Paris (c. 16th century) (Loudon, 2000; Shorter, 2012). Patients can be seen sharing beds whilst nurses wrap those patients who have died.

In the 1770's the highest annual mortality rate during an epidemic year in the London General Lying-in Hospital was 3980 per 100,000 deliveries (Gordon, 1975; Great Britain General Register Office, 1839). In the Vienna Maternity Hospital during the 1820's, the highest annual mortality rate of an epidemic year was 7450 per 100,000, and in the Paris Maternité during the 1830's the highest annual mortality rate of an epidemic year was 8800 per 100,000 (Loudon, 2000; Barnes, 1865). These rates compare sharply with those of poor women attended to at home by charity midwives. For example, from 1831 to 1843, the rate of mortality due to puerperal sepsis amongst home births attended to by the Royal Maternity Charity in London was 100 per 100,000 births, whilst the mortality rate at the London General Lying-in Hospital was over 6000 per 100,000 births (Gordon, 1975; Macfarlane et al., 1984). During epidemic periods, case fatality in

lying-in hospitals could soar to over 80%. In two of the most devastating epidemics, in the Hôtel Dieu and another in Edinburgh in 1746, the case fatality was 100% - every woman in the wards died (Churchill, 1849; Loudon, 2000).

In the eighteenth and nineteenth centuries, terrible childbed fever epidemics tore through not only established hospitals, but also towns and more rural geographic areas. One of the most famous epidemics, and the earliest to be described in detail by the accoucheur Alexander Gordon, was that which occurred in Aberdeen, Scotland from 1789 to 1792. In the first few months of the epidemic (late 1789 to early 1790), there was a 100% case fatality. Throughout the remainder of the epidemic the case fatality oscillated from approximately 20% to nearly 70% (Gordon, 1975). Another example occurred in the town of Abingdon, a few miles south of Oxford, England. In the spring of 1814 there were twenty women who developed puerperal sepsis, of which nearly all died (Loudon, 2000).

These epidemics are today widely accepted as having been caused by Group A *streptococcus*, mainly due to the fact that puerperal fever epidemics closely correlated with other less invasive group A streptococcal infections, particularly erysipelas. Erysipelas is a skin infection or cellulitis usually caused by Group A *streptococcus*. It was Alexander Gordon who first realised that there was a link between the two infections during the epidemic in Aberdeen. He noted that concurrent with the puerperal fever epidemic, there was also an epidemic of erysipelas. He noted that whilst some midwives had no patients who died, others had more patients who died than lived. Further, the midwives with high a case fatality often were infected themselves with erysipelas on their arms, or had delivered a mother with erysipelas immediately before

tending to an eventually fatal case or series of cases. He writes in his *Treatise on the Epidemic of Puerperal Fever of Aberdeen* published in 1795,

> *"That the cause of this disease was a specific contagion, or infection, I have unquestionable proof . . . [it] seized such women only, as were visited, or delivered, by a practitioner, or taken care of by a nurse, who had previously attended patients affected by the disease." (Royal College of Physicians, 2013; Gordon, 1975)*

It was by the same mechanisms that puerperal sepsis epidemics occurred in lying-in hospitals as it did in towns. In lying-in hospitals midwives, barber-surgeons or accoucheurs would carry out frequent vaginal examinations and successively deliver women without any form of antisepsis in between. In addition, because women were crowded onto the wards and often shared beds, direct transmission of Group A *streptococcus* from one woman, with either erysipelas or puerperal fever, to their bed-partner would have been possible. It is not clear how often bed linen would have been washed, although it is certain that sheets were not disinfected because these techniques had not yet been invented.

Similar transmission also occurred in towns. Shortly after lying-in hospitals became popularised, obstetric practices began to be formed outside larger cities. These practices usually consisted of an accoucheur and several midwives who would very often attend several births in one day. Since there was no understanding of the link between disease and hygiene, bed linen, blankets, and operating clothes were only washed at the end of the day, if at all. Therefore a physician or a midwife could have transmitted the bacteria to a woman giving birth either upon infection with erysipelas or by simply carrying the bacteria on soiled bedclothes and dressings from one woman to the next.

As accounts of epidemics in lying-in hospitals and towns became more frequently known, what did people think caused this illness? Physicians and midwives agreed that puerperal sepsis was in some way contagious and seasonal, peaking in the winter. Germ theory, however, was not developed until the late nineteenth century. Unlike other diseases that were known to be contagious, there was no obviously understood source or visual place of infection as there is in smallpox or scabies. Theories on the causes of puerperal sepsis were numerous. They ranged from inflammation of the uterus, peritoneum, bowels, or intestines, to putrid breast milk, to a form of typhus (Lindeboom, 1969; Churchill, 1849). One of the later and prevailing theories of the period was that of 'miasma' or 'bad air' from which people were thought to fall ill. Alexander Gordon noted in his treatise that,

> *". . . I have evident proofs that every person, who has been with a patient in the Puerperal Fever, became charged with the atmosphere of infection, which was communicated to every pregnant woman, who happened to come within its sphere." (Loudon, 2000; Gordon, 1975; King, 2004)*

The confusion or clash of theories was best illustrated by Charles White, a physician from Manchester, in his "Treatise on the Management of Pregnant and Lying-in Women", published in 1773 (Radcliffe, 1989; White, 1773). He firmly disagreed with the common midwifery practice of closing all windows, keeping a hot fire and piling on soiled blankets and bed-linens so that the woman would not 'catch cold'. Instead he advocated for fresh cool air and absolute cleanliness of linen so that there would be no smells or odours to cause the miasma. Alexander Gordon also advocated for fumigation (burning or 'thorough purification') of patient linen and clothing. In addition, he advised midwives and physicians to "carefully wash themselves" (Radcliffe, 1989; Gordon, 1975) if they had cared for patients with puerperal fever before attending to further

patients. Unwittingly, Charles White and Alexander Gordon offered the first glimpse of antisepsis to prevent childbed fever.

It was not until seventy years later that a young physician across the Atlantic put forth a treatise on the indisputable evidence of medical professionals as vectors of puerperal fever. In 1843 Oliver Wendell Holmes, published the results of a scholarly review of all published reports of puerperal fever epidemics in the *New England Quarterly Journal of Medicine*. He emphasised the thesis of his work, which was:

> *"The disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses." (Radcliffe, 1989; Holmes, 1843; Holmes, 1855)*

He went on to write,

> *"The time has come when the existence of a private pestilence in the sphere of a single physician should be looked upon not as a misfortune, but a crime; and in the knowledge of such occurrences, the duties of the practitioner in his profession, should give way to his paramount obligations to society." (LaCroix, 2003; Holmes, 1843; Holmes, 1855)*

Not surprisingly, Holmes' contribution was disputed, at times vehemently, by eminent obstetricians of the day. Charles Meigs, professor and chair of midwifery at Jefferson College wrote in response to Holmes that, "Doctors are gentlemen, and gentlemen's hands are clean." (Loudon, 1986; Meigs, 1854)

Almost at the same time, a similar story was unfolding independently in Vienna. In the 1850's the Vienna Lying-in hospital was the largest in the world with approximately 7,000 births per year (Loudon, 2000). In comparison, the London General Lying-in hospital only had 200 to 300 births per year. Because of the large volume of patients, in

1833 the hospital was divided into two clinics which admitted patients on alternating days. In 1839 one clinic was allocated to serve as the teaching hospital for male medical students training to be obstetricians, and the other was allocated to female midwifery students. After the teaching allocation, the mortality rate of the physicians' clinic rose to three times that of the midwifery clinic (9840 per 100,000 deliveries vs. 3880 per 100,000 deliveries) (Loudon, 1986; Loudon, 2000). In 1846 a physician by the name of Ignaz Semmelweis was appointed as assistant to the physicians' teaching clinic. He soon realised that the mortality difference was a result of medical students and physicians going directly from postmortem dissections to examinations on the wards without washing their hands in between.

It was this realisation and an early cluster-randomised controlled trial of a disinfecting regimen that lead to the posthumous recognition of Semmelweis as the father of antisepsis. Semmelweis instituted a policy in which medical students were required to wash their hands after postmortem dissections in a solution of chloride of lime. Mortality rates in the first clinic subsequently fell back to those equal to the midwifery clinic. Oddly, Semmelweis did not publish the results of his findings until many years later, which coincided with the onset of severe mental illness. The result was a treatise that was muddled and interspersed with the ravings of a man who had clearly lost his mind (Loudon, 2000; Shorter, 2012). Preceding the publication, Semmelweis's verbal attempts to disseminate his views on 'cadaverous particles' and antisepsis were met with opposition from his contemporaries, much like the experience of Oliver Wendell Holmes.

Despite the dogged resistance to Holmes and Semmelweis, the climate of opinion eventually swayed in the latter half of the nineteenth century. This occurred for several reasons. Firstly, Holmes, Semmelweis and their predecessors had created enough controversy on the topic of contagion and antisepsis to begin to cast doubt in budding and open-minded obstetric practitioners. Secondly, the vehicle of transmission was eventually confirmed by the development of germ theory (that microorganisms are the cause of disease) by Louis Pasteur in 1865 and Robert Koch in the 1870's and 1880's. Lastly, the introduction and acceptance of antisepsis in surgery and childbirth by Joseph Lister in the 1860's resulted in a remarkable decrease in puerperal morbidity and mortality that continued into the twentieth century.

Through the eighteenth and nineteenth centuries, with the rise of lying-in hospitals, formalisation of midwifery and obstetric practice, and the changing climate of opinion towards contagion and antisepsis, what was the burden of puerperal sepsis on a larger population basis? Although there are fairly accurate accounts of specific epidemics during the eighteenth and nineteenth centuries, it is more difficult to estimate the incidence of puerperal sepsis across Europe. In England it has been estimated that two to three women per 1,000 maternities during non-epidemic periods and more than 25 women per 1,000 maternities during epidemic periods died from the condition (Loudon, 2000). In 1838, according to the First annual report of the Registrar-General of births, deaths, and marriages in England, there were 399,712 births (Gordon, 1975; Great Britain General Register Office, 1839). Using estimated non-epidemic rates, 800 to 1,200 mothers would have died of puerperal sepsis in England that year. The actual number is most likely higher given the frequency of epidemics. As French physician

Armand Trousseau said, whilst commenting on the epidemic rates at the Beaujon Lying-in hospital in Paris,

> *"It is a model hospital that there rules a mortality so enormous that if it were the type for the whole country, out of 900,000 to 950,000 labours taking place yearly, there would be 80,000 deaths, and France would be a desert in less than fifty years." (Loudon, 2000; Barnes, 1865)*

In comparison to other endemic diseases at the time such as dysentery, smallpox, typhoid, and tuberculosis, the crude mortality rate from puerperal sepsis was lower, however it was consistently the leading reported cause of maternal death during the 1700s and 1800s. As rates were similar to England if not higher in other European countries at the time, undoubtedly millions of mothers died across Europe from puerperal fever.

The first half of the twentieth century saw remarkable advances in the treatment of puerperal sepsis over a relatively short period of time. At the turn of the century, vaccines had already been discovered and were in limited use. Antibiotics, however, were yet to come. The challenge to scientists was to isolate a compound that would be lethal to bacteria, but non-toxic to humans. In 1910 this was achieved. The German scientist Paul Erlich developed the first antibiotic, 'compound 606' (a "magic bullet" as he called it), that was effective against syphilis. In 1932, Gerhard Domagk successfully treated mice infected with streptococcus using a dye derivative called Prontosil. Importantly, this compound contained a sulphonamide chemical group, which soon became the next "magic bullet". When the English physician Leonard Colebrook demonstrated the effectiveness of sulphonamides on women with streptococcal sepsis in three separate clinical trials between 1932 and 1935, the effectiveness of sulphonamides was definitively established. Since the compound was not patentable (the chemical

structure had already been described in 1908), in 1936 pharmaceutical companies began to widely produce the drug, a watershed event in the treatment of bacterial infection. Not long after, Alexander Fleming who was a colleague of Colebrook, discovered penicillin, the first antibiotic that was effective against both streptococcus and staphylococcus. From 1944 to 1945 penicillin became widely available, launching the modern era of medicine.

At the turn of the century until the introduction of sulphonamides in 1936, rates of puerperal sepsis mortality were on average 175 per 100,000 births per year in England and Wales (Gordon, 1975; Macfarlane et al., 1984). From 1936 to 1943, they had fallen to below 30 per 100,000, which is a testament to the impact of sulphonamides. By 1950, after the introduction of penicillin, the rate was four and by 1960 there was only one death per 100,000 births (Figure 2) (Churchill, 1849; Loudon, 2000). Between 1985 and 1987, the rate of death from puerperal sepsis in England was nearly zero (Gordon, 1975; Loudon, 2000). This dramatic decrease in puerperal sepsis mortality was mirrored in America and the rest of Europe, and thus brings us to the modern story of maternal sepsis.

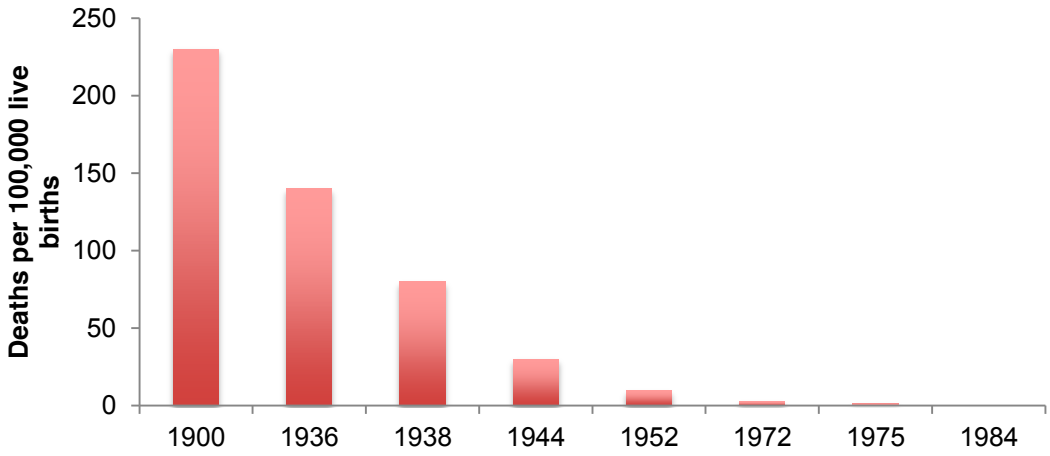


Figure 2. Mortality rates from puerperal sepsis in England and Wales from 1900-1984 (White, 1773; Macfarlane et al., 1984).

Chapter 2

Review of maternal sepsis mortality and severe morbidity

Part 1. History to present day – overview of global maternal mortality from sepsis, and epidemiological determinants in the UK

Part 2. Severe maternal morbidity from sepsis – a structured literature review

Part 1. History to present day – overview of global maternal mortality from sepsis, and epidemiological determinants in the UK

2.1 Introduction

The modern story of maternal sepsis includes both antenatal and postnatal sepsis. Throughout the history of maternal sepsis, there have always been many more cases occurring during the puerperium than during pregnancy. This is because until a woman goes into labour, there are highly effective physiological barriers in place to prevent bacterial infection: low pH of the genitourinary tract (in which most bacteria cannot survive), intact membranes and a closed cervix. During labour, delivery and the puerperium, all of these barriers are lost: membranes rupture, the cervix opens, the pH of the genitourinary system becomes more neutral and the endometrium suffers abrasion (effectively a wound) with the delivery of the placenta. Equally, after a Caesarean section, a woman is at much higher risk of infection either at the surgical site or internally if contamination has occurred during the operation. Diagnosed severe antenatal sepsis, therefore, has always been a more rare event. Not surprisingly, historical clinical accounts of maternal sepsis have been dominated by puerperal fever with rare mention of severe infection during pregnancy.

After the introduction of antibiotics however, the gap in the incidence between antenatal and postnatal sepsis mortality became much smaller; rates of puerperal sepsis fell, whilst rates of antenatal sepsis remained relatively constant. Subsequently, antenatal sepsis became increasingly recognised. The 1938 Fifth Edition of the International

Classification of Diseases (ICD), (then called the International List of Causes of Death) only contained codes for puerperal infection. When this was revised to the 6th Edition in 1948 a new code appeared for 'sepsis of childbirth and the puerperium', in addition to codes for infections of the genitourinary tract during pregnancy (Macfarlane, 2004).

Data sources for the incidence of maternal mortality also began to include all causes of maternal sepsis rather than just puerperal fever. However, since the incidence of maternal mortality overall declined in the second half of the twentieth century, many high-income countries stopped keeping detailed records of maternal death. One of the few exceptions was the UK. (Scandinavian countries and the Netherlands also kept records.) Data about maternal deaths in England were first collected through the Office of the Registrar General in 1838 when general death certification was introduced. In an effort to gather more detailed information, local enquires into maternal deaths began in Aberdeen, Scotland in 1917 (Scottish Board of Health et al., 1928; Loudon, 1986). These enquires spread throughout the UK and in 1932 the UK Ministry of Health began sending out a standardised reporting form to all maternity and child welfare authorities. This reporting system eventually became known as the UK Confidential Enquires into Maternal Deaths and still exists today (Macfarlane, 2004), and is now coordinated by the recently established MBRRACE-UK collaboration.

2.2 Recent trends in maternal mortality from sepsis in the UK

Using data from the Maternal Death Enquires, it is clear that a significant change in the rate of maternal sepsis mortality has occurred in the past two decades. In contrast to the steep and steady decline in maternal sepsis deaths over most of the twentieth century, the rate unexpectedly and quite sharply increased from 1988 to 1990 and has since remained on this course with a near tripling in the rate over the last two decades (Figure 3). In the late 1980's the sepsis maternal mortality rate (MMR) was 0.4 per 100,000 maternities, whilst in the period from 2006-2008 the MMR increased to 1.13 per 100,000 (Cantwell et al., 2011). This rate places sepsis as the leading cause of direct maternal death in the UK, surpassing that of hypertensive disorders.

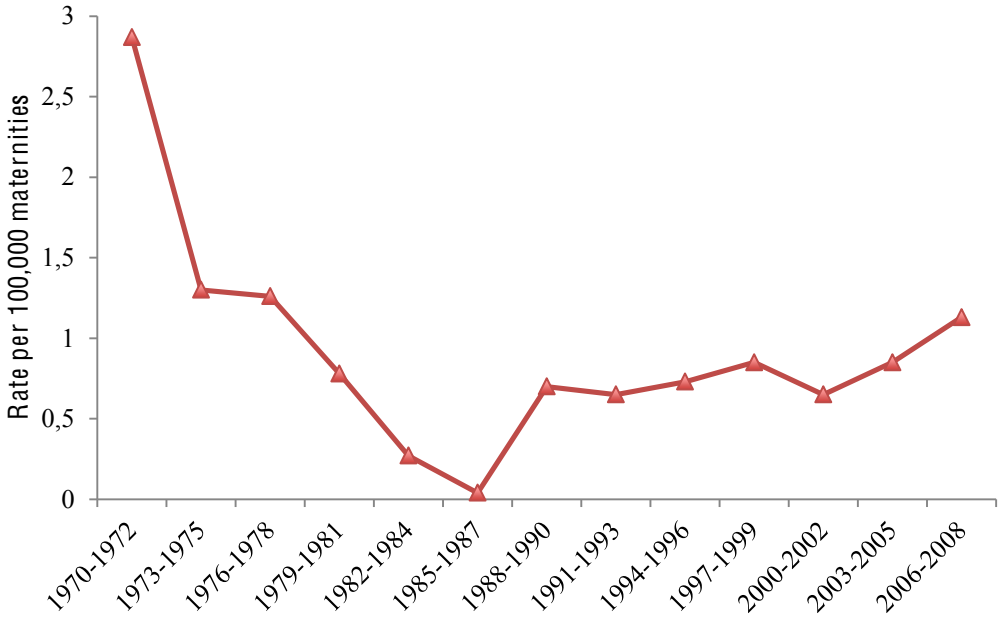


Figure 3. Incidence of maternal sepsis mortality in the UK from 1970 to 2008.

2.3 Causes and epidemiological determinants of the trend in the UK

What has caused the increase in maternal sepsis deaths in the UK? The answer is almost certainly multifaceted, but not yet entirely clear. One of the most important factors is likely to be the increased incidence and severity of sepsis in the general population, which has occurred both in Europe (Padkin et al., 2003; Vincent et al., 2009) and the USA (Martin et al., 2003; Esper & Martin, 2007; Dombrovskiy et al., 2007). This is mainly attributed to an increase in invasive streptococcal infections (Zakikhany et al., 2011; Carapetis et al., 2005; Lamagni et al., 2009) and an emergence of hypervirulent strains of Gram-positive Streptococcus pyogenes or group A streptococcus (Aziz & Kotb, 2008).

2.3.1 The role of β-haemolytic group A *streptococcus* (streptococcus pyogenes)

In the most recent triennial report from the UK Confidential Enquiries into Maternal Deaths (2006-2008), group A streptococcus was responsible for 13 out of 29 (45%) genital tract sepsis deaths (Cantwell et al., 2011). Similar findings were also reported for maternal deaths in the Netherlands (Schutte et al., 2010; Schuitemaker et al., 1998).

Louis Pasteur first described streptococci in 1897, and in the 1920's the American microbiologist Rebecca Lancefield further categorised the genus into groups according to surface antigen. It was the A group that was consistently identified in epidemics of puerperal fever, which also led to its acceptance as the causative organism in historical epidemics in Europe and North America. With the advent of penicillin in 1945, maternal deaths from group A *streptococcus* dropped to nearly zero and non-fatal maternal infections from Gram-negative organisms such as *Escherichia coli* became dominant.

Since the mid 1990's, however, there has been a re-emergence of group A streptococcus as a leading cause of sepsis in the general population (Carapetis et al., 2005; Abouzeid et al., 2005). In the UK, there was a peak in 2003 of group A *streptococcus* cases reported to the UK Health Protection Agency. This coincided with a peak in maternal deaths caused by group A *streptococcus* during that year, and since then the incidence of maternal deaths has continued to increase.

The natural reservoir of group A *streptococcus* is in the human nose and throat, and it is most commonly transmitted during seasonal influenza periods on aerosolised droplets. The organism is also found in the mucosal membranes of the intestines and vaginal tract, and is known to be able to cross intact membranes (Royal College of Obstetricians and Gynaecologists, 2006). Thus, genital tract colonisation can occur directly through improper hand hygiene with subsequent contamination of the perineum, or secondarily via a site of skin breakage, or initial infection elsewhere such as the respiratory tract. Approximately 5-30% of the population are asymptomatic carriers of the organism (Health Protection Agency, Group A Streptococcus Working Group, 2004) (Patterson, 1996), and carriage rates are known to be higher amongst certain populations such as military personnel, prisoners and hospital workers. Group A *streptococcus* can cause a variety of clinical diseases including (but not limited to) pharyngitis, scarlet fever and genital tract sepsis.

Genetically, group A *streptococcus* strains can be classified according to genotype (according to M and T antigens or by the *emm* gene), of which there appears to be a predominance of genotype *emm*28 amongst women with genital tract sepsis; approximately one-third of cases are caused by *emm*28 strains. In contrast, *emm*1 strains

predominate in group A streptococcal pharyngitis (Luca-Harari et al., 2008; Luca-Harari et al., 2009). Perplexingly, there is no genotype that consistently causes a particular infection (Luca-Harari et al., 2009). Subtype M1 has been isolated in cases of maternal sepsis and likewise, *emm*28 has been isolated in cases of pharyngitis. In a recent review of new understandings of group A *streptococcus*, Lynskey et al. discuss the increase in mortality associated with *emm*1, which has remained prevalent in the UK for the past 25 years (Lynskey et al., 2011). Whilst there is an association between *emm*28 and maternal sepsis, it appears that *emm*1 is more strongly associated with maternal mortality (Lynskey et al., 2011). It is also not yet understood what causes virulence or focus of infection. Whether it is the transmission from a carrier to a susceptible non-carrier that causes clinical infection, or whether an organism can become pathogenic whilst in the natural host is still to be determined.

Regardless of the cause of virulence or the particular strain, it is highly probable that many epidemics of the past were caused by respiratory transmission by an unknowing asymptomatic carrier. This also explains the seasonality of group A streptococcal infections. Since the time of Alexander Gordon, it has been observed that epidemics usually occur or worsen during the winter, coincidental with the influenza season. As people with influenza or the common cold cough and sneeze, group A *streptococcus* is also spread on aerosolised droplets. Of concern is that rates of all streptococcal infections in the general UK population, including those caused by group A *streptococcus* have been increasing steadily (Figure 4) (Lamagni et al., 2009). Additionally, since 1994 it has re-emerged as the predominant causative organism in maternal sepsis deaths (Lucas et al., 2012).

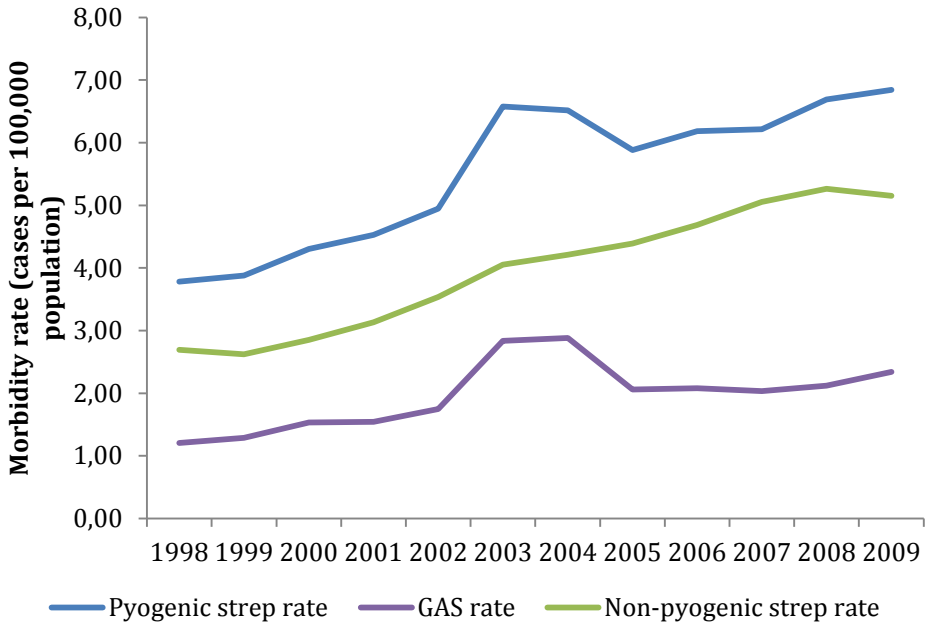


Figure 4. Rates of all pyogenic and non-pyogenic streptococcal infections and group A *streptococcus* (GAS) reported to the UK Health Protection Agency from 1998 to 2009 (Health Protection Agency, 2012).

Other organisms that commonly colonise the genitourinary tract, such as Escherichia coli (E. coli) can also cause maternal sepsis. Although there have been fewer deaths from E. coli compared to group A *streptococcus*, it is still not known to what extent this organism plays a role in severe maternal sepsis morbidity. Other causative organisms of maternal sepsis are listed in Table 1.

Table 1. Common causative organisms of maternal sepsis.

Common causative organisms	
Gram-positive	*Streptococcus:* groups A, B, D *Streptococcus pneumoniae* *Staphylococcus aureus*
Gram-negative	*Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Acinetobacter spp.*
Anaerobes	*Clostridium spp.*

2.3.2 Changes to operative deliveries

A factor that that has coincided with the increase in maternal deaths from sepsis since the mid 1980's is the increasing rate of caesarean section. There has been a marked increase in the rate of caesarean section delivery, specifically emergency caesarean section delivery (Figure 5) (Hospital Episode Statistics, 2012). Over the course of 33 years from 1955 to 1988, the rate of caesarean sections increased gradually from approximately 2.5% to 11% by an average of a quarter of a percent per year. However, from 1989 to 1990 the rate increased by more than 1% per year and continued to increase until plateauing at nearly 25% in 2005. As seen in Figure 5, the rate of increase in emergency caesarean sections has been much greater, compared to elective caesarean sections. Elective caesarean sections have increased by an average of only 0.2% per year since 1990 (Hospital Episode Statistics, 2012).

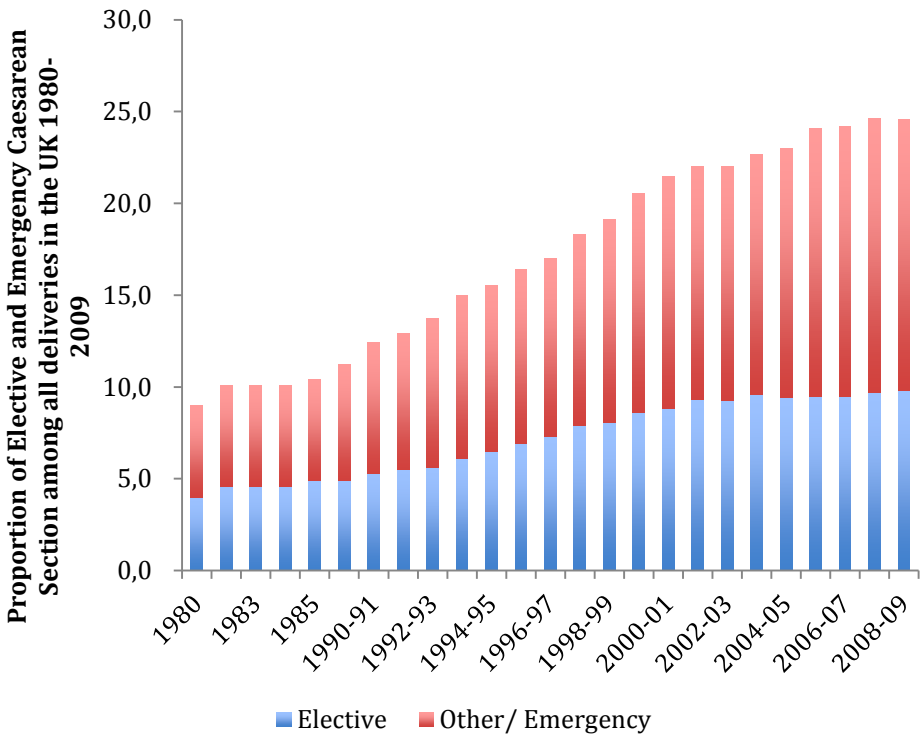


Figure 5. Proportion of elective and emergency caesarean section deliveries in the UK from 1980 to 2009 (Hospital Episode Statistics, 2012).

In addition to caesarean sections, the techniques used in operative vaginal delivery also appear to have shifted since 1988. Prior to that year there was limited practice of the ventouse during operative vaginal delivery (less than 1%). In 1988, however, ventouse usage began to increase substantially whilst usage of forceps decreased at an almost equal rate (Figure 6). When looking at rates of maternal sepsis deaths, there appears to be a secondary increase in 2003 (Figure 3). Interestingly, this seems to have coincided with a renewed usage of forceps, contributing to an overall increase in operative vaginal delivery rates.

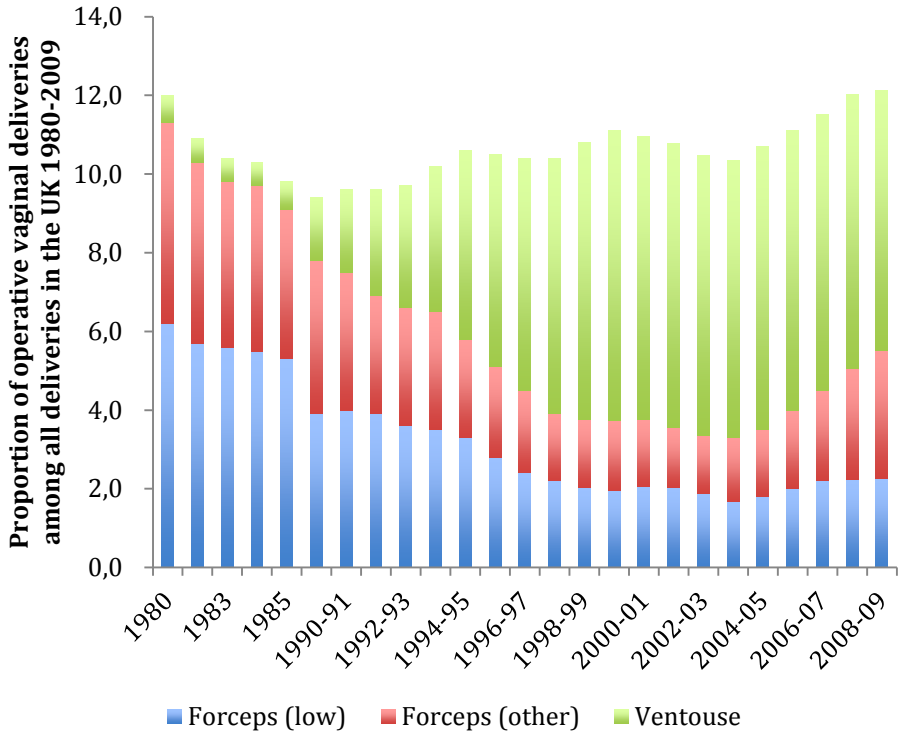


Figure 6. Rate of operative vaginal deliveries (according to method) in the UK from 1980 to 2009 (Hospital Episode Statistics, 2012).

2.3.3 Migration and travel

Another change that was also occurring during these years was the pattern of migration in Europe coupled with increasing travel abroad by UK residents. This is important because large movements within and between populations naturally facilitate shifts in circulating strains of organisms. This will be discussed in the context of Group A *streptococcus* in section 2.3.6. Following the dissolution of the Soviet Union in 1990, there was an influx of immigrants to Western Europe including to the UK. In the UK, the mid 1980s was the start of a net positive increase in migration into the country (Figure 7). Between 1985 and 1993, over 2.1 million people migrated to the UK (Office for National Statistics, 2013). In addition, UK residents travelled abroad approximately 30 million times per year (90 million in total) over the three year period (Figure 8) (Smith, 2010). Since 1990, the number of visits abroad by UK residents has doubled to approximately 60 million visits per year.

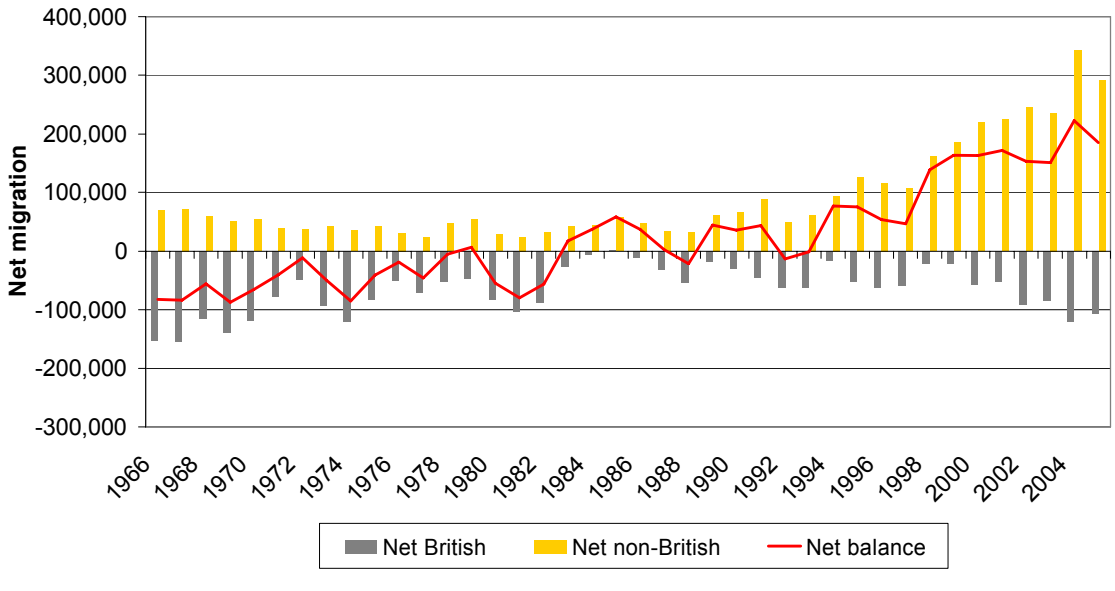


Figure 7. Net British and non-British migration to/from the UK, 1966-2005 (Reproduced from: Institute for Public **Policy Research (IPPR), Britain's** Immigrants: an economic profile, 2007 (Sriskandarajah et al., 2007).

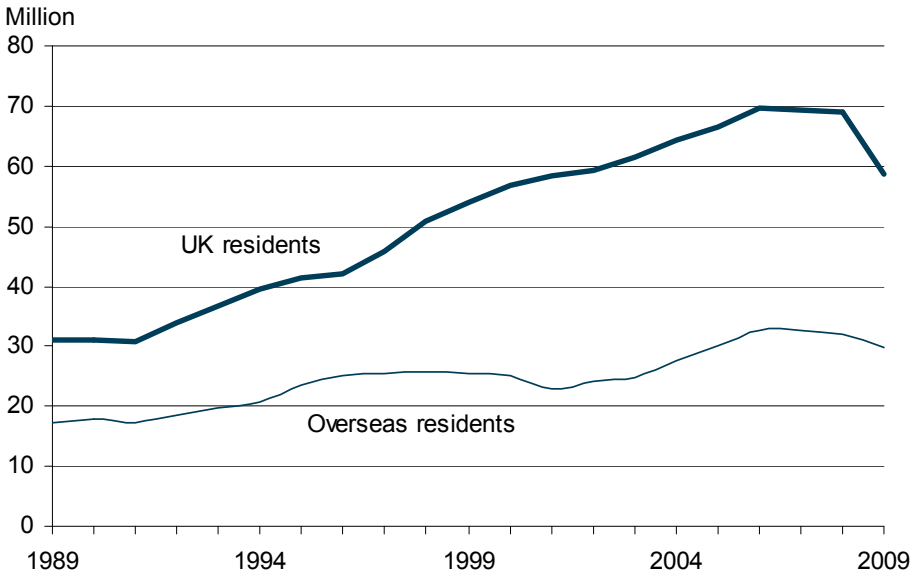


Figure 8. Number of visits by overseas residents to the UK and UK residents abroad (Reproduced from: Office for National Statistics, Travel Trends, 2009 (Smith, 2010)).

2.3.4 Obesity

Another determinant potentially contributing to trends in maternal sepsis in the UK is the increase in rates of obesity amongst pregnant and peripartum women (Heslehurst et al., 2007). The risk of maternal sepsis being potentially associated with obesity has not been well described, although obesity has been implicated in poor wound healing (primarily in relation to Caesarean section) (Sebire et al., 2001; Usha Kiran et al., 2005; Robinson et al., 2005; Martens et al., 1995; Beattie et al., 1994), genitourinary (Sebire et al., 2001) and uterine infection (Usha Kiran et al., 2005) in the obstetric population.

2.3.5 Immunology and physiology

Pregnant and peripartum women are intrinsically vulnerable to infection due to immunological and physiological factors, which compound the underlying pathogenesis of an invasive infection. During pregnancy, the maternal immune response is down-

regulated to protect the immunologically distinct fetus from maternal inflammatory responses (Mor & Cardenas, 2010; Mor et al., 2011; Mason & Aronoff, 2012). As such, there is a reduction in cell-mediated immunity (T-cell proliferation), which plays an important role in immune response to pathogens. Onset of labour also disrupts crucial physiological barriers against bacterial infection (Paruk, 2008). Likewise, after caesarean section a woman is at much higher risk of exposure to pathogens at the surgical site and in the endometrium. Lastly, pregnant and peripartum women often present with symptoms of systemic inflammatory response syndrome (SIRS) as a result of ruptured membranes and changing biochemistry commensurate with labour, even without the presence of an infection. Since SIRS is also a biomarker of sepsis, a serious infection can often be masked.

2.3.6 Relationship between group A streptococcus and epidemiological determinants

In order to understand how trends in maternal sepsis mortality rates and epidemiological determinants in the UK might be related, we must look again at the organism level. In the mid to late 1980s, although carriage rates of group A *streptococcus* amongst migrants and travellers were most likely similar to that of the UK population, movement in the population may have helped to facilitate a shift in circulating strains of group A *streptococcus*. Any kind of a shift in circulating strains would have been complicated by the fact that there was an epidemic flu season in 1989 to 1990 (Scaber et al., 2011). There were 23,046 deaths from flu in the UK during that season (Public Health Wales, 2013), which was four to five times greater than normal. Of additional consideration is that in the mid 1980s it became standard practice for obstetricians, midwives and partners/family members to no longer wear surgical facemasks during delivery.

Caesarean section, as with any surgery, carries a risk of infection particularly at the surgical site. In addition, risk of sepsis is greatly increased if the woman already has an intrauterine infection or chorioamnionitis prior to the section. Likewise, women who undergo an operative vaginal delivery will do so only after a failed spontaneous delivery. This may follow a prolonged labour in which the woman's vaginal tract is highly exposed to pathogens. If community-acquired group A *streptococcus* had been increasing in the general population, which was exacerbated by an epidemic flu in 1989, and if there had been a shift in dominant strains thereby causing heightened virulence in non-carrier susceptible women, particularly pregnant and peripartum women with a modulated immune state, could these conditions coupled with changes in invasive deliveries that inherently carry a higher risk of infection have set the trend for the next two decades?

The extent to which epidemiological determinants are interrelated remains speculative. However, current epidemiological investigation can elucidate the risk factors for severe maternal sepsis morbidity and mortality; this in turn can further drive the epidemiological understanding of how changes in those risk factors may have precipitated and contribute to the current increasing trends in maternal mortality from sepsis.

2.4 Is the trend in maternal sepsis mortality also occurring in other countries?

Decades after the development of effective low-cost antibiotics, sepsis remains a leading cause of preventable maternal death worldwide. Particularly in settings where the greatest barrier to intervention is poverty, maternal death from sepsis is a continuing representation of maternal health inequality. In high-income settings maternal death from sepsis is rare, although the noted recent increase in several countries raises concern at all levels.

2.4.1 Definitions and under-reporting

Before discussing trends in maternal mortality in other countries, reporting issues that exist must be discussed. Currently, there are several challenges in defining maternal mortality from sepsis, which lead to under-reporting. One of these challenges is the differing of two international definitions for puerperal or postpartum sepsis (Table 2) (Bouvier-Colle et al., 2012; Technical working group, 1992). Vital statistics (registration) systems use the International Classification of Diseases (ICD-10) definition, whilst maternal death reviews or confidential enquiries into maternal deaths generally use the World Health Organization (WHO) definition. Although recommending a different definition, WHO global estimates and reports must rely in many places on country vital registration data, which use ICD-10.

Definitions		Clinical criteria*	
ICD-10	A rise in temperature above 38.0C (100.4F) sustained for more than 24h or recurring between the end of the first and 10th day after childbirth, miscarriage, or termination of pregnancy	SIRS	At least two of the following: Temperature >38 or <36C Heart rate >90 beats/min Respiratory rate >20 breaths/min or PaCO2<32 mmHg (4.3 kPa) White cell count: >12000 cells/µl or <4000 cells/µl or 10% immature/band forms
		Sepsis	SIRS with infection
WHO	Infection of the genital tract occurring at any time between the onset of rupture of membranes or labour and the 42nd day postpartum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, abnormal smell/foul odor of discharge and delay in the rate of reduction of the size of the uterus	Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status
		Septic shock	Sepsis associated with hypotension, despite adequate fluid resuscitation along with the presence of perfusion abnormalities as listed for severe sepsis. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured

Table 2. International definitions, clinical criteria and common causative organisms of maternal sepsis. *1992 American College of Chest Physicians and the Society of Critical Care Medicine definitions (Bone et al., 1992).

In a recent study on the use of maternal mortality data for monitoring trends over time in the European Union, Bouvier-Colle et al, found that there is significant under-reporting of maternal deaths using routine registration data (Cross et al., 2010; Bouvier-Colle et al., 2012). Other studies have reported similar findings (Cantwell et al., 2011; Turner et al., 2002; Gissler et al., 1997; Deneux-Tharaux et al., 2005; Donati et al., 2011; Schuitemaker et al., 1997). Maternal death audits or confidential enquiries into maternal deaths, which are more specific and in-depth than vital statistics are designed in part to address these data challenges. Few countries, however, have such systems in place. Currently only the UK, Finland, France, The Netherlands, Slovenia, Australia and South Africa supplement vital statistics data with routine maternal death auditing or enquiries (Technical working group, 1992; Bouvier-Colle et al., 2012).

In low-income countries substantial under-reporting of maternal deaths often occurs in areas where the burden of maternal sepsis is the greatest (Bouvier-Colle et al., 2012; Cross et al., 2010). Many births and subsequent maternal deaths in these countries take place at home or after hospital discharge without postnatal follow-up and thus go undocumented. In addition, the discrepancy in determining the point after birth at which a sepsis death may be related to the birth is particularly problematic. Adding to this challenge is the misclassification of maternal deaths in countries with a high prevalence of endemic diseases such as HIV, malaria and tuberculosis. In mothers with co-morbid diseases that are not unique to pregnancy, it can be unclear if the cause of death should be classified according to the underlying disease (indirect cause) or sepsis (direct cause).

This issue of direct versus indirect classification of maternal sepsis death is one faced by all reporting systems. Currently the focus of direct causes of maternal death from sepsis is the genital tract. However the total burden of maternal sepsis including other foci of infection, such as the respiratory tract, is much larger. Thus, as an understanding of maternal immune function and host-pathogen interactions evolve, so too will be the challenge of how we classify maternal sepsis deaths. Some studies are already beginning to adopt more general definitions which include both genital tract sepsis and sepsis arising from other sources but occurring in pregnancy or postpartum (Turner et al., 2002; Cantwell et al., 2011; Gissler et al., 1997; Deneux-Tharaux et al., 2005; Donati et al., 2011).

2.4.2 Global perspective of maternal mortality from sepsis

With an understanding of the biases and challenges that result in underreporting, sepsis is still a leading cause of preventable maternal death in both high and low-income countries. Sepsis is estimated to account for 10% of maternal deaths worldwide, with the greatest burden in Southeast Asia and Africa. In these regions, sepsis is estimated to account for 13.2% and 10% of maternal deaths respectively (World Health Organization, 2011). Sadly, the estimated ratios in many sub-Saharan African countries are higher than those of the pre-antibiotic era in western countries (Figure 9). The most robust data from this region come from the Confidential Enquiries into Maternal Deaths in South Africa. During the most recent measurement period (2008 to 2010), the institutional maternal mortality rate (MMR) due to genital tract sepsis was 9.34 per 100,000 live births; 14.6% of direct maternal deaths were from sepsis, of which the majority (71.4%) were found to be avoidable (National Committee for the Confidential Enquiries into Maternal Deaths, 2012). Notably, the total MMR from sepsis including home births for South Africa has been estimated to be 1.8 to 3.6 times higher than the institutional rate (National Committee for the Confidential Enquiries into Maternal Deaths, 2012; Pattinson, 2011).

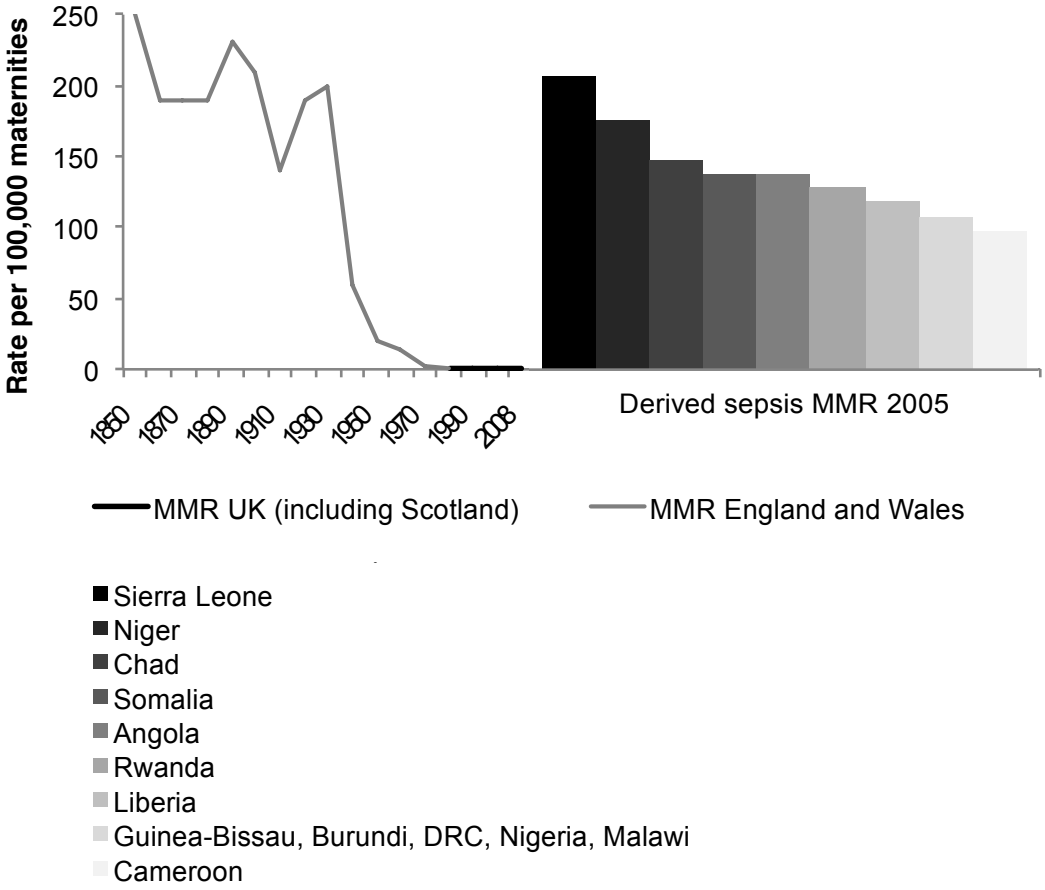


Figure 9. Sepsis MMR in England and Wales and the UK (1850-2008) (Loudon, 2000; Confidential Enquiry into Maternal and Child Health CEMACH, 2008; Cantwell et al., 2011) compared to derived sepsis MMRs in high-incidence sub-Saharan African countries (Khan et al., 2006; Department of Reproductive Health and Research, 2008).

Overall, global rates of sepsis maternal mortality have decreased as progress has been made towards Millennium Development Goal-5 (MDG-5: to reduce the MMR by three quarters between 1990 and 2015, and to achieve universal access to reproductive health by 2015) (Musgrove, 1993; World Health Organization, 2011). However with progress come challenges, and most developing world regions remain far off track from target rates. In an important review of health system infection control measures in low-income countries, Hussein and colleagues, highlight the delicate balance that exists between providing skilled obstetric care as the most effective means of decreasing maternal

mortality, and the increased need for vigilant infection control measures as the provision of institutionalised birth settings increases (Hussein et al., 2011). Many low-income countries are at a transitional point in which more women than ever before are delivering in healthcare facilities. As tragically experienced by western countries until the early 20th century, despite knowledge of infection transmission, sepsis epidemics swept through maternity wards as a result of birth attendants treating many women consecutively without proper aseptic techniques. In resource-poor settings, where the number of skilled birth attendants is still severely limited as are medical supplies, this context may be of current concern.

Increases in maternal mortality from sepsis have also occurred in high-income countries other than the UK. In The Netherlands, the sepsis MMR has also increased, but to a lesser degree than in the UK; from 0.5 per 100,000 live births (1983-1992) to 0.7 per 100,000 (1993-2006) (Kramer et al., 2009; Schutte et al., 2010). Additionally in the USA, a recent national study by Bauer and colleagues found that the MMR from sepsis increased from 1998 to 2008 by 10% per year with an overall MMR of 0.95 per 100,000 deliveries for the 11-year period (95% CI 0.76-1.2 per 100,000 deliveries, respectively). Maternal mortality is an important indicator of health care system performance (Wildman et al., 2004) in both high and low-income countries. As such, even a small increase in the maternal mortality rate may represent a greater magnitude of severe morbidity and challenges to the overall system of care.

Based on current literature, it does not appear that this trend is consistent across high-income countries, however significantly more international data will be needed to make a valid determination. In France the sepsis MMR has decreased steadily since 1996

(Bouvier-Colle et al., 2011; Benhamou et al., 2009). In Australia the rate of maternal death from sepsis is very low with only one reported death in the most recent confidential enquiry (Sullivan et al., 2008).

2.5 Proximal risk factors for maternal sepsis mortality

Determining risk factors for maternal sepsis mortality is surprisingly difficult. This is mainly because, fortunately, few deaths occur where there are resources to accurately measure risk (countries with maternal death reviews), rendering studies insufficiently powered to draw robust conclusions. Risk factors identified thus far in other high-income countries are summarised in Table 3. The causal pathways and interactions of many of these factors, however, are poorly understood.

Table 3. Risk factors for severe maternal morbidity and mortality from sepsis. (Maharaj, 2007; Sriskandan, 2011)

High-income countries	Caesarean section Emergency caesarean section Prolonged rupture of membranes Retained products of conception Early labour Multiple vaginal examinations (>5) Obesity Diabetes Anaemia Failure to recognise severity	Low-income countries	Caesarean section Emergency caesarean section Poverty Unhygienic birth conditions Lack of skilled birth assistants Long distance to healthcare facility Unavailable medical supplies Young age Primiparity Anaemia HIV, Tuberculosis, Malaria Failure to recognise severity

In high-income countries, caesarean section has repeatedly been shown to be a major risk factor for severe infectious morbidity (Maharaj, 2007; Leth et al., 2009). Compared to women who have a vaginal birth, women who have a caesarean section have a five to 20-fold greater risk of severe infection such as endometritis or wound infection (Smaill & Gyte, 2010). Obesity is also a significant emerging factor (Acosta et al., 2012;

Confidential Enquiry into Maternal and Child Health CEMACH, 2008; Lucas et al., 2012). Obesity is known to be immunosuppressive (Huttunen & Syrjänen, 2010; Nave et al., 2011; Huttunen & Syrjänen, 2012; Karlsson & Beck, 2010), although the effect of it superimposed onto the immunomodulated state of pregnancy is unclear, and will be an important area for future research. Strikingly, and as discussed in section 2.3.2, in contrast to other factors the rates of both caesarean section and obesity have increased dramatically worldwide in recent decades (Lu et al., 2001; Knight et al., 2010; Thomas, 2006; Smaill & Gyte, 2010).

In low-income countries, poverty is the single most important and overarching determinant of maternal mortality from sepsis. Related to this are the more proximal factors of unhygienic birth conditions, delivery without birth assistants, long distance to healthcare facility, and lack of availability of antibiotics and/or other medical supplies (Table 1) (Ronsmans & Graham, 2006; Sriskandan, 2011). In addition, immunosuppression due to HIV/AIDS compounded by opportunistic infections such as tuberculosis greatly increase the risk of severe postpartum infections (Björklund et al., 2005; Ronsmans & Graham, 2006; Maharaj, 2007).

Critically, in both high and low-income countries, failure to recognise the severity of an infection by the woman herself, family members, birth attendants and hospital staff is a common avoidable factor (National Committee for the Confidential Enquiries into Maternal Deaths, 2012; Cantwell et al., 2011; Appelboam et al., 2010).

2.6 What is currently being done to address severe sepsis?

In light of the worldwide increase in general sepsis incidence, the Surviving Sepsis Campaign (SSC) was launched in 2002 as a major international initiative to provide standardised evidence-based recommendations for the management of severe sepsis, including intervention bundles for early goal directed therapy (Levy et al., 2010). Numerous articles and guidelines have recently reviewed the SSC bundles as well as critical factors in clinical presentation and diagnosis of maternal sepsis (Lucas et al., 2012; Maharaj, 2007; Paruk, 2008; van Dillen et al., 2010; Cantwell et al., 2011; Sriskandan, 2011; Royal College of Obstetricians and Gynaecologists, 2012b; Royal College of Obstetricians and Gynaecologists, 2012a; Barton & Sibai, 2012). Currently, the 'resuscitation bundle' and 'management bundle' are recommended for obstetric patients in the UK (Royal College of Obstetricians and Gynaecologists, 2011).

In an important recent study, Levy and colleagues presented the findings of a prospective multinational cohort study of the outcomes of the SSC in intensive care units in the USA and Europe (Levy et al., 2012). The authors identified differences in the models of intensive care resourcing and use. Their findings suggest greater early direct referral to intensive care in the USA, compared with greater expert care once admitted to intensive care in Europe. Additionally, although clinical care was delivered expeditiously in Europe, patients reached intensive care later, and were therefore sicker as indicated by higher unadjusted mortality rates. Although this study was not specific to maternal outcomes, the findings have significant bearing on obstetric care.

In low-resource settings it has been observed that SSC early goal directed therapy is often started long after initial diagnosis as a result of late referral and shortage of

intensive care beds, which critically impact the efficacy of early goal directed therapy (Bozza & Salluh, 2010). A subsequent proposal is that an emphasis on improving access to skilled professional care (as outlined by MDG-5) with accurate and early assessment associated with general measures such as hydration, blood cultures, and antibiotics would obviate the need for frequent provision of early goal directed therapy, and thereby be more cost-effective (Bozza & Salluh, 2010; Ho et al., 2006). Whether in high or low-resource settings, a ubiquitous key message across all efforts is that maternal mortality from sepsis is preventable, and early recognition is vital to achieving that outcome.

2.7 Conclusions

A general increase in invasive group-A streptococcal infection underpins the recent increase in maternal sepsis mortality in the UK, however other epidemiological determinants and risk factors are interrelated and may also play a role including obesity and caesarean section. Despite the reality of underreporting, sepsis remains a leading cause of preventable maternal death worldwide. The need for robust data and subsequent analysis in both high and low-income countries is apparent, and will significantly increase the understanding of risk factors and causal pathways with a view to effective prevention strategies. The clarity that this research will bring however, is only of value if combined with early recognition and management of sepsis, which is key to saving mothers' lives.

Part 2. Severe maternal morbidity from sepsis – a structured literature review

2.8 Introduction

As discussed in Part 1 of this chapter, determining risk factors for maternal sepsis mortality, is surprisingly difficult. This is because, fortunately, few deaths occur where there are resources to accurately measure risk (for example, in countries with maternal death reviews), rendering studies insufficiently powered to draw robust conclusions. As also discussed in Part 1, although mortality as a result of pregnancy related sepsis is uncommon in countries with developed healthcare systems, it remains a leading cause of preventable maternal death (van Dillen et al., 2010). Importantly, for each maternal death, the number of women with severe life-threatening morbidity is likely to be much greater. In high-income countries, assessing factors associated with severe morbidity ('near miss' or serious acute maternal morbidity (SAMM)) has become a valuable method for developing intervention strategies 'upstream' of a sentinel event such as death (Pattinson & M. Hall, 2003).

Severe maternal sepsis is a challenging condition to study in this regard for several reasons. The first is that severe maternal sepsis can occur at any point in pregnancy, labour or the postpartum period. Each of these periods has specific and differing physiological considerations. Second, standardised definitions of sepsis severity in the non-obstetric population are often not applicable to pregnant and peripartum women. These women often present with symptoms of systemic inflammatory response syndrome (SIRS) as a result of ruptured membranes and changing biochemistry

commensurate with labour and delivery, in the absence of an infection. Since systemic inflammatory response syndrome (SIRS) is the clinical marker of sepsis, a real infection can be difficult to recognise due to this masking effect. Third, although women *often* present with symptoms of SIRS, symptoms at presentation are highly variable in peripartum women compared to the non-obstetric population. This high degree of variability, in addition to a low incidence, has resulted in few epidemiological studies of severe maternal sepsis, and a lack of standardised clinical definitions for recognition and measurement of severity.

2.8.1 Study objectives

The objective of this review was to assess definitions and measures of severity, incidence, risk factors and aetiology of severe maternal sepsis morbidity in countries with developed healthcare systems.

2.9 Methods

This structured review was conducted using the Cochrane systematic review methodology as a guide (Higgins & Green, 2011). Only one reviewer (CA) made inclusion/exclusion decisions and undertook data extraction. A literature search was conducted in February 2011 and repeated in October 2013, and results were updated accordingly.

2.9.1 Inclusion criteria

The population criteria were pregnant, peripartum, or postpartum women in 'advanced economy' countries as defined by the International Monetary Fund (IMF) (Fund, 2005).

The outcome of interest was severe maternal sepsis. The study designs of interest were descriptive studies and observational epidemiological studies (cohort, case-control, and cross-sectional). The components of this review, inclusion and exclusion criteria are summarised in Table 4. All studies included in the results of this review provided data on measures of sepsis severity, incidence or risk factors.

Table 4. Review selection criteria.

Review Component	Inclusion criteria	Exclusion criteria
Populations	Pregnant, peripartum or postpartum women in 'advanced economy' countries (as defined by the IMF)	Non-obstetric individuals; or individuals from low-income countries
Outcomes	Sepsis, severe sepsis, septic shock, or maternal death due to sepsis	Infection without sepsis
Study design	Descriptive or observational epidemiological (cohort, case-control, cross-sectional)	Experimental epidemiological studies, case-studies, case-series and case studies

2.9.2 Search methods for identification of studies

A comprehensive search of MEDLINE was carried out using a combined search strategy. The Medical Subject Headings (MeSH) ‘sepsis’ and ‘pregnancy’ were used in conjunction with text search terms. Studies on neonatal sepsis as well as studies on malaria or HIV were excluded. These parameters yielded the following search string:

("Sepsis/epidemiology"[Mesh] AND "Postpartum Period"[Mesh]) OR
("Sepsis/epidemiology"[Mesh] AND "Pregnancy"[Mesh]) OR
("Sepsis/epidemiology"[Mesh] AND maternal) OR (("Sepsis/epidemiology"[Mesh] AND obstetric) NOT neonat* NOT malaria* NOT immunodeficien*)

Additional country-specific MEDLINE searches using text terms ‘sepsis’ and country name were carried out. These searches were conducted for all 35 IMF advanced economy countries. The following is an example of the search string for Japan:

(Sepsis[Title/Abstract] AND Japan AND obstetric) OR (Sepsis[Title/Abstract] AND Japan AND puerper*) OR (Sepsis[Title/Abstract] AND Japan AND maternal[Title/Abstract])

Bibliographies of clinical practice guidelines and previous review articles were also manually searched for additional articles.

2.9.3 Risk of bias

No language restrictions were applied to the search methodology. However, since this was primarily a review of MEDLINE, there is a risk of selection bias towards studies published in English or with translated English abstracts. In particular, the reviewer did not have access to Asian language databases and thus could not assess the completeness of literature from the five Asian IMF advanced economy countries captured within this review (Hong Kong, Japan, Singapore, South Korea and Taiwan).

2.10 Results

From the combined searches 471 articles were identified. After title and abstract screening, 57 were retained for full text evaluation. After applying the search inclusion criteria 27 articles were included in the review (Figure 10).

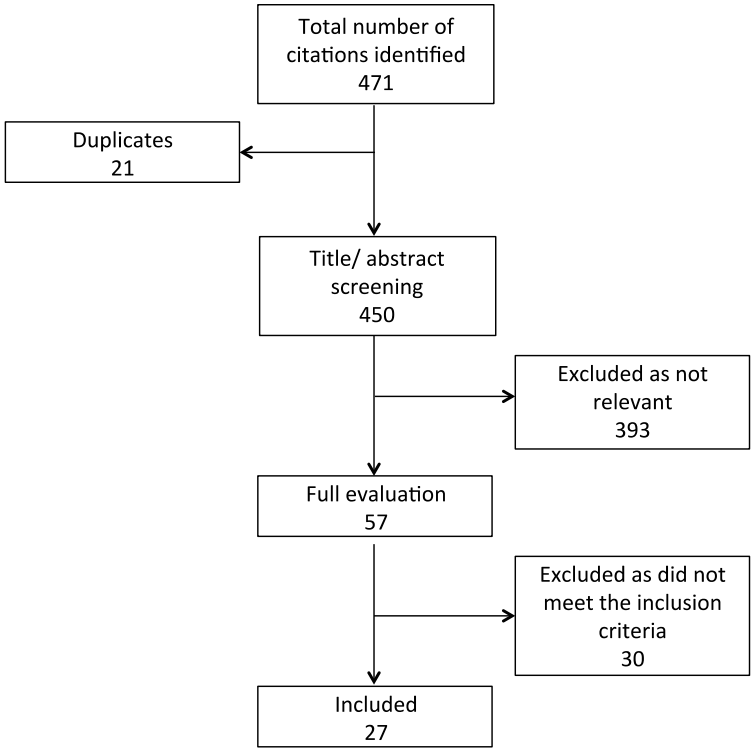


Figure 10. Flow diagram of the process of article screening and final inclusion.

2.10.1 Definitions and measures of severity

One of the several challenges in defining maternal sepsis is the temporality of the condition; sepsis can occur during the course of pregnancy, labour or the postpartum period. As mentioned in Part 1, there are two international definitions for puerperal sepsis (postpartum sepsis), however they differ from one another (Table 2). The ICD-10 classification defines puerperal sepsis as occurring during the period from the end of the first to the end of the 10th day after childbirth or abortion. The WHO alternatively defines puerperal sepsis as occurring at any time between the onset of rupture of

membranes or labour and the 42nd day postpartum. Immediately there is some controversy in determining the point after birth at which an infection may still be related to the birth. Additionally, there are currently no clinical definitions for sepsis, or degree of severity, for women in pregnancy or labour.

In 1992 the American College of Chest Physicians and Society of Critical Care Medicine held a consensus conference to standardise the definitions of sepsis severity (SIRS, sepsis, severe sepsis and septic shock) in the non-obstetric population (Table 5) (Bone et al., 1992). Although other conferences have been held since then to improve these definitions, in practice and published literature, the 1992 definitions have remained dominant. Recently, as the incidence of maternal sepsis has increased, confusion has arisen over the use of these definitions for pregnant and peripartum women, since it is accepted that the clinical signs and symptoms of severe infection differ in this population. Adding to this confusion is a lack of consensus on whether there should be comprehensive criteria for *all* maternal sepsis encompassing both the pregnancy and postpartum periods; and if so, a standardised set of clinical definitions.

Table 5. Non-obstetric 1992 definitions of sepsis (Bone et al., 1992).

SIRS*	At least two of the following: Temperature >38 or <36C Heart rate >90 beats/min Respiratory rate >20 breaths/min or PaCO2<32 mmHg (4.3 kPa) White cell count: >12000 cells/μl or <4000 cells/μl or 10% immature/band forms
Sepsis	SIRS with infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status
Septic shock	Sepsis associated with hypotension, despite adequate fluid resuscitation along with the presence of perfusion abnormalities as listed for severe sepsis. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured

* SIRS = systemic inflammatory response syndrome

Amongst countries with advanced economies, there have been seven population-based studies of severe obstetric sepsis morbidity, each using a different strategy to identify severe 'near-miss' cases. The only study to have modified the clinical parameters of SIRS was by Waterstone and colleagues (Waterstone et al., 2001). In a 2001 study of maternal morbidity in the South-East Thames region of England, Waterstone defined an elevated heart rate as >100 beats per minute (compared to >90) and an elevated white blood cell count to be >17,000 cells per microliter (compared to >12,000). Since then, there has been no validation or additional study using these parameters. In 2004, Brace and colleagues looked at the very severest end of the sepsis spectrum in a study of septicaemic shock reported directly from all 22 consultant-led maternity units in Scotland (Brace et al., 2004).

In 2008 Callaghan and colleagues conducted a US national study of severe maternal morbidity during hospitalisations for delivery. The authors identified cases of severe maternal sepsis as women who had an International Classification of Disease 9th Revision, Clinical Modification (ICD-9-CM) code for septicaemia (038.0), ICD-9-CM diagnosis and procedure codes indicating a specific severe complication such as acute organ dysfunction, in addition to a length of stay of three or more days, or postpartum transfer to another hospital (Callaghan et al., 2008). The estimates in this study were updated in a 2012 study using the same criteria and definitions (Callaghan et al., 2012). Further discussion of incidence rates will only refer to the latest 2012 study.

In 2009, as part of the National study of Ethnic determinants of Maternal Morbidity in The Netherlands (LEMMoN), Kramer et.al., defined severe sepsis as admission to an intensive care unit (ICU) for severe sepsis or any sepsis case that was determined to be severe morbidity by the clinician (Kramer et al., 2009). The latest study from 2013 on maternal sepsis during hospitalisation for delivery was also a national study conducted in the USA by Bauer and colleagues (Bauer et al., 2013). This study followed the Callaghan criteria defining severe sepsis as those with an ICD-9 code of septic shock, or those with a sepsis code in addition to an ICD-9 code for acute organ dysfunction associated with sepsis or a procedure code indicating a severe complication. Death from sepsis in this study was defined as a disposition code indicating death in the hospital with a concurrent diagnosis of sepsis. This study, however, did not validate cases by accounting for length of hospital stay as in the Callaghan studies. In yet another population-based study from the USA of severe morbidity during hospitalisations for delivery, Wanderer and colleagues defined severe sepsis according to ICD-9 codes associated with ICU admission (Wanderer et al., 2013).

Four population-based studies were also conducted by the author during the course of this DPhil between 2011 and 2013, however these will be discussed separately in chapters 4-7.

There have been several hospital-based studies of severe maternal sepsis (Mabie & Sibai, 1990; Kilpatrick & Matthay, 1992; Bouvier-Colle et al., 1996; Bewley & Creighton, 1996; Lapinsky et al., 1997; Baskett & Sternadel, 1998; Mahutte et al., 1999; Murphy & Charlett, 2002; Quah et al., 2001; Leung et al., 2010; Snyder et al., 2013; Timezguid et al., 2011). These studies all defined severe sepsis based on the management criteria of transfer to an intensive care unit (ICU).

Since a main objective of most of these studies was to estimate the incidence of severe maternal sepsis in the population, retrospective management classification of severity, for example based on ICU admission or length of stay, is a reasonable and, in most cases, the only available strategy. However, if we look to these studies for a potential diagnostic criterion for severe obstetric sepsis, it is apparent that there is a gap in diagnostic classification applicable during the course of illness. According to the methods of Waterstone and colleagues, since there was no clinically based, measurable definition for severe obstetric sepsis, the standard definition was modified to "take into account the physiological changes in pregnancy". Over a decade since the Waterstone study, a clinically based, measurable definition for severe obstetric sepsis is still absent.

Using the standard definitions of sepsis, the defining marker of severe sepsis is organ dysfunction. Some may raise the question of why organ dysfunction, which should be readily identifiable in both the obstetric and non-obstetric population, is not then a

sufficient criterion for severe sepsis in pregnant and peripartum women. The answer perhaps lies in the 'continuum of severity' concept and what is defined as a 'near-miss'. One aim of standardising obstetric sepsis definitions is to enable clinicians to accurately identify women who are in danger of rapidly progressing to a life-threatening state, i.e. to avoid a 'near-miss'. Is the point of recognition, therefore, when a woman begins to exhibit signs of organ dysfunction or before?

Sepsis, as currently defined, encompasses a wide spectrum of illness severity. Two women may both have sepsis as per the standard definition of SIRS with the pathological presence of an infection. One woman, however, may only be mildly ill, whilst the other woman could be seriously ill with a severe infection on the cusp of organ dysfunction, which could rapidly progress to shock. Since sepsis with acute organ dysfunction is frequently fatal (J. Hall et al., 2005), clinical obstetric definitions separating 'uncomplicated sepsis', severe sepsis and 'critical sepsis' would be beneficial in order to prompt rapid medical intervention before a poor outcome for both mother and infant.

There also appears to be a role for modified clinical definitions downstream of organ dysfunction, although this would be less useful for preventive efforts. Multiple organ system dysfunction syndrome occurs when homeostasis cannot be maintained. Several prognostic scoring systems, based on non-obstetric definitions, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III and Sepsis-related Organ Failure Assessment (SOFA) (Balci et al., 2004), have been developed to assess the physiological severity of multiple organ system dysfunction syndrome. Evidence of the need to modify the clinical criteria for the obstetric population may be

seen in the conflicting sensitivity of these scoring systems when applied to pregnant and peripartum women (Fernández-Pérez et al., 2005; Afessa et al., 2001). In a US study of obstetric intensive care unit admissions for SIRS, Afessa and colleagues found that the APACHE II system overestimated actual mortality, whilst other studies found that this system underestimated mortality compared to non-obstetric patients (Lewinsohn et al., 1994; Scarpinato & Gerber, 1995).

2.10.2 Incidence of severe morbidity

With regards to morbidity, since definitions of sepsis vary, so do reported incidence rates. It is particularly problematic to compare studies that have based severe morbidity on management criteria, since intensive care organisation, availability and length of stay differ between countries (Vincent et al., 1997). The following results, therefore, are reported per country (except for the multinational MOMS morbidity study discussed below).

The only multinational study of maternal sepsis morbidity incidence was the Mothers Mortality and Severe Morbidity (MOMS) initiative, which in the mid 1990's collected population-based data from regions of 11 western and northern European countries (Zhang et al., 2005). The study collected data on sepsis using the standard non-obstetric definition. They reported an incidence rate of 0.8 (95% CI 0.7-0.9) per 1,000 deliveries. Although this study did not collect data on severe sepsis, it provides some indication of the magnitude of illness including the less severe end of the sepsis spectrum throughout this region of Europe.

Eighteen studies meeting the review search criteria reported severe sepsis incidence rates (Table 6). Amongst UK regional studies, the incidence of severe sepsis morbidity ranged from 1.0-4.0 per 10,000 deliveries (Waterstone et al., 2001; Brace et al., 2004). UK hospital-based rates ranged from 0.5-5.0 per 10,000 deliveries (Bewley & Creighton, 1996; Murphy & Charlett, 2002). In The Netherlands and the USA, national incidences were found to be 2.0 per 10,000 deliveries (Kramer et al., 2009; Callaghan et al., 2012), and in France a regional study found the incidence to be 3.0 per 10,000 births (Girard et al., 2001). A more recent hospital based study from France estimated the incidence rate to be 0.7 per 10,000 deliveries (Timezguid et al., 2011).

Amongst the studies that comprise many years of data, three studies discussed incidence trends. Callaghan et.al. demonstrated that severe morbidity overall has increased since the early 1990s in the USA. The recent study by Bauer and colleagues also found that severe sepsis has increased in the USA from 0.6 per 10,000 deliveries in 1998 to 1.6 per 10,000 deliveries in 2008 (Bauer et al., 2013). Another recent study from the USA by Wanderer et.al. found (similar to Callaghan) the rates to increase from 1.0 per 10,000 deliveries in 1999 to 1.7 per 10,000 deliveries in 2008 (Wanderer et al., 2013). Comparison between maternal mortality and morbidity rates suggest that the risk of severe morbidity is approximately five to ten times greater than that of maternal death.

Table 6. Summary of severe sepsis morbidity studies and incidence rates.

Country	Study population/ Author	Years of Study	Incidence rate per 10,000 deliveries
UK	**Regional**		
	Waterstone *et.al.*	1997-1998	4.0
	Brace *et.al.*	2001-2002	1.0
	Hospital		
	Murphy *et.al.*	1988-1999	0.5
	Bewley *et.al.*	1991-1992	5.0
The Netherlands	**National**		
	Kramer *et.al.*	1993-2006*	2.0
USA	**National**		
	Callaghan *et.al.*	1991-2003	2.0
	Bauer *et.al.*	1998-2008	0.2
	Regional		
	Wanderer *et.al.*	1999-2008	3.0
	Hospital		
	Kilpatrick and Matthay	1985-2003	2.0
	Mabie and Sibai	1986-1989	4.0
Canada	**Hospital**		
	Baskett and Sternadel	1980-1993	1.0
	Lapinsky *et.al.*	1990-1994	1.0
	Mahutte *et.al.*	1991-1997	3.0
France	**Regional**		
	Girard *et.al.*	1995	3.0
	Hospital		
	Bouvier-Colle *et.al.*	1996**	1.0
	Timezguid *et al.*	1993-2008	0.7
Singapore	**Hospital**		
	Quah *et.al.*	1998-1999	2.0
Hong Kong	**Hospital**		
	Leung *et.al.*	1998-2007	9.0

* Data on maternal deaths collected from 1993-2006; data on maternal morbidity collected through the LEMMoN study from 2004-2006

** Study period was not reported, therefore the year the study was publised is listed in the table

2.10.3 Risk Factors and Aetiology

Most of the information that exists about risk factors for severe maternal sepsis is derived from developing country data. Although low-income countries face a vastly greater burden of sepsis morbidity and mortality, the risk factors for this condition may differ greatly in higher income countries. Maternal sepsis in low-income countries is largely associated with unhygienic birth conditions and inadequate antenatal and obstetric care (Maharaj, 2007).

In high-income countries where advanced and comprehensive obstetric care is the standard, it is not entirely clear what the prevailing proximal and distal risk factors are. As a result, risk factors for puerperal infection or post-caesarean infection (which can both lead to sepsis) are often cited interchangeably as risk factors for maternal sepsis. Amongst women who have a caesarean section, risk factors for infectious morbidity are: prolonged labour, premature rupture of membranes, lower socioeconomic status, high number of prenatal visits, multiple vaginal examinations during labour, internal fetal monitoring, urinary tract infection, anaemia, blood loss, obesity, diabetes, general anaesthesia, development of subcutaneous hematoma, and bacterial vaginosis (Beattie et al., 1994; Desjardins et al., 1996; Gibbs, 1980; Killian et al., 2001; Magann et al., 1995; Olsen et al., 2008; Webster, 1988; Watts et al., 1990; Lucas et al., 2012).

Caesarean section is of particular concern in high-income countries because of the frequency of the procedure. In the UK and the USA, caesarean section accounts for approximately 25% to 30% of all births respectively. Caesarean section, especially for emergency indications, increases the risk of intrauterine (Smaill & Gyte, 2010) and surgical site infections (Maharaj, 2007), which are known precursors of sepsis if

undetected. In a recent Cochrane review of prophylactic antibiotics by Smaill and Gyte, it was found that women who undergo a caesarean section have a five to 20 times greater risk of developing infectious morbidity, compared to women who give birth vaginally (Smaill & Gyte, 2010).

Two population-based epidemiological studies have been conducted with the aim of identifying risk factors for maternal sepsis specifically (Waterstone et al., 2001) (Bauer et al., 2013) (Table 7). (The Waterstone study investigated risk factors for maternal sepsis as a sub-analysis of all-cause maternal morbidity.) Maternal infections that are clinically known to increase the risk of developing sepsis are: pyelonephritis, chorioamnionitis, septic abortion, and endometritis (Fernández-Pérez et al., 2005; Lucas et al., 2012). In addition, several microbiological and epidemiological factors that have been implicated in the recent literature and are the subject of on-going surveillance are: a shifting predominance of causative organisms from Gram-negative to Gram-positive organisms (particularly group A *streptococcus*), the prevalence of polymicrobial and fungal infections, drug resistance and nosocomial transmission.

Table 7. Risk Factor and adjusted odds ratios (ORs) according to study.

Risk factor	Adjusted OR (95% CI)
Waterstone *et.al.* (UK) 2001	
Non-white race	7.02 (1.49-33.15)
Smoker	3.56 (1.16-10.87)
Previous pre-eclampsia	6.61 (1.81-24.18)
Anaemia	29.48 (2.50-347.83)
Caesarean section (emergency)	11.85 (4.42-31.73)
Bauer *et.al.* (USA) 2013	
Age ≥35 years	1.5 (1.2–1.8)
Black ethnic group	2.1 (1.7–2.6)
Public health insurance	1.6 (1.4–1.9)
>1000 deliveries per year	1.9 (1.4–2.4) to 2.1 (1.3–3.4)
Rescue cerclage	9.8 (3.0–32.7)
Prophylactic cerclage	3.4 (1.8–6.2)
Preterm premature rupture of membranes	2.5 (1.8–3.5)
Retained products of conception	4.5 (2.8–7.4)
Multiple gestation	1.8 (1.2–2.5)
Congestive heart failure	135 (93.6–194.6)

2.10.4 The role of group A *streptococcus*

As discussed in relation to maternal mortality from sepsis, group A *streptococcus* has emerged as a major causal organism, and it is also a likely causal organism of severe life-threatening morbidity. Group A *streptococcus* is a perplexing organism because in addition to maternal sepsis, it can cause other disease manifestations such as pharyngitis, scarlet fever, and invasive streptococcal-shock ('toxic shock') syndrome and necrotising fasciitis. The pathogenesis of these various disease processes whereby the same bacteria can cause different clinical outcomes is not yet fully understood. Specific strains seem to be overrepresented amongst certain infections, however other strains are also represented across all infections. European surveillance has reported a surplus of emm28 genotype strain amongst vaginal isolates (Luca-Harari et al., 2009),

and in Denmark puerperal sepsis was the most common clinical infection associated with emm28 (Luca-Harari et al., 2008). It is thought that the overall pathogenic potential of certain strains or the emergence of hypervirulent subclones have brought about the upsurge in invasive group A streptococcal infection in recent years (Lynskey et al., 2011).

2.11 Conclusions

Lack of clear definitions for sepsis severity can be potentially hazardous to the obstetric population for whom symptoms of infection are often masked by the physiological changes of pregnancy and delivery. At the root of this problem is scarce epidemiological data on which to base measurable parameters or to understand the risk factors for different grades of maternal sepsis severity. Although maternal deaths from sepsis are rare in high-income countries, even a slight increase in mortality is likely to represent a much greater burden of severe illness. Increasing rates of severe sepsis in the general population and the re-emergence of invasive group A streptococcal infection, emphasise the need for standardised sepsis severity criteria in the obstetric population. The risk of dying from sepsis increases greatly when organ system dysfunction occurs, which is the non-obstetric definition of 'severe sepsis'. The goal of any clinician is to recognise a deteriorating condition before this point. Therefore, defining an extra point on the continuum scale between sepsis and septic shock would be beneficial for preventing a life-threatening situation. This will be discussed in additional detail in Chapter 8.

Chapter 3

Research questions, aims and objectives

3.1 Introduction to analytical chapters

In chapter 2 the current literature and current understanding of maternal sepsis mortality and severe morbidity was reviewed. It is clear that there are several distal epidemiological determinants and proximal risk factors for maternal sepsis. Amongst the few population-based studies that have been performed, there is a lack of clarity on risk factors because definitions used to define sepsis severity differ between studies. There is a large body of literature implicating caesarean section as a risk factor for severe sepsis morbidity and mortality, however, it is still not clear whether caesarean section is a cause or an outcome (as in the case of emergency caesarean section), and how this may be related to increasing rates of obesity amongst the obstetric population. Further investigation of other potential risk factors that smaller studies do not have the statistical power to identify is needed, for example, if there is a risk of sepsis associated with operative vaginal delivery, and what the role of group A streptococcal infection is in severe sepsis morbidity. Until these risk factors are evaluated in population-based studies, the extent to which they contribute to the risk of mortality and severe morbidity in the UK remain poorly understood.

3.1.1 Research aim and objectives

The overall aim of this research is to elucidate the epidemiology of severe maternal sepsis in the UK, in order to inform strategies to prevent poor outcomes.

The specific objectives were to investigate in the UK:

1. The incidence of severe maternal sepsis;
2. The risk factors for severe maternal sepsis;

3. The main causative organisms;
4. How severe maternal sepsis is managed;
5. The outcomes of severe sepsis;
6. The factors that are associated with poor outcomes; and
7. If this trend is similarly occurring in other countries and the associated risk factors for comparison to those found in the UK.

3.1.2 Organisation of component studies and structure of the thesis

The aims and objectives are addressed by the analytical chapters 4-7, which address these questions using a quantitative-methods approach through four population-based epidemiological studies (two case-control and two cohort studies) of:

- Sepsis and severe maternal sepsis in the North NHS region of Scotland over a 23-year period using a case-control design (Chapter 4);
- The incidence, risk factors, causative organisms, sources of infection and outcomes of mothers with severe maternal sepsis in the UK using a national case-control design (Chapter 5);
- Women with severe maternal sepsis in the first 24 hours of critical care unit admission in the UK using a national cohort design (Chapter 6); and
- All women with sepsis and severe maternal sepsis who delivered in the state of California, USA over a three year period using a cohort design (Chapter 7).

The last study (Chapter 7) utilised data from outside the UK in order to address objective 7, because the dataset used was the only data source available for which a robust study of risk factors along the continuum of sepsis severity was possible.

Chapter 4

Maternal sepsis: A Scottish population-based case control study

4.1. Introduction

There are several well-established risk factors for maternal sepsis including caesarean section (Smaill & Gyte, 2010; Yokoe et al., 2001; Maharaj, 2007; Kramer et al., 2009) and anaemia (Maharaj, 2007; Kramer et al., 2009; van Dillen et al., 2010) as discussed in Chapter 2. However the risk associated with these factors had not been recently described in the UK at the population level; the only other population-based study of severe maternal sepsis was conducted by Waterstone and colleagues from 1997-1998 in the South East Thames region of the UK (Waterstone et al., 2001). In addition, several factors such as obesity and operative vaginal delivery had been shown to be associated with severe maternal infection in studies from other countries, but not described in relation to severe maternal sepsis in either the UK or other countries.

Obesity, for example, has been implicated in poor wound healing (primarily in relation to caesarean section) (Sebire et al., 2001; Usha Kiran et al., 2005; Robinson et al., 2005; Martens et al., 1995; Beattie et al., 1994), genitourinary (Sebire et al., 2001) and uterine infection (Usha Kiran et al., 2005) in the obstetric population. The LEMMoN study from The Netherlands recently estimated the relative risk of maternal sepsis associated with being overweight (BMI $\geq$25 and <30) to be 1.6 (95% CI 0.9-2.8), although this was not statistically significant (Kramer et al., 2009). In the UK, as in other developed countries, obesity rates including women of reproductive age have been increasing rapidly (Heslehurst et al., 2007). In the mid-2000's, approximately 20% of pregnant women in the UK were obese (Heslehurst et al., 2007; Kanagalingam et al., 2005). In 2003-2005, 33% of mothers who died directly from sepsis in the UK were obese, and 48% had a caesarean section, all of whom were either overweight or obese (Confidential

Enquiry into Maternal and Child Health CEMACH, 2008); this trend however was not identified in the 2006-2008 triennium report of the UK Confidential Enquiry into Maternal Deaths (Cantwell et al., 2011).

Similar to obesity, operative vaginal delivery had been implicated as a risk factor for severe maternal infection in studies performed in Canada and the USA (Liu et al., 2005; Lydon-Rochelle et al., 2000), but not specifically identified as a risk factor for severe maternal sepsis. In a Canadian population based study, Liu et.al. found that women delivered by vacuum extraction or forceps had an odds of 1.24 (CI=1.09-1.41) and 1.62 (CI=1.40-1.87) respectively, of major puerperal infection (Liu et al., 2005). Lydon-Rochelle also found in a U.S. population based study that women who had an operative vaginal delivery were 20% more likely (RR=1.2) to be re-hospitalised within 60 days of delivery due to uterine infection (Lydon-Rochelle et al., 2000).

4.1.1 Study objectives

The objective of this study was to identify the risk factors for uncomplicated sepsis and severe sepsis, including under-studied factors such as obesity (BMI≥30) and operative vaginal delivery, amongst pregnant, intrapartum and immediately postpartum women using a robust UK data source.

4.2. Methods

4.2.1 Study design

This was an anonymised case-control study of all cases of maternal sepsis amongst antepartum, intrapartum and postpartum women recorded in the Aberdeen Maternal and Neonatal Databank (AMND) between 1986 and 2009. Data were analysed using a case-control design because of the nature of the data, the relative rarity of maternal sepsis in the UK, and because there are multiple known risk factors for maternal sepsis. In a case-control design the outcome is the defining data criteria and allows for the evaluation of multiple exposures. Thus, in order to assess risk factors in this study, all cases were compared with non-septic controls. Although *all* cases of maternal sepsis were included, for convenience of extracting and handling the data, a control sample was selected for comparison.

4.2.2 Data source

This study was conducted using data from the University of Aberdeen, Aberdeen Maternity Hospital, a tertiary care maternity hospital for the NHS North of Scotland region. The hospital is the only tertiary referral hospital in the area, serves a large and well-defined geographical region and has approximately 5,000 births per year. All pregnancy related events have been recorded in the Aberdeen Maternal and Neonatal Databank (AMND) since 1950. The population in this geographical region is relatively stable; only 3.8% of women recorded in the databank were found to have migrated away from the region (University of Aberdeen, 2014). All fertility-related events as well as socio-demographic data are recorded in the database. In addition, records from the database are validated by periodically comparing records from the database with the original hard copy patient records (which are kept in all cases). Data entry, coding

protocols and consistency rates for internal validation and valid ranges of measurable variables are described in previous studies (Bhattacharya et al., 2010; Humphrey & J. S. Tucker, 2009; Bhattacharya & Campbell, 2005).

The stability of the population in addition to the scope, comprehensiveness and accuracy of the database made it a valuable resource for this research. For the reasons stated, trends over time could be studied with a relatively low risk of bias. For example, if there was a large degree of population movement (as in movement away from the region due to changing socioeconomic conditions), it would be difficult to confidently assess whether rates of sepsis were truly increasing (or decreasing) within a population, or if changing demographics underlie the trend. The comprehensiveness and accuracy of information not routinely collected in hospital episode or vital statistics registries (such as sociodemographic and detailed clinical delivery characteristics) also allowed for inferential analyses to be carried out on under-studied risk factors, such as obesity and operative vaginal delivery.

4.2.3 Selection of cases and controls

Outcome variables used to define the cases were: uncomplicated sepsis and severe sepsis. All cases were identified as those with an ICD-9 sepsis code:

- 038.0-038.9 (septicaemia);
- 634.0-639.0 (sepsis following abortion);
- 670.2 (puerperal sepsis); and
- 785.5 (septic shock).

Severe ('near-miss') sepsis cases were identified as those with an ICD-9 code of septic shock, or according to previously validated criteria defined by Martin, et.al. (Martin et al., 2003), which were those cases with an additional ICD-9 code for acute organ dysfunction associated with sepsis (Table 8). All other cases of sepsis are referred to as 'uncomplicated'. All cases with an ICD-9 code for sepsis had a clinical diagnosis of SIRS in addition to a culture-confirmed diagnosis of infection. Four controls per case that did not have an ICD-9 code for sepsis were frequency matched on year of delivery and otherwise randomly selected from the AMND. Controls were not matched based on any other criteria, such as age or parity, because this would have excluded the possibility of assessing these criteria as risk factors.

Table 8. ICD-9 Classification of Acute Organ Dysfunction Associated with Sepsis.

Type of Organ Failure	ICD-9 code	Description
Cardiovascular	458.0	Hypotension, postural
	785.5	Shock
	785.51	Shock, cardiogenic
	785.59	Shock, circulatory or septic
	458.0	Hypotension, postural
	458.8	Hypotension, specified type, not elsewhere classified
	458.9	Hypotension, arterial, constitutional
	796.3	Hypotension, transient
Renal	584	Acute renal failure
	580	Acute glomerulonephritis
	585	Renal shutdown, unspecified
Hepatic	570	Acute hepatic failure or necrosis
	572.2	Hepatic encephalopathy
	573.3	Hepatitis, septic or unspecified
Haematological	286.2	Disseminated intravascular coagulation
	286.6	Purpura fulminans
	286.9	Coagulopathy
	287.3-5	Thrombocytopenia, primary, secondary, or unspecified
Metabolic	276.2	Acidosis, metabolic or lactic
Neurological	293	Transient organic psychosis
	348.1	Anoxic brain injury
	348.3	Encephalopathy, acute
	780.01	Coma
	780.09	Altered consciousness, unspecified

4.2.4 Sample size

The sample size of this study was limited by the population incidence of maternal sepsis, since all available cases were included. Using the predictor variable of obesity to illustrate the study power, with 89 cases and four controls per case, and using the prevalence of exposure to obesity in the control population which was 19%, the study had 90% power at $p<0.05$ (two-sided) to detect a statistically significant odds ratio (OR) of 2.4 or greater.

4.2.5 Statistical Analyses

Frequencies of demographic and clinical variables were tabulated for uncomplicated sepsis and severe sepsis case groups and compared with controls using two sided chi square tests for categorical variables, and a t-test or Wilcoxon ranksum test as appropriate for continuous variables. A P-value of <0.05 was considered statistically significant. Three-year rolling averages were calculated for rates of uncomplicated and severe sepsis for ease of interpretation over the 23-year study period. Point estimates with 95% confidence intervals (CIs) for three-year averages of overall sepsis case rates for the periods 1987-1989, 1997-1999 and 2007-2009 were also calculated. The chi square test for trend was used to test for significant trends over time.

4.2.5.1 Univariable logistic regression

Univariable (unadjusted) logistic regression analyses were carried out to initially identify demographic and clinical factors associated with uncomplicated maternal sepsis and severe sepsis. Odds ratios (OR) with 95% CIs were estimated. The reference group for each categorical variable was determined by the largest group or for ease of interpretation.

Confounding was initially assessed by stratification and cross-tabulation using the Cochran-Mantel-Haenszel test. This was done in order to give an indication of which variables should be retained in the final multivariable regression models. The Cochran-Mantel-Haenszel test was used because the dependent variable (sepsis) was binary. Since there was a large number of variables, this test was only performed on those variables that had a plausible relationship with another explanatory variable and the outcome. The following variables were tested for an association with the outcome (uncomplicated sepsis) stratified by age categories: primiparity ($P<0.001$), obesity ($P=0.002$), anaemia ($P<0.001$), premature rupture of membranes ($P=0.704$), prolonged labour ($P=0.359$) and caesarean section ($P<0.001$); and the following variables were tested for an association with sepsis stratified by primiparity: premature rupture of membranes ($P=0.742$), prolonged labour ($P=0.039$), and caesarean section ($P<0.001$). These tests indicated that there was confounding between the variables age and primiparity, obesity, anaemia and caesarean section; and between primiparity and caesarean section.

4.2.5.2 Multivariable logistic regression

Regression modelling for uncomplicated sepsis and severe sepsis outcomes was performed separately, and the case groups were mutually exclusive. It must be noted that the with only 14 cases in the severe sepsis outcome group, multivariable regression modelling was performed for exploratory purposes only and with the understanding that the results of the model may be unreliable due to low power.

For each model, significant variables from univariable regression, those risk factors identified in other studies, or those factors that were plausible confounders, were

included in an initial unconditional multivariable logistic regression model. In order to avoid over-adjustment, since there was a large number of variables and inclusion of all of the variables would have been likely to result in a high degree of collinearity (since some clinical variables were closely related), a backward stepwise elimination method was used to derive a final parsimonious model. The stepwise method was used to (1) assess whether exclusion of a variable significantly affected the fit of the model, and (2) whether its exclusion significantly changed the coefficients of the other predictor variables in the model, which were examined at each exclusion step. This method was also used to further assess possible confounding and the relationship between the variables.

Variables were eliminated according to the methodology described by Altman (Altman, 1991), in which the first variable eliminated was that which had the smallest association with the outcome (that with the largest P-value). The first variable eliminated in the uncomplicated sepsis model was previous miscarriage, followed by labour induction, prolonged labour, premature rupture of membranes, preeclampsia and blood loss of ≥500 ml). As each variable was eliminated, a likelihood ratio test was performed to test if the excluded variable resulted in a significant difference in the log likelihood of the model (compared to the model with the variable included). Variables that were significant in the initial full model or the Cochran-Mantel-Haenszel tests at $P<0.05$ were not removed. Potential confounding factors that were not significant in the initial multivariable regression and did not significantly affect the fit were thus excluded from the final model. For the uncomplicated sepsis model, these variables were: premature rupture of membranes, labour induction, prolonged labour, blood loss of ≥500 ml, preeclampsia, and previous miscarriage. The software package used for this analysis

included an automated backward stepwise variable selection routine, however the analyses in this study were performed manually in order to investigate the intermediate changes in significance of other variables at each step.

Since only two cases occurred antenatally and removal of these cases did not significantly change the regression results, antenatal cases were retained in the final regression models. Final multivariable regression results were adjusted for calendar time and all other factors in the model. Adjustment for calendar time was carried out in order to account for possible changes in practice (such as caesarean section) over time.

The variable for age was tested for departure from linearity graphically by first plotting the aOR of sepsis against year of age, which showed a negative linear correlation between aOR and age. Then, in order to assess the effect of outliers, the residuals (error terms) of the model were plotted against year of age since the presence of outliers become more apparent in the residuals plot. There were no obvious outliers and in addition, the points in a residual plot were randomly dispersed around the horizontal axis indicating that treatment of age as a linear term was a good fit for the data. These tests were performed in order to assess whether the variable should be evaluated as a continuous or categorical variable in the model. With no evidence of departure from linearity for this variable, it was treated as a continuous linear term in the analysis, but presented as a categorical variable in the results table for ease of interpretation.

4.2.5.3 Post model checking procedures

Post model checking procedures were carried out for both models. Plausible interactions between demographic and clinical variables were tested in the full regression models by adding interaction terms and then using likelihood ratio tests with a significance level of $P<0.01$. Interaction between the following variables was tested: age and parity; age and anaemia; obesity and type of delivery. The likelihood ratio test was used to assess if the magnitude of the effect of an explanatory variable on the outcome differed depending on the level of another explanatory variable. In practice, the test was used to assess whether there was a significant difference in the log likelihood of the model without the interaction term compared to the log likelihood of the model with the addition of the interaction term. (A significant difference would require further exploration of the predicted odds stratified by the different levels of the effect modifier.) It was also possible to use Wald's test for interaction. However Wald's test approximates the likelihood ratio test, thus the likelihood ratio test has been recommended as slightly more robust (Long & Freese, 2006). The likelihood ratio test was therefore used in this and all subsequent analyses. No significant interactions were identified in the final adjusted models.

The fit of the model was assessed using Hosmer-Lemeshow's goodness-of-fit test with a significance level of $P<0.05$. This test was used to assess how well the model fit the data, or in other words if there is a significant departure of the model's predicted frequencies from the observed data (Archer & Lemeshow, 2006). This was necessary to ensure that the coefficient estimates of the model were not biased in some way, which would lead to the potential for invalid conclusions (Altman, 1991). Another common test that could have been used to test the fit of the logistic regression models was the

Chi-square goodness-of-fit test. However this test has been found to not perform well if there are one or more continuous variables in the model and if the sample size is small (Morgan et al., 2011). The Hosmer-Lemeshow's goodness-of-fit test has been found to perform better under these conditions (Morgan et al., 2011). P-values for both models in this study were >0.05 indicating that the models fit the data well; a P-value of <0.05 would indicate a poor-model fit.

The validity of the models (that the model assumptions had not been violated) were tested by checking that the residuals were random and were thus not correlated with the independent variables in the models. In order to do this, standardised Pearson residuals were correlated with the linear predictor variable of age using Pearson's correlation coefficient with a significance level of P<0.05; there was no significant correlation between the residuals and age indicating that the models were valid.

4.2.6 Software

Stata statistical software 11 (StataCorp, College Station, TX) was used for all analyses.

4.2.7 Data management

Anonymised data were received as an SPSS file and Stat/Transfer was used to covert the file to Stata. The AMND has a query system in place to detect internal inconsistencies (Bhattacharya et al., 2010), however data were also manually checked by the author (CA) for missing data or errors that may have occurred during the file conversion process. This was done by visually inspecting the data and by performing relevant tabulations.

4.2.8 Research ethics approval

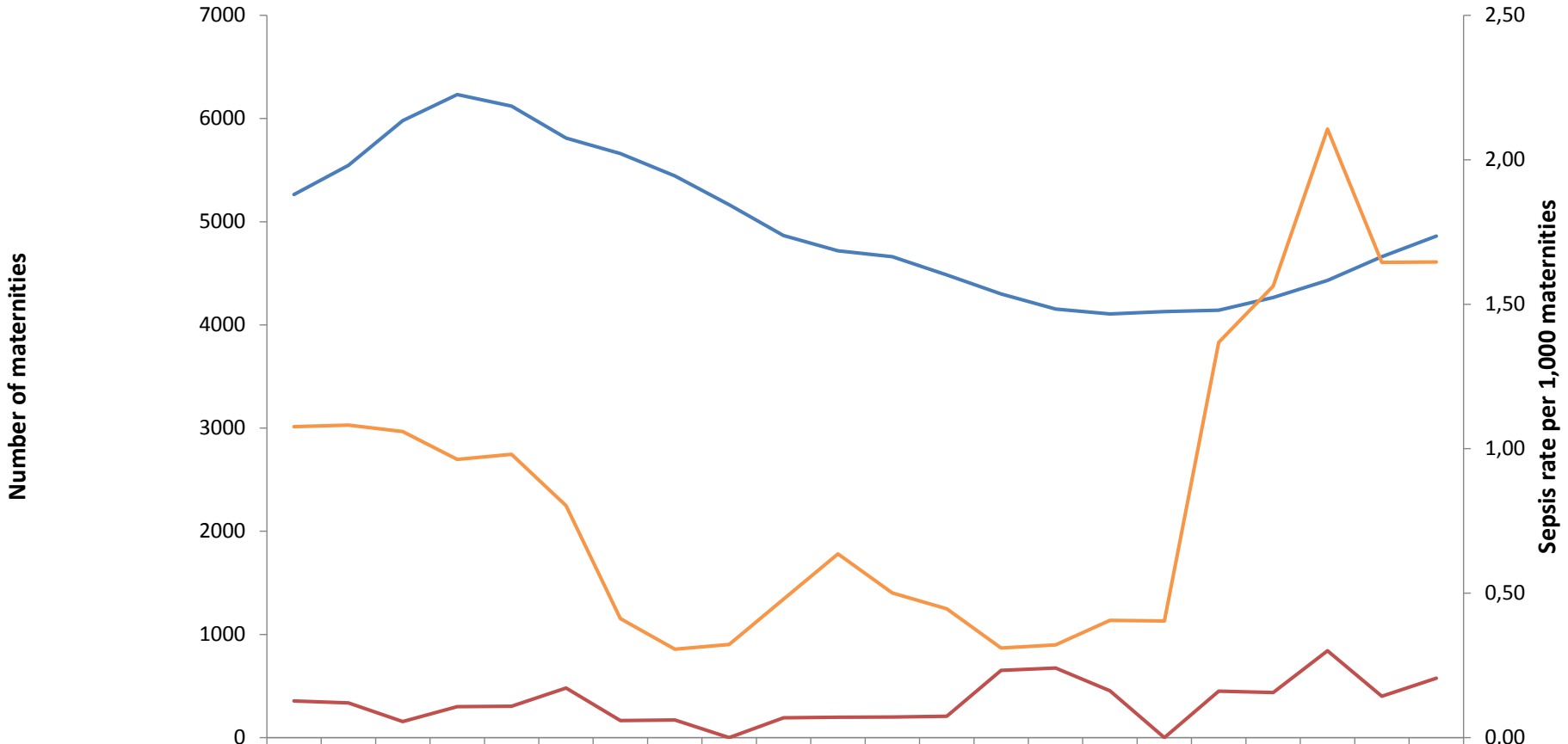
Under the terms of operation of the AMND the research ethics committee approval for use of anonymised data was not required. Approval of the research protocol was obtained from the Steering Committee of the AMND prior to data extraction. The protocol for the study can be found in Appendix 2.

4.3 Results

4.3.1 Incidence and rates

The total study population consisted of: 89 cases of uncomplicated maternal sepsis, 14 cases of severe maternal sepsis and 412 controls. The majority of all cases occurred postpartum and before hospital discharge: 98.9% (n=88) of uncomplicated sepsis cases and 92.9% (n=13) of severe cases. One uncomplicated sepsis case occurred antepartum, and one severe case was diagnosed with an infection during delivery, which later progressed to septic shock postpartum. Sepsis case rates for the 23-year study period are shown in Figure 11. Whilst rates of severe sepsis remained relatively constant over the study period, rates of sepsis overall have increased significantly since 2003 (p=0.002) compared to the previous two decades. Point estimates for three-year averages of overall sepsis case rates for the periods 1987-1989, 1997-1999 and 2007-2009 were: 1.08 per 1,000 maternities (95% CI 0.64-1.71), 0.43 (95% CI 0.16-0.93), and 1.65 (95% CI 1.05-2.45) respectively. Point estimates for three-year averages of severe sepsis for the same periods were: 0.12 per 1,000 maternities (95% CI 0.01-0.43), 0.07 (95% CI 0.00-0.40), and 0.21 (95% CI 0.02-0.50).

Figure 11. Incidence of all sepsis and severe sepsis cases per 1,000 maternities from 1986-2009 in Aberdeen (three-year rolling averages).



	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total maternities	5264	5546	5979	6233	6120	5811	5660	5444	5165	4867	4718	4661	4483	4300	4154	4107	4130	4143	4266	4432	4660	4860
Sepsis case rate overall	1,08	1,08	1,06	0,96	0,98	0,80	0,41	0,31	0,32	0,48	0,64	0,50	0,45	0,31	0,32	0,41	0,40	1,37	1,56	2,11	1,65	1,65
Severe sepsis case rate	0,13	0,12	0,06	0,11	0,11	0,17	0,06	0,06	0,00	0,07	0,07	0,07	0,07	0,23	0,24	0,16	0,00	0,16	0,16	0,30	0,14	0,21

4.3.2 Demographic and medical characteristics

The distribution of several demographic and medical characteristics differed significantly between the three groups (Table 9). The proportion of women from black or other minority ethnic groups was greater amongst cases: 5.7% of uncomplicated sepsis cases and 21.4% of severe cases, compared to no controls. The average age of women with uncomplicated sepsis and severe sepsis were younger than controls: mean age 28.2 (SD 5.6) and 27.4 (SD 6.2) respectively compared to 31.3 years (SD 4.5). A larger proportion of cases were multiparous and also had a previous miscarriage. Additionally, the proportion of mothers with anaemia was progressively larger amongst uncomplicated cases and severe cases: 67.4% and 92.9% respectively compared to 37.6% of controls. Although the rate of obesity was significantly greater amongst cases, obesity amongst severe sepsis cases was similar to that of controls. Gestation at booking, marital status, and diabetes did not differ significantly between groups. One obese woman amongst the cases and one obese woman amongst the controls had type 1 diabetes.

Table 9. Demographic and medical characteristics of cases and controls (1986-2009). Figures are numbers (%) of women unless otherwise stated.

	Uncomplicated sepsis	Severe sepsis	Controls	P-value*
	n=89	n=14	n=412	
Ethnic group†				
White	82 (94.3)	11 (78.6)	408 (100.0)	<0.001
Black	2 (2.3)	1 (7.1)	--	
Asian	3 (3.5)	2 (14.3)	--	
Mean (SD) age (years)	28.2 (5.6)	27.4 (6.2)	31.3 (4.5)	<0.001
Parity				0.001
0	25 (28.1)	5 (35.7)	178 (43.2)	
1	39 (43.8)	5 (35.7)	179 (43.5)	
≥2	25 (28.1)	4 (28.6)	55 (13.3)	
First booking				0.53
First trimester	77 (86.5)	14 (100.0)	316 (82.7)	
2nd or 3rd trimester	12 (13.5)	0 (0.0)	66 (17.3)	
Marital status				0.216
Married	59 (66.3)	11 (78.6)	297 (72.1)	
Single supported	17 (19.1)	2 (14.3)	73 (17.7)	
Single unsupported	10 (11.2)	1 (7.1)	33 (8.0)	
Divorced or separated	3 (3.4)	0 (0.0)	9 (2.1)	
Median (IQR) BMI†	26 (23-30)	24 (22-25)	24 (22-28)	0.05
Obese	32 (36.0)	2 (14.3)	78 (18.9)	0.002
Anaemia	60 (67.4)	13 (92.9)	155 (37.6)	<0.001
Diabetes (type 1)	2 (2.3)	0 (0.0)	3 (0.7)	0.26
Any previous miscarriage	6 (6.7)	2 (14.3)	12 (2.9)	0.023

Note categories are mutually exclusive

*Difference in distribution between all cases and controls; χ^2 test ; Fisher's exact test for <5 observations; t-test for mean age; ranksum test for median BMI

†Among those reported: Ethnic group total missing=6 (1.2%), cases=2 (1.9%) and controls=4 (1.0%); BMI total missing=27 (5.2%), cases=12 (11.6%) and controls=15(3.6%)

4.3.3 Delivery characteristics

Several delivery characteristics also differed significantly across the three groups (Table 10). A larger proportion of severe cases had premature rupture of membranes (PROM) and an induced labour compared to controls. More uncomplicated and severe cases were delivered by caesarean section: 48.3% and 64.3% respectively compared to 25.3% of controls. A larger proportion of severe cases also had a manual removal of the placenta (21.4% vs. 4.7% of controls, p=0.04) and lost ≥500 ml of blood (71.4% vs. 23.9% of controls, p=0.02) during delivery. The rate of severe preeclampsia, pre-term birth and babies admitted to the neonatal intensive care unit was also significantly higher amongst cases.

Table 10. Clinical delivery characteristics of cases and controls. Figures are numbers (%) of women.

	Uncomplicated sepsis	Severe sepsis	Controls	P-value*
	n=89	n=14	n=412	
Premature rupture of membranes (>18 hours before labour onset)†	5 (7.6)	2 (25.0)	38 (10.2)	0.84
Type of membrane rupture†				
Artificial	32 (43.8)	3 (27.3)	190 (49.5)	0.19
Spontaneous	41 (56.2)	8 (72.7)	194 (50.5)	
Type of labour				0.004
Spontaneous	46 (51.7)	3 (21.4)	251 (60.9)	
Induced	31 (34.8)	9 (64.3)	139 (33.7)	
Elective Caesarean	12 (13.5)	2 (14.3)	22 (5.3)	
Prolonged labour (Stage 1 and 2 >12 Hours)†	28 (41.2)	5 (45.5)	133 (35.0)	0.25
Mode of delivery				<0.001
Spontaneous vaginal	29 (32.6) **(63.0)	2 (14.3) **(40.0)	202 (49.2) **(65.8)	
Operative vaginal‡	17 (19.1) **(37.0)	3 (21.4) **(60.0)	105 (25.5) **(34.2)	
Caesarean section	43 (48.3)	9 (64.3)	104 (25.3)	

Note categories are mutually exclusive

*Difference in distribution between all cases and controls; χ2 test ; Fisher's exact test for <5 observations

†Among those reported: Premature rupture of membranes total missing=70 (13.6%), cases=29 (28.2%) and controls=41 (10%); type of membrane rupture total missing=47 (9.1%), cases=19 (18.4%) and controls=28 (6.8%)

‡ Operative vaginal delivery includes the use of: forceps, Kiellands forceps, vacuum extraction, assisted breech, and breech extraction

**Proporion of all vaginal deliveries

Table 10. Continued

	Uncomplicated sepsis	Severe sepsis	Controls	P-value*
	n=89	n=14	n=412	
Type of placental delivery				0.55
Controlled cord traction	83 (93.3)	10 (71.4)	380 (93.4)	
Maternal effort	1 (1.1)	1 (7.1)	8 (2.0)	
Manual removal	5 (5.6)	3 (21.4)	19 (4.7)	
Blood loss at delivery (ml)				0.001
<200	15 (16.9)	3 (21.4)	110 (26.8)	
≥ 200 < 500	40 (44.9)	1 (7.1)	202 (49.3)	
≥ 500	34 (38.2)	10 (71.4)	98 (23.9)	
Perineal wound	30 (33.7) **(65.2)	2 (14.3) **(40.0)	253 (61.4) **(82.4)	0.42
Antibiotics during pregnancy or delivery††	37 (41.6)	3 (21.4)	176 (42.7)	0.48
Complications in current pregnancy				
Severe pre-eclampsia	16 (18.0)	3 (21.4)	31 (7.5)	0.001
Haemorrhage, abruptio placentae, or placenta previa	12 (13.5)	2 (14.3)	43 (10.4)	0.55
Pre-term birth	17 (19.1)	3 (21.4)	30 (7.3)	<0.001
Baby admitted to NICU	27 (30.3)	4 (28.6)	62 (15.0)	<0.001

Note categories are mutually exclusive

*Difference in distribution between all cases and controls; χ2 test ; Fisher's exact test for <5 observations

**Proporion of all vaginal deliveries

†† Antibiotics administered prior to discharge from the labour ward

NICU = Neonatal intensive care unit

4.3.4 Rates of modes of delivery and antibiotic usage

Over the 23-year study period, the proportion of spontaneous vaginal deliveries decreased whilst the proportion of operative vaginal deliveries and caesarean sections increased significantly (P<0.001; P=0.009; P<0.001 respectively). Antibiotic usage (prior to discharge from the labour ward) amongst cases and controls increased steadily from 1986 to 1996 (P<0.001) and plateaued from 1997 to 2009. Although there was no significant difference between cases and controls in the total proportion of antibiotic usage across all modes of delivery, amongst the sepsis cases who had a caesarean section, 38.5% received antibiotics during pregnancy or delivery, which was significantly lower than the 70.2% of controls who had a caesarean section and received antibiotics (P<0.001). Antibiotic usage amongst controls who had a caesarean section increased significantly over time (P=0.003).

4.3.5 Factors associated with uncomplicated and severe sepsis

After adjusting for changes over time and other factors in each model respectively, factors significantly associated with both uncomplicated sepsis and severe sepsis were: younger age, multiparity, anaemia, operative vaginal delivery and caesarean section (compared to spontaneous vaginal delivery) (Table 11). Obesity was significantly associated with uncomplicated sepsis; this association was not present with severe sepsis, however there was insufficient power to exclude a real relationship as the CIs were very wide based on very small numbers. Additionally, operative vaginal delivery and pre-term birth were significantly associated with uncomplicated sepsis, whilst induced labour was significantly associated with severe sepsis.

Table 11. Unadjusted and adjusted odds ratios for factors associated with uncomplicated and severe sepsis.

	Uncomplicated Sepsis				Severe Sepsis			
	(Unadjusted)		(Adjusted)		(Unadjusted)		(Adjusted)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Demographic characteristics								
Age (years)								
<25	4.94	2.64-9.22	5.15	2.43-10.90	5.10	1.32-19.78	10.17	1.86-55.52
25-34	2.88	1.68-4.93	2.56	1.37-4.78	2.63	0.74-9.27	3.26	0.61-17.41
>34	1*		1*		1*		1*	
Parity								
0	1*		1*		1*		1*	
1	7.13	3.90-13.01	7.44	3.64-15.23	4.47	1.10-18.15	6.31	0.94-42.55
≥2	3.54	1.91-6.56	6.29	2.88-13.77	4.15	1.17-14.72	12.04	2.07-69.90
Late booking (2nd or 3rd trimester)	0.96	0.49-1.88			--	--		
Marital status								
Married	1*				1*			
Single supported	1.17	0.65-2.13			0.74	0.16-3.41		
Single unsupported	1.52	0.71-3.26			0.82	0.10-6.54		
Divorced or separated	5.03	0.99-25.55			--			
Medical characteristics								
Obese	2.4	1.46-3.96	2.12	1.14-3.89	0.71	0.16-3.25		
Smoked during pregnancy	1.46	0.86-2.48			0.30	0.04-2.36		
Anaemia	3.43	2.11-5.58	3.44	1.93-6.13	21.55	2.79-166.38	18.49	1.97-173.14
Diabetes	3.13	0.52-19.04			--	--		
Any previous miscarriage	2.41	0.88-6.60			5.56	1.12-27.61		

Results adjusted for calendar time and for all factors listed in the table.

* Reference group

'--' indicates no comparison group, i.e. zero incidence in either case or control group.

Table 11. Continued

	Uncomplicated Sepsis				Severe Sepsis			
	(Unadjusted)		(Adjusted)		(Unadjusted)		(Adjusted)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Clinical delivery characteristics								
Premature rupture of membranes	0.72	0.27-1.90			2.92	0.57-14.99		
Type of membrane rupture								
Artificial	1*				1*			
Spontaneous	1.25	0.76-2.08			2.61	0.68-9.99		
Induced labour	1.05	0.65-1.70			3.54	1.16-10.75	3.92	1.02-15.35
Prolonged labour	1.30	0.77-2.20			1.55	0.46-5.17		
Type of delivery								
Spontaneous vaginal	1*		1*		1*		1*	
Operative vaginal†	1.13	0.59-2.15	2.20	1.02-4.87	2.89	0.47-17.54	6.39	0.72-56.46
Caesarean section	2.88	1.70-4.88	3.23	1.65-6.34	8.74	1.85-41.19	13.35	2.08-85.68
Manual placenta removal	1.22	0.44-3.35			2.16	0.26-17.68		
≥ 500 mL blood loss at delivery	1.97	1.21-3.19			7.96	2.44-25.94		
Perineal wound	0.32	0.20-0.52			0.10	0.02-0.47		
Antibiotics during pregnancy or delivery‡	0.95	0.60-1.52			0.37	0.10-1.33		
Severe pre-eclampsia	2.69	1.40-5.18			3.35	0.89-12.65		
Haemorrhage, abruptio placentae, or placenta previa	1.34	0.67-2.65			1.43	0.31-6.60		
Pre-term birth	3.00	1.58-5.74	2.46	1.11-5.47	3.47	0.92-13.13		

Results adjusted for calendar time and for all factors listed in the table.

* Reference group

†Operative vaginal delivery includes the use of: forceps, Kiellands forceps, vacuum extraction, assisted breech, and breech extraction.

‡ Antibiotics administered prior to discharge from the labour ward

4.4 Discussion

4.4.1 Summary

Sepsis is now the leading cause of direct maternal death in the UK (Cantwell et al., 2011) giving rise to an urgent need to describe the risk factors for obstetric sepsis morbidity in order to target points of clinical intervention. Although the risk of wound infection (a major cause of puerperal infection (Maharaj, 2007) associated with obesity has been extensively described (Sebire et al., 2001; Usha Kiran et al., 2005; Robinson et al., 2005; Magann et al., 1995; Heslehurst et al., 2007; Doherty et al., 2006; Giuliani et al., 2002; Bianco et al., 1998; Johnson et al., 1987; Edwards et al., 1978), this is the first population-based study to report specifically on the increased risk of maternal sepsis associated with obesity, controlling for method of delivery. In addition, this study provides insight about several under-studied risk factors for maternal sepsis including operative vaginal delivery and maternal age, whilst corroborating other previously identified risk factors.

4.4.2 Comparison of methods to other studies

In this study, the analytical approach and the method of multivariable regression modelling differs from the previous population-based study by Waterstone and colleagues (Waterstone et al., 2001) that also utilised inferential analyses to explore risk factors for severe maternal sepsis in the UK. Furthermore, in the Waterstone study, the case sample size was very small (N=17). The authors do not fully describe the multivariable regression modelling strategy, but do state that variables that were thought to be clinically important but not significant in the univariable analysis were included in the adjusted model. The authors adjusted for nine variables in the multivariable model,

however with this number of predictor variables and only 17 cases (and 2,350 controls), the results are likely to be prone to a lack of precision as evidenced by the wide confidence intervals of the estimates.

With the number of cases in the Waterstone study, in order to detect a statistically significant difference in the odds of severe sepsis for each factor tested, either the odds ratios would have to be very large, or the population prevalence of the factor would have to approach 50% (if the odds ratios were smaller). The population proportions of the factors tested as well as results of the unadjusted analyses are not shown, however the lack of association between severe sepsis and some of the variables such as age, diabetes, hypertension, induction of labour and manual placenta removal are very likely due to low power. Indeed with 17 cases it is likely that some of these factors were not present at all in the case population.

The present study in Aberdeen faced similar power issues particularly with the severe sepsis model with only 14 cases. Therefore, an effort was made to include a small number of parameters in the multivariable model in order to maintain sufficient power to generate more precise estimates in both the uncomplicated sepsis and severe sepsis models. In contrast to Waterstone's approach, the stepwise method was used in this study as a systematic method to derive the most parsimonious model that was nevertheless sufficiently parameterised to fit the data well. Post model-checking procedures indicate that the method was successful.

Uncertainty in the severe sepsis results was however inevitable, which is why it was important to study uncomplicated sepsis alongside the severe sepsis outcome group. The

large degree of uncertainty in the severe sepsis model is shown by wide confidence intervals for most identified risk factors. The results of the analysis of severe sepsis, therefore, must be interpreted as exploratory; future studies in a larger population are needed in order to validate and elucidate the risk factors for severe sepsis. With this caveat, sepsis occurs in a spectrum of severity, and therefore many of the risk factors for uncomplicated sepsis are also likely risk factors for severe sepsis. Demonstrating this relationship, significant risk factors identified in the study's respective case groups largely mirror each other. (Risk factors along the continuum of sepsis severity will be discussed further in Chapter 7.)

4.4.3 Trends

Over the study period there was a significant increase in the incidence of maternal sepsis in this population from 2003 onwards, compared to the average decreasing trend since 1986. There were no changes in diagnostic coding that would explain this increase, as all maternal events were recorded according to ICD-9 codes during the entire study period. One possible explanation for this increase is that 2003 was a peak year in the UK for β-haemolytic Group A streptococcal (*Streptococcus pyogenes*) infection (Lamagni et al., 2005; Scaber et al., 2011; Lamagni et al., 2009), which has traditionally been a major cause of maternal and puerperal sepsis morbidity and mortality (Cantwell et al., 2011; Loudon, 2000). Interestingly, case rates increased across all modes of delivery, which could either indicate nosocomial or community acquired infection. As microbiological data were not available for this study, further investigation is needed to assess the impact of Group A *streptococcus* (GAS) as well as other causative organisms on maternal sepsis and possible routes of infection.

In addition to the prominent increase in the sepsis case rate seen subsequent to 2003, there was also an average decreasing trend seen in the incidence of all maternal sepsis from 1986 to 2003. This drop may be partly explained again by GAS activity in the UK. Rates of superficial manifestations of GAS infection, such as scarlet fever, mirror rates of invasive GAS infection (Dennis et al., 2008) such as maternal sepsis. Although surveillance of the GAS organism did not begin until the following decade, 1988 was a peak year for scarlet fever in the UK. It is likely that this was also a peak year for invasive infection, with a subsequent decrease in following years. Increasing antibiotic usage may have also helped to precipitate the reduction in maternal sepsis case rates during this period.

Although overall antibiotic usage amongst cases and controls increased over the study period and proportionally there was no significant difference in antibiotic usage between cases and controls, it is possible that cases received antibiotics as a treatment course for sepsis, whilst controls received antibiotics as prophylaxis or in immediate response to infection before progression to sepsis. It was not possible to explore this further as time of administration was not available. Additionally, despite a recent move to offering antibiotics to all women undergoing a caesarean section since 2004 under the UK National Institute for Health and Clinical Excellence (NICE) guidelines (National Institute for Clinical Health Excellence, 2011) (in the absence of Scottish Intercollegiate Guidelines Network (SIGN) guidelines), less than half of all cases who had a caesarean section received antibiotics prior to discharge from the labour ward, even from 2004 onwards, compared to the majority of controls who had a caesarean section.

4.4.4 Obesity

It is generally accepted that obese pregnant women are at increased risk of wound infection with sepsis as a possible sequela, in part due to poor vascularity of subcutaneous adipose tissue. This increased risk is particularly evident following caesarean section (Robinson et al., 2005; Martens et al., 1995; Beattie et al., 1994; Johnson et al., 1987), which obese women undergo much more frequently than normal weight women (Knight et al., 2010; Sebire et al., 2001; Usha Kiran et al., 2005; Murphy et al., 2001). The extent to which obesity may independently predispose women to maternal sepsis, however, has not been well described. In this analysis, after controlling for mode of delivery, obese women had twice the odds of developing uncomplicated sepsis compared to normal weight women. Since more obese women are delivered by caesarean section, and caesarean section is a known risk factor for sepsis, in order to test for possible confounding, the 'mode of delivery' variable was removed from the model. This, however, did not appreciably change the association between obesity and sepsis. These results indicate that obesity, independent of mode of delivery, is a risk factor for maternal sepsis. Although this study did not find an association between obesity and severe sepsis, it is difficult to reach a definitive conclusion about the relationship between obesity and severe sepsis based on the very small numbers in this study.

4.4.4.1 Obesity and diabetes

Physiologically, aside from wound infection, it is not yet clear how obesity impacts on metabolic processes, thus affecting established risk factors for maternal sepsis such as vaginal pH levels and increased glycogen storage during pregnancy (Paruk, 2008). Contributing to this lack of clarity is the strong association between obesity and diabetes (both gestational and insulin-dependent mellitus), which occur at higher rates amongst

obese pregnant women (Knight et al., 2010; Ehrenberg et al., 2002; Kuczmarski et al., 1994), and that diabetic compared to non-diabetic women, are at increased risk of infection during pregnancy (Stamler et al., 1990) and postpartum (Takoudes et al., 2004). In the present study the proportion of diabetics amongst uncomplicated sepsis cases (2/89; 2.3%) was greater than in controls (3/412; 0.7%), however the very low population prevalence precluded detection of a significant difference or associated risk compared to controls. It is possible that certain sepsis disease processes mediated by obesity, operate independently of diabetes, however larger future studies are needed to clarify the relationship between these factors. Furthermore, the degree to which pre-diabetes, impaired glucose tolerance and gestational diabetes may play a role in the risk of sepsis, remain to be investigated.

4.4.5 Maternal age

An interesting finding from this population was that younger maternal age was a significant risk factor for uncomplicated sepsis and severe sepsis with five times the adjusted odds of sepsis compared to women >34 years. This finding is contrary to previous studies. Older women are at increased risk for several pregnancy complications and studies on or including maternal sepsis have reported findings commensurate with this general trend. Kramer et.al. found that women aged 35 or older had a estimated relative risk of 1.6 (95% CI 0.9-2.8) for developing sepsis in The Netherlands[18]. Similarly, Girard et.al. found that pregnancy after the age of 35 was a risk factor for severe maternal morbidity including sepsis in the Lorraine region of France (Girard et al., 2001). In the Aberdeen population being younger than 25, which was younger than the mean age for either case group, was strongly predictive of sepsis. Women younger than 25 had five times the odds of developing uncomplicated sepsis and ten times the

odds of developing severe sepsis, compared to women older than 34 years. Despite the finding that younger maternal age was associated with all sepsis in this study, multiparity was also strongly associated with sepsis. This seemingly contradictory confluence resulted from the fact that cases tended to be younger and multiparous, whilst controls tended to be older and primiparous. It is possible that this observation may replicate patterns of community-acquired infection, particularly GAS, but this cannot be confirmed using these data.

4.4.6 Operative vaginal delivery

One under-studied risk factor that emerged from the present study was the association between operative vaginal delivery (forceps, vacuum extraction or assisted breech), and maternal sepsis. Women who had an operative delivery had over twice the odds of uncomplicated sepsis compared to women who had a spontaneous vaginal delivery. This finding is consistent with the few previous studies to have investigated this risk factor in Canada and the USA (Liu et al., 2005; Lydon-Rochelle et al., 2000).

4.4.7 Anaemia

Regarding anaemia, this condition can also be caused by blood-loss during delivery or by sepsis itself. Given that results of routine testing for antenatal anaemia are recorded in the AMND and the proportion of anaemia also found in the control population, it is very likely that these cases were identified antenatally at booking or later, however we did not have exact details regarding temporality. The association of anaemia with sepsis was independent of mode of delivery and blood loss, supporting other findings that anaemia is an independent risk factor for sepsis, although the mechanism of this association is not yet understood and cannot be assumed to be causal.

4.4.8 Preterm birth and labour induction

Preterm birth and labour induction, which were significantly associated with uncomplicated sepsis and severe sepsis respectively, have also been previously cited (Kramer et al., 2009). Induction of labour is now common in obstetric practice. A national study from The Netherlands found that induction of labour was associated with a 5.2 relative risk of sepsis (Kramer et al., 2009). This same study found that preterm birth had a 10.3 relative risk of sepsis (Kramer et al., 2009). The Aberdeen results seem to support these findings.

4.4.9 Agreement with previous studies

This study corroborates several previously cited risk factors for maternal sepsis. In keeping with findings from Waterstone et. al. (Waterstone et al., 2001), multiparity and caesarean section were significant predictors of sepsis. These are well known risk factors and have also been identified in other studies (Maharaj, 2007; Kramer et al., 2009). Due to the homogeneity of the control population, it was not possible to evaluate the role of ethnicity (Kramer et al., 2009). However, given that there is very little ethnic variation in Aberdeen, it was striking that approximately 8% of cases were of non-white ethnic origin, whilst all controls were white.

4.4.10 Study limitations

In this study, there was sufficient power in order to confidently demonstrate associations between uncomplicated sepsis and high prevalence predictive factors in multivariable regression. However due to the low population prevalence of type 1 diabetes and manual placenta removal, there was insufficient power to exclude the role of chance in

the association between these variables and the odds of sepsis. Sources of infection and causative organisms were not available in the data available. It was also not possible to definitively ascertain the temporality of antibiotic usage in relation to mode of delivery or placental removal, however it is possible that cases mostly received treatment antibiotics for sepsis, whilst controls received prophylactic or early stage treatment antibiotics. Similarly, it was not possible to comment on the temporality of preterm birth and other factors, e.g. mode of delivery, as either a risk factor or an outcome of infectious morbidity, although the findings and those from other studies indicate that they are clearly associated with maternal sepsis. And lastly, since this study was geographically limited to one area of the UK, elements that are unique to this population, such as ethnicity, may not be representative of the wider UK population.

4.5 Conclusion

In this study obesity was identified as a significant risk factor for uncomplicated maternal sepsis, in addition to younger maternal age, operative vaginal delivery and other known risk factors. Women with sepsis who had a caesarean section were less likely than controls to have received antibiotics, highlighting the need for prophylaxis. The association observed between operative vaginal delivery and maternal sepsis emphasises the importance of strict aseptic technique and infection control measures in clinical practice. The association between obesity and uncomplicated maternal sepsis is also of clinical significance given the concurrent trend in maternal obesity in the UK.

This study, however, despite using a large population database, had limited power to investigate factors associated with severe maternal sepsis. In order to validate the possible risk factors identified in this study and to comprehensively evaluate the magnitude of severe maternal sepsis morbidity in the UK, it was clear that a study with a much larger sample size was needed. In the next chapter, results of the UKOSS national case-control study of severe maternal sepsis are presented.

Chapter 5

Severe Maternal Sepsis in the UK: a National Case-Control Study

5.1 Introduction

The study reported in the previous chapter demonstrated that rates of maternal sepsis in the North NHS region of Scotland had increased dramatically from 2003, consistent with the pattern of maternal deaths in the UK. Obesity and operative vaginal delivery were also identified as risk factors for sepsis. Importantly however, the study lacked the statistical power to fully investigate factors associated with severe maternal sepsis. It was also not possible to explore factors such as ethnicity, which were relatively homogeneous in the regional population. In addition, it has not been possible in previous studies to investigate the temporality of certain factors associated with severe sepsis such as caesarean section. Thus key information gaps remained in the understanding of the aetiology of severe maternal sepsis. These were: the number of women affected nationally, causative organisms, sources of infection, and risk factors for severe sepsis and poor outcomes such as septic shock. Sepsis progresses along a spectrum of severity, so clarity about these factors has important implications for clinical management and infection control strategies to avoid maternal deaths.

5.1.1 Study objectives

The objectives of the study presented in this chapter were to estimate the incidence, describe the causative organisms and sources of infection through a descriptive analysis, and to identify the risk factors for severe maternal sepsis in the UK through a case-control study.

5.2 Methods

5.2.1 Study design

This was a national prospective case-control study of all peripartum women diagnosed with severe sepsis (including septic shock), irrespective of the source of infection, in all obstetrician-led maternity units in the UK from June 2011 to May 2012. A case-control study design was chosen because of the rarity of the condition and the lack of a source of national data to allow a cohort study to be undertaken. The UK Obstetric Surveillance System (UKOSS) surveillance system, as discussed below, is designed to collect data on rare disorders of pregnancy, whereby the system is prospectively notified of cases meeting specific criteria. This is a convenient model for studying rare health outcomes such as severe maternal sepsis. Thus, in order to assess risk factors for developing severe sepsis in this study, all cases were compared with non-septic controls. In order to assess the risk of progression to septic shock, cases with a diagnosis of septic shock were compared to all other cases with severe sepsis that did not develop septic shock.

5.2.2 Data source – UKOSS

This study was conducted using the UKOSS (National Perinatal Epidemiology Unit (NPEU), 2014). The UKOSS methods have been described in detail elsewhere (Knight et al., 2005). In brief, UKOSS is used to conduct descriptive, case-control and anonymised cohort studies through a prospective, monthly case-collection scheme using a network of collaborating clinicians. This network includes up to four nominated reporting clinicians (obstetricians, midwives, anaesthetists, and risk managers) in each obstetrician-led maternity unit in the UK. Nominated clinicians coordinate case reports from all clinicians in their units, and for this study were asked to report, via a monthly report card, how many women met the case definition for severe sepsis. Clinicians were

asked to return all cards including those with no cases to report in order for participation to be monitored and the denominator population for the study to be confirmed. Clinicians who reported a case were then sent a data collection form with a unique UKOSS identification number, requesting anonymous detailed information on obstetric and medical history, diagnosis, management and outcomes. Reporting clinicians were also asked to complete a data collection form for two women meeting the control definition. If completed data collection forms were not returned, up to five reminders were sent. Where data were missing or invalid, clinicians were contacted for the correct information. All data were double entered into a customised database and cases were verified to confirm they met the case definition and to exclude duplicate reports.

UKOSS is managed by a steering committee. The committee comprises an expert panel of obstetricians, midwives, anaesthetists, epidemiologists, public health physicians and infectious disease specialists. Members are representatives of UK National Health Service (NHS) Trusts, various university institutions and organisations including the relevant Royal Colleges, professional organisations and Public Health England. UKOSS operates within the National Perinatal Epidemiology Unit (NPEU) at the University of Oxford (National Perinatal Epidemiology Unit (NPEU), 2014).

5.2.3 Definitions

Since there is currently no standardised definition for severe sepsis in pregnant and peripartum women, the study definition was developed based on previous literature and by consensus discussion of the UKOSS steering committee (Knight et al., 2005). In the non-obstetric population, consensus definitions of sepsis severity (systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock) were

developed in 1992 (Table 5) (Bone et al., 1992). As discussed in Chapter 2, these definitions and subsequent improvements, however, are difficult to apply to pregnant and peripartum women since clinical signs and symptoms of severe infection differ in this population. Specifically, SIRS can both be a sign of ruptured membranes and changing biochemistry associated with labour and delivery, as well as a clinical marker of severe infection. Therefore the clinical parameters of SIRS in the presence of an infection are often altered in the obstetric population.

5.2.3.1 Developing the case definition

In developing the case definition, three factors were taken into consideration: (1) clinical criteria (as discussed in Chapter 2) since pregnant and peripartum women often have altered SIRS parameters; (2) some women may not meet the clinical criteria for severe sepsis, but are nevertheless admitted to critical care for sepsis or die of sepsis; and (3) some women may not have, or are not diagnosed with, severe sepsis according to clinical criteria and may not be admitted to critical care but are nevertheless thought to have severe sepsis. Another consideration in developing the case definition was the scope of sepsis; to date the UK Confidential Enquires into Maternal Deaths separates direct and indirect causes of death and thus only considers genital tract causes for sepsis (Cantwell et al., 2011). Following this categorisation would narrow the case definition and would be consistent with the maternal death data collection to 2008. However, important cases of sepsis and sepsis deaths due to other causes such as respiratory tract infection would be missed. On the other hand, widening the case definition to 'all cause' sepsis had the potential to overload the UKOSS reporting system, particularly in the event of a severe influenza season.

Because there were no previous studies and thus a need for information on the total burden of severe sepsis in the obstetric population, it was decided that 'all cause' maternal sepsis would be used for the case definition, with the burden on the reporting system carefully monitored. With this case definition it would be possible to separately calculate incidence rates and risk factors for genital tract sepsis for comparison to maternal death reports without excluding data from the entire analysis. In order to account for the altered SIRS criteria in the obstetric population, the 'obstetric SIRS' definition was adopted from the 2001 Waterstone et al study (Waterstone et al., 2001) of severe obstetric morbidity. Clinical management (level 2 or level 3 critical care admission) and if the woman died were also taken into account. The final case definition is shown in Table 12.

Table 12. UKOSS severe sepsis case definition.

Any pregnant or recently pregnant woman (up to 6 weeks postpartum) diagnosed with severe sepsis (irrespective of the source of infection). Report only cases diagnosed as having severe sepsis by a senior clinician.

A severe sepsis case would be expected to include one of the following groups:

1. Death related to infection or suspected infection
2. Any women requiring level 2 or level 3 critical care (or obstetric HDU type care) with severe sepsis or suspected sepsis
3. Clinical diagnosis of severe sepsis

   As a guide, a clinical diagnosis of severe sepsis would usually be associated with two or more of the following:

   a. Temperature >38°C or <36°C 4 hours apart, on 2 occasions
   b. Heart rate >100 beats/ minute persisting for over 4 hours, on 2 occasions
   c. Respiratory rate >20/ minute for over 4 hours or PaCO2 <32 mm Hg, on 2 occasions
   d. White cell count >17,000/ml or <4,000/ml or with >10% immature band forms, on 2 occasions

Lastly, in order to ensure that all possible cases were reported or 'captured', the language of the case definition on the data collection form was made intentionally broad. For example, qualifiers such as "would be expected to include" and "would usually be associated with" were used. However, for analysis purposes, all cases included had to meet one of the three criteria stated in the case definition. In this way, there was a slight difference between the case-capture definition and the analysis case definitions.

5.2.3.2 Selection of controls

Controls were women who did not have severe sepsis and delivered immediately before each case in the same hospital. The clinician reporting each case was asked to supply anonymised data for two control women who delivered at the hospital at the closest time before the case.

5.2.4 Development of the data collection form

The data collection form was developed by the author based on previous literature and in consultation with of the UKOSS steering committee. All UKOSS data collection forms have eight standard sections:

- Section 1 – Woman's details
- Section 2 – Previous obstetric history
- Section 3 – Previous medical history
- Section 4 – This pregnancy – antenatal information
- Section 5 – Delivery details
- Section 6 – Outcomes
- Section 7 – Additional information
- Section 8 - Reporting clinician details

Standard UKOSS questions are contained in each section, and in addition, questions specific to severe sepsis were added to each section as relevant. Sepsis-specific questions were derived from previous literature on possible risk factors. In addition, questions were added to ascertain the timing of sepsis in relation to delivery details, for example, when severe sepsis was diagnosed and if and when septic shock was diagnosed.

Questions regarding the timing of clinical criteria were also added for two purposes. The first purpose was to ensure that the clinical criteria were met in each case. The second purpose was to evaluate the timing of sepsis onset from the first sign of SIRS, and also to ascertain whether the woman was ill before delivery. The temporality of sepsis in relation to delivery is critically important for assessing mode of delivery as a risk factor and for understanding the pathogenesis of sepsis. This type of analysis has not been possible in other studies.

The case and control data collection forms were evaluated on two separate occasions by the UKOSS steering committee. The final questionnaire was agreed upon and approved by the steering committee. Lastly, the UKOSS data manager checked the internal consistency and agreement of the questions. Case and control data collection forms can be found in Appendix 5.

5.2.5 Data gathering and coding

Upon receiving a case notification via the monthly reporting card, the UKOSS team dispatched a data collection form to the clinician. If a completed data collection form was not received back by the UKOSS team after six weeks, a second form was sent out,

and a third form four weeks thereafter. If there was still no response after a further four weeks, the clinician was contacted by telephone. Once the data collection forms were returned, the data were examined to confirm each case met the case definition, otherwise cases were designated as 'not a case'. Cases and controls were then allocated a unique UKOSS identification number. No names, addresses, dates of birth, hospital or NHS numbers were collected in accordance with the UKOSS ethics approval of anonymous data collection without patient consent (North London REC1. (ref 10/H0717/20); Appendix 4). Responding clinicians were asked to keep their own record of the unique study number and the patient identifiers in order to facilitate elimination of duplicate reports.

Free text in each data collection form was coded twice by two separate coders, including the author (CA), in order to check for errors and inconsistencies. The numerical codes were assigned according to a coding dictionary used for all UKOSS studies. A new section was developed by the author and added to the coding dictionary for sepsis-specific codes, and new codes were added as required for all other sections.

5.2.6 Data entry and management

Data were double entered into a customised database. Duplicate reports were eliminated by comparing hospital and date of notification and confirmed through follow-up with the reporting clinicians. The UKOSS database has a query system in place to detect internal inconsistencies, however the author (CA) also checked for any inconsistencies or coding errors that may have occurred. This was done by visual inspection of the data and by performing tabulations of related variables.

5.2.7 Statistical software

Stata statistical software 11 (StataCorp, College Station, TX) was used for all analyses.

5.2.8 Statistical Analyses

5.2.8.1 Incidence

The incidences of severe maternal sepsis and septic shock with 95% confidence intervals (CIs) were estimated using the number of maternities (number of women giving birth to live and still births) reported in the most recent national birth data (2011) (Office for National Statistics, 2012; Northern Ireland Statistics and Research Agency, 2012a; General Register Office for Scotland, 2013) as the denominator. Sources of infection, causative organisms and sepsis severity characteristics were tabulated for all cases, and stratified according to parturition status, as patterns of disease are known to differ between pregnant and postpartum women (Paruk, 2008).

5.2.8.2 Risk factor analyses

For risk factor analyses, sociodemographic, medical history and delivery characteristics with *a priori* evidence of an association with sepsis were compared between cases and controls, and between sepsis cases with and without septic shock respectively. Sources of infection and causative organisms were also assessed as risk factors in the latter comparison because this information was available for both groups. Proportions were compared using Pearson's chi-square test and Fisher's exact test where there were ≤5 observations in a single cell. All P-values were two-sided, and a P-value of <0.05 was considered statistically significant.

5.2.8.3 Univariable logistic regression

The odds of severe sepsis and septic shock associated with each factor were initially estimated using univariable unconditional logistic regression. Odds ratios (OR) with 95% CIs were estimated. The reference group for each categorical variable was determined by ease of interpretation or by the largest group. Confounding was initially assessed by stratification and cross-tabulation using the Cochran-Mantel-Haenszel test. Since there were a large number of variables, this operation was only performed on those that had a plausible relationship with another explanatory variable and the outcome. The following variables were tested for an association with the outcome (severe sepsis) stratified by age categories: low socioeconomic status (manual or unemployed) (P=0.124), single marital status (P=0.119), primiparity (P=0.021) and caesarean section (P<0.001); and the following variables were tested for an association with severe sepsis stratified by low socioeconomic status: black or other minority ethnic group (P=0.009), late booking (P=0.349), obesity (P=0.881), and pre-existing medical problems (P<0.001). These tests indicated that there was confounding between the variables age and primiparity; age and caesarean section; low socioeconomic status and black or other minority ethnic group; and low socioeconomic status and pre-existing medical problems.

5.2.8.4 Multivariable logistic regression

After univariable regression, an adjusted analysis was carried out using multivariable unconditional logistic regression. Since there was a large proportion of women with an unknown source of infection, causative organism and socio-economic group, the subcategories of ‘unknown’ and ‘no laboratory confirmed infection’ were included for these variables in all analyses.

For both severe sepsis and septic shock outcome groups, factors were included in the models in two stages. First, all *a priori* sociodemographic and medical history factors, with the exception of previous caesarean deliveries and previous pregnancy problems (as these were dependent on parity), and delivery status (since the control population were all women who were postnatal), were included in a primary model. Second, delivery factors were then adjusted for *a priori* risk factors using a more parsimonious approach in order to avoid over adjustment given the large number of variables; results were adjusted only for *a priori* factors from the primary model which were known risk factors as identified in previous studies, were significant in the primary model or were plausible confounders. Over-adjustment can occur when a confounding factor also mediates some association between another explanatory variable and the outcome, which results in adjusting for the effect the model aims to estimate (Altman, 1991). A possible hospital-clustering effect was tested for by re-running the final models using robust standard errors; with no appreciable change in any of the confidence intervals, adjustment for this effect was determined to be unnecessary.

In the Aberdeen study (Chapter 4), the stepwise approach was used for multivariable regression modelling, which differs from the model strategy used in this study. The reason that the stepwise approach was used in the Aberdeen study was that the sample sizes were very small. Given the low power, a method was needed to derive the most parsimonious models possible for more accurate estimates. In this study, there was a substantially larger sample size, and thus greater power. This allowed for the use of a more Bayesian approach, as opposed to a purely statistical approach, to building the model. This strategy allows for the addition of variables that have a plausible relationship to the outcome, even though they may not have been significant in the

univariable or primary multivariable models. Using this strategy, only those variables that were *not* known risk factors or plausible confounders were eliminated in the second stage clinical model.

The continuous variables of age and BMI were tested for departure from linearity graphically (aOR plotted against the linear predictor), and secondarily tested by adding a first-order fractional polynomial to the multivariable model with subsequent likelihood ratio testing at a significance level of $P<0.01$ (Royston et al., 1999). Possible outliers were also inspected by plotting the standardised model residuals against the linear predictors. There was no evidence of serious outliers or departure from linearity for the variable age and it was therefore treated as a continuous linear term in the analysis, but presented as a categorical variable in the results table for ease of interpretation. There was evidence of a non-linear relationship with BMI, which was subsequently treated as a categorical variable in all regression models.

Delivery characteristics were evaluated for postpartum cases only, as this set of risk factors pertained specifically to delivery. Results of both stages of adjustment are reported as unadjusted odds ratio (uORs), adjusted odds ratios (aORs) and their 95% CIs for severe sepsis in Tables 14-15. For ease of presentation of risk factors for progression to septic shock, results are reported only for factors included in the final adjusted models and are reported in a single table (Table 16).

5.2.8.5 Post model checking procedures

Likelihood ratio tests with a significance level of $P<0.01$ were also used to check for interactions between variables. Interactions were tested for between the following

variables: ethnic group and socioeconomic status; age and parity; BMI and mode of delivery; age and premature rupture of membranes. No significant interactions were identified in the final adjusted models.

The fit of the models were assessed using Hosmer-Lemeshow's goodness-of-fit test with a significance level of $P<0.05$; all final models had a P-value >0.05, indicating that the models fit the data well.

5.2.8.6 Cumulative risk

In addition to understanding the risk of severe sepsis associated with particular factors after controlling for all other variables in the logistic regression models, the risk of severe sepsis as a function of the number of risk factors was also estimated. This was done in order to understand if there was an association between an increasing number of factors and risk of severe sepsis, since many women in this study had multiple risk factors. For this analysis, the number of significant adjusted risk factors was counted for each case and control. Case and control groups were then compared using univariable logistic regression with 'zero risk factors' as the reference group.

5.2.8.7 Genital-tract sepsis analysis

Lastly, all analyses were re-run with cases of severe genital-tract sepsis only compared to controls in order to assess whether risk factors (such as mode of delivery) differ for this dominant source of infection compared to all sources of severe maternal sepsis.

5.2.9 Sample size and power

Within a one-year study period, it was anticipated there would be approximately 320 cases of severe sepsis based on an estimated incidence of 4 per 10,000 maternities (Waterstone et al., 2001). For the severe sepsis risk factor analysis, with two controls per case and for a risk factor prevalence of at least 5% in control women, with 320 cases the study was estimated to have had 80% power at $P<0.05$ (two-sided) to detect a statistically significant odds ratio (OR) of 2.3 or greater. The actual number of cases and controls identified during the study period gave an estimated power of 80% at the 5% level of significance to detect an OR of 2.1 or greater, for the same risk factor prevalence level. For the septic shock risk factor analysis, for a risk factor prevalence of at least 15% in women without septic shock, the analysis had 80% power at the 5% level of significance to detect an OR of 2.6 or greater.

5.2.10 Research ethics committee approval

This study was approved by the London Research Ethics Committee (ref 10/H0717/20). The protocol for the study can be found in Appendix 4.

5.3 Results

5.3.1 Incidence

During the study period, all 214 UK hospitals with obstetrician-led maternity units participated in UKOSS, representing 100% participation. There was a total of 486 cases of severe sepsis reported, of which data collection was complete for 90% (Figure 12), and data were obtained for 757 controls. There was a total of 365 confirmed cases of

severe sepsis out of 780537 maternities in the UK (Office for National Statistics, 2012; Northern Ireland Statistics and Research Agency, 2012a; General Register Office for Scotland, 2013), representing an incidence of 4.7 per 10,000 maternities (95% CI 4.2-5.2) and corresponding to approximately 50 women with severe sepsis for every maternal sepsis death. There were 134 (36.7%) antepartum and 231 (63.3%) postpartum cases. Seventy-one women (20%) developed septic shock, which represents an incidence of 0.91 per 10,000 maternities (95% CI 0.71-1.15) and corresponds to approximately 9 women with septic shock for every maternal sepsis death; 47 (66.2%) were admitted to intensive care.

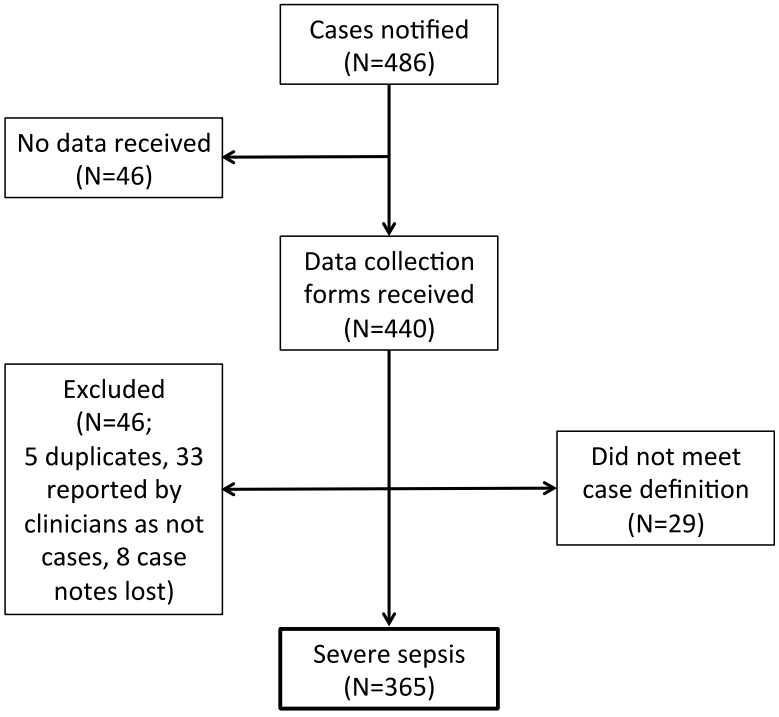


Figure 12. Case reporting and completeness of data collection.

5.3.2 Sources, causative organisms and severity

Laboratory confirmed infection was reported for 233 (63.8%) severe sepsis cases and a source of infection was identified for 270 cases (74.0%). The distribution of sources of

infection, causative organisms and severity characteristics are shown in Table 13 and Figure 13. Overall, the largest proportion of cases was due to genital tract infection (31.0%) and the most common organism causing infection was *Escherichia coli* (*E. coli*) (21.1%). However, the distribution of both the source and causative organism differed significantly between antepartum and postpartum women (P<0.0001 for both), as did the risk of septic shock. Of all cases, 78% (n=286) received level-two or intensive care and five women died (Table 13). Of the women who died, two had infection with E.coli and three women had an unknown causative organism. Eight percent (n=29) of women with severe sepsis had either a miscarriage or a termination of pregnancy.

Table 13. Characteristics of infection in antepartum and postpartum women with severe sepsis.

	Antepartum n (%)	Postpartum* n (%)	Total n (%)	p-value
	n=134 (36.7)	n=231 (63.3)	n=365	
Source of infection				<0.0001
Genital tract	27 (20.2)	86 (37.2)	113 (31.0)	
Urinary tract	45 (33.6)	27 (11.7)	72 (19.7)	
Wound	0 (0.0)	33 (14.3)	33 (9.0)	
Respiratory	12 (9.0)	8 (3.5)	20 (5.5)	
Other	10 (7.5)	22 (9.5)	32 (8.8)	
Unknown	40 (29.9)	55 (23.8)	95 (26.0)	
Organism				<0.0001
Escherichia coli	33 (24.6)	44 (19.1)	77 (21.1)	
Group A streptococcus	2 (1.5)	30 (13.0)	32 (8.8)	
Group B streptococcus	13 (9.7)	17 (7.4)	30 (8.2)	
Other streptococcus	6 (4.5)	15 (6.5)	21 (5.7)	
Staphylococcus	2 (1.5)	21 (9.1)	23 (6.3)	
Mixed organisms	5 (3.7)	14 (6.1)	19 (5.2)	
Other	12 (9.0)	13 (5.6)	25 (6.9)	
Unknown	5 (3.7)	1 (0.4)	6 (1.6)	
No laboratory confirmed infection	56 (41.8)	76 (32.9)	132 (36.2)	
Severity				
Level 2 or 3 admission	103 (76.9)	183 (79.2)	286 (78.4)	0.598
Level 2 admission	64 (47.8)	107 (46.3)	171 (46.9)	0.79
Level 3 admission**	39 (29.1)	75 (32.5)	114 (31.2)	0.504
Septic shock	16 (11.9)	55 (23.8)	71 (19.5)	0.006
Death	2 (1.5)	3 (1.3)	5 (1.4)	0.915

Leve 2 = High dependency care unit (HDU); Level 3 = Intensive care unit (ITU)
* Includes 1st/2nd trimester losses (N=29)
** Irrespective of level 2 admission

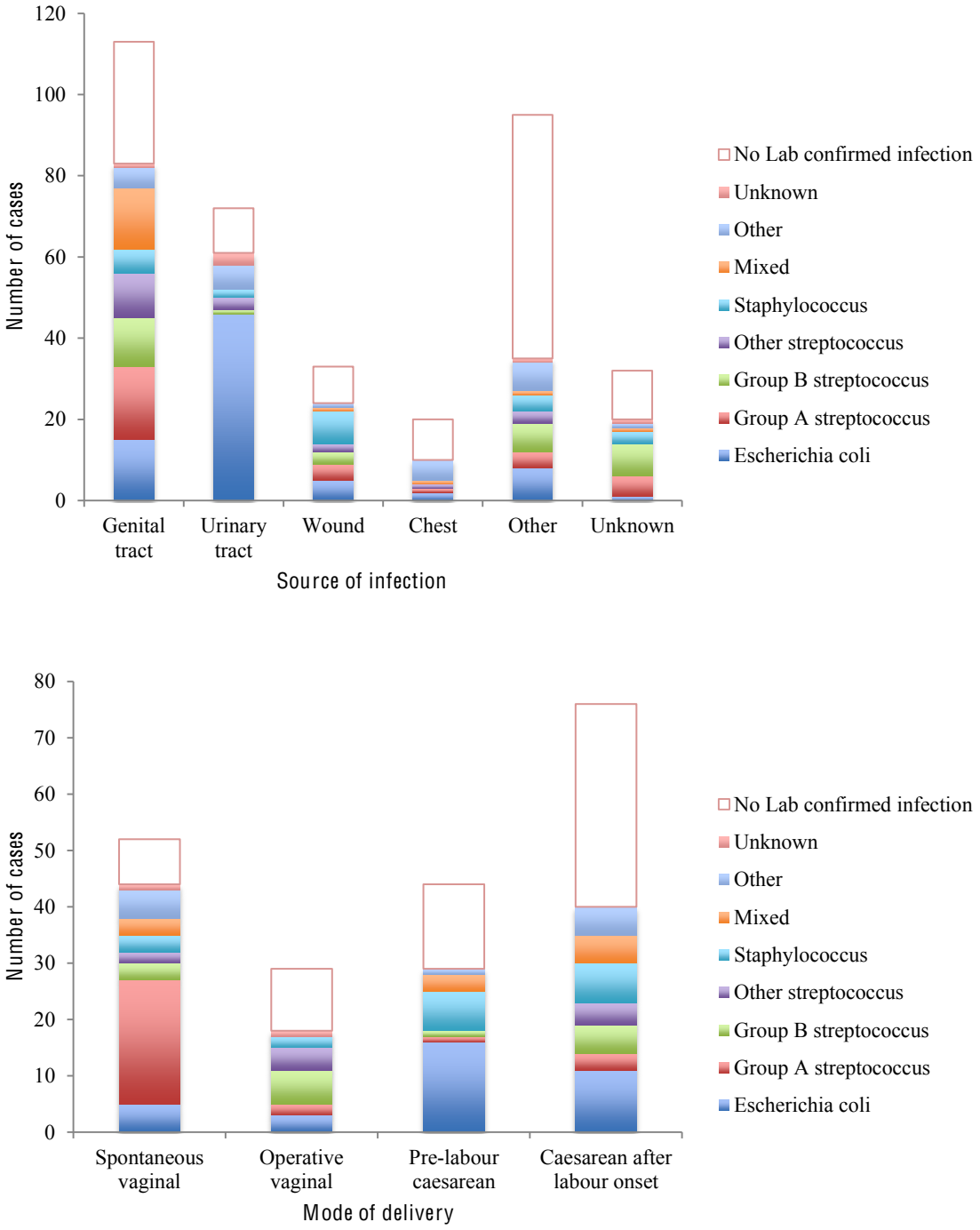


Figure 13. Distribution of causative organism by source of infection and mode of delivery.

5.3.3 Time course

The median time between delivery and sepsis for postpartum cases was 3 days (interquartile range 1-7 days). There were 296 cases with a date and time of the first sign of SIRS and severe sepsis diagnosis; for 83% (n=245) of all cases and 85% (n=49) of septic shock cases there was <24 hours between the first sign of SIRS and diagnosis of severe sepsis; and for 89% (n=264) of all cases and for 95% (n=55) of septic shock cases there was <48 hours between the first sign of SIRS and diagnosis of severe sepsis. For 86% (n=95) of women who were readmitted there was <24 hours between the first sign of SIRS and diagnosis of severe sepsis. Additionally, for 50% (n=16) of women with a group A streptococcal infection there was <2 hours and for 75% (n=24) <9 hours between the first sign of SIRS and diagnosis of severe sepsis.

5.3.4 Risk factors for severe sepsis

Sociodemographic and medical history characteristics of women with severe sepsis compared to control women are listed in Table 14. After adjustment and compared to controls, women who were of black or of another minority ethnic origin, were primiparous, had a pre-existing medical problem, and had a febrile illness or were taking antibiotics in the two weeks prior to delivery were at significantly increased odds of severe sepsis. In addition to significant *a priori* factors, postpartum women who had an operative vaginal delivery, pre-labour caesarean section or a caesarean section after the onset of labour, or had a complication of delivery were at significantly increased odds of severe sepsis (Table 15). Of note, among all women who had a caesarean section, 96.6% of cases and 94.8% of controls received prophylactic antibiotics at delivery. The odds of severe sepsis increased significantly as a function of the number of risk factors women had (P<0.001)(Figure 14).

Table 14. Unadjusted and adjusted odds ratios for severe sepsis associated with sociodemographic and medical factors; all severe sepsis cases compared with controls.

	Cases n (%)* n=365	Controls n (%)* n=757	χ^2 P-value	uOR (95% CI)	aOR**95% CI
Risk Factor					
Sociodemographic factors					
Age (years)			<0·001		
<25	117 (32·0)	159 (21·0)		1·73 (1·29-2·32)	1·38 (0·96-2·00)
25-34	186 (51·0)	438 (57·9)		1	1
≥35	62 (17·0)	160 (21·1)		0·91 (0·65-1·28)	1·00 (0·67-1·51)
Ethnic group			0·003		
White	221 (60·7)	525 (69·5)		1	1
Black and other minority	143 (39·3)	230 (30·5)		1·48 (1·14-1·92)	1·82 (1·32-2·51)
Socio-economic group			0·001		
Managerial and professional occupations	68 (19·7)	189 (25·6)		1	1
Intermediate	63 (18·2)	147 (20·0)		1·19 (0·79-1·79)	1·17 (0·73-1·88)
Manual	96 (27·8)	224 (30·4)		1·19 (0·83-1·72)	1·26 (0·81-1·94)
Unemployed	29 (8·0)	46 (6·1)		1·75 (1·02-3·01)	1·56 (0·82-2·97)
Unknown	109 (29·9)	151 (19·9)		2.00 (1·38-2·91)	1·63 (1·02-2·61)
Marrital status			0·006		
Single	85 (23·3)	124 (16·4)		1·54 (1·13-2·10)	1·13 (0·75-1·69)
Married or Cohabitating	280 (76·7)	630 (83·6)		1	1

* Percentage of individuals with complete data

** Adjusted for all factors in the table. Age treated as a continuous linear terms in the analysis, but presented as categorical terms.

Table 14. Continued

	Cases n (%)* n=365	Controls n (%)* n=757	χ^2 P-value	uOR (95% CI)	aOR**95% CI
Risk Factor					
Obstetric and medical factors					
Late booking (≥12 weeks)			0·18		
Yes	85 (23·3)	150 (19·8)		1·23 (0·91-1·66)	1·08 (0·77-1·50)
No	280 (76·7)	607 (80·2)		1	1
Parity			0·001		
0	197 (54·1)	330 (43·6)		1·53 (1·19-1·96)	1·6 (1·17-2·20)
≥1	167 (45·9)	427 (56·4)		1	1
Previous caesarean deliveries			0·002		
Yes	47 (12·9)	96 (12·7)		1·33 (0·89-2·0)	
No	121 (33·2)	330 (43·7)		1	
Previous pregnancy problems			0·001		
Yes	65 (18·0)	141 (18·7)		1·31 (0·90-1·90)	
No	100 (27·6)	284 (37·6)		1	
Multiple pregnancy			0·036		
Yes	10 (2·8)	8 (1·1)		2·63 (1·03-6·73)	2·8 (0·81-9·72)
No	354 (97·3)	746 (98·9)		1	1
Smoked during pregnancy			0·103		
Yes	99 (27·4)	173 (22·9)		1·27 (0·95-1·69)	1·13 (0·81-1·57)
No	262 (72·6)	581 (77·1)		1	1

* Percentage of individuals with complete data

** Adjusted for all factors in the table. Age treated as a continuous linear terms in the analysis, but presented as categorical terms.

Table 14. Continued

	Cases n (%)* n=365	Controls n (%)* n=757	χ^2 P-value	uOR (95% CI)	aOR**95% CI
Risk Factor					
BMI at booking (kg/m^2)			0·982		
<18.5	15 (4·1)	29 (3·8)		1·1 (0·58-2·11)	0·71 (0·32-1·60)
18.5<25	159 (43·6)	339 (44·8)		1	1
25<30	96 (26·3)	196 (25·9)		1·04 (0·77-1·42)	1·1 (0·77-1·57)
≥30	95 (26·0)	193 (25·5)		1·05 (0·77-1·43)	1·2 (0·83-1·74)
Diabetes			0·35		
Yes	10 (2·7)	29 (3·8)		0·71 (0·34-1·47)	0·8 (0·35-1·83)
No	355 (97·3)	728 (96·2)		1	1
History of pyelonephritis/ urinary tract infection			<0·001		
Yes	36 (9·9)	33 (4·4)		2·4 (1·47-3·92)	1·31 (0·71-2·42)
No	329 (90·1)	724 (95·6)		1	1
History of sexually transmitted infection			0·029		
Yes	26 (7·2)	31 (4·1)		1·8 (1·05-3·09)	1·63 (0·91-2·90)
No	336 (92·8)	723 (95·9)		1	1

* Percentage of individuals with complete data

** Adjusted for all factors in the table. Age treated as a continuous linear terms in the analysis, but presented as categorical terms.

Table 14. Continued

	Cases n (%)* n=365	Controls n (%)* n=757	χ^2 P-value	uOR (95% CI)	aOR**95% CI
Risk Factor					
Pre-existing medical problems***			<0·001		
Yes	120 (32·9)	171 (22·7)		1·67 (1·27-2·20)	1·4 (1·01-1·94)
No	245 (67·1)	583 (77·3)		1	1
Invasive antenatal procedures****			0·57		
Yes	5 (1·38)	11 (1·46)		0·94 (0·32-2·73)	0·66 (0·18-2·42)
No	358 (98·6)	742 (98·5)		1	1
Febrile illness or antibiotics in 2 wks before delivery			<0·001		
Yes	153 (41·9)	42 (5·6)		12·29 (8·45-17·86)	12·07 (8·11-17·97)
No	212 (58·1)	715 (94·5)		1	1

* Percentage of individuals with complete data

** Adjusted for all factors in the table. Age treated as a continuous linear terms in the analysis, but presented as categorical terms.

*** Major pre-existing medical problems (% cases vs. controls) include: asthma (10·0 vs. 17·0%), Endocrine disorders (5·8 vs. 9·4%), haematological disorders (9·2 vs. 7·0%), Mental health/ psychiatric disorders (13·3 vs. 12·9%), renal disorders (7·5 vs. 1·8%) and unknown medical problem (18·3 vs. 15·8%).

**** Chorionic villus sampling (CVS) or amniocentesis

Table 15. Unadjusted and adjusted odds ratios for severe sepsis associated with delivery factors in postpartum cases compared with controls.

	Postpartum cases n (%)*	Controls n (%)*	P-value	uOR (95% CI)	aOR**95% CI
	n=231	n=757			
Risk Factor					
Delivery factors					
Premature rupture of membranes			0·476		
Yes	21 (13·7)	74 (11·6)		1·21 (0·72-2·03)	0·98 (0·53-1·81)
No	132 (86·3)	562 (88·4)		1	1
>5 vaginal examinations			0·04		
Yes	53 (23·1)	127 (17·1)		1·46 (1·02-2·09)	1·09 (0·66-1·79)
No	176 (76·9)	615 (82·9)		1	1
Fetal blood sampling			0·003		
Yes	19 (8·2)	27 (3·6)		2·42 (1·32-4·44)	1·03 (0·48-2·19)
No	212 (91·8)	730 (96·4)		1	1
Fetal scalp electrode			0·027		
Yes	32 (13·9)	67 (8·9)		1·66 (1·06-2·60)	1·14 (0·64-2·06)
No	199 (86·2)	690 (91·2)		1	1

* Percentage of individuals with complete data

** Adjusted for all factors in the table as well as age, ethnic group, socioeconomic group, parity, multiple gestation, history of UTI, pre-existing medical problems and febrile illness or antibiotics in the two weeks prior to presentation.

Table 15. Continued

	Postpartum cases n (%)* n=231	Controls n (%)* n=757	P-value	uOR (95% CI)	aOR**95% CI
Risk Factor					
Delivery factors					
Labour induction			0·563		
Yes	62(26·8)	218 (28·8)		0·91 (0·65-1·26)	1·13 (0·75-1·70)
No	169 (73·2)	539 (71·2)		1	1
Mode of delivery			<0·001		
Spontaneous vaginal	51 (25·5)	443 (58·8)		1	1
Operative vaginal	29 (14·5)	100 (13·3)		2·52 (1·52-4·17)	2·49 (1·32-4·70)
Pre-labour caesarean	44 (22·0)	119 (15·8)		3·21 (2·05-5·04)	3·83 (2·24-6·56)
Caesarean after labour onset	76 (38·0)	92 (12·2)		7·18 (4·72-10·92)	8·06 (4·65-13·97)
Complications of delivery***			0·46		
Yes	79 (34·2)	279 (36·9)		0·89 (0·65-1·21)	1·69 (1·09-2·63)
No	152 (65·8)	478 (63·1)		1	1

* Percentage of individuals with complete data

** Adjusted for all factors in the table as well as age, ethnic group, socioeconomic group, parity, multiple gestation, history of UTI, pre-existing medical problems and febrile illness or antibiotics in the two weeks prior to presentation.

*** Complications of delivery (% cases vs. controls) include: episiotomy (12·3 vs. 13·9%), tears (2nd-4th degree) (6·5 vs. 18·2%), manual removal of placenta (1·3 vs. 1·5%), postpartum haemorrhage (4·3 vs. 2·3%) and other complications of caesarean section (uterine angle tear; difficult delivery of infant; ureter/bladder damage; bowel perforation; multiple adhesions; other) (10·4 vs. 0·7%).

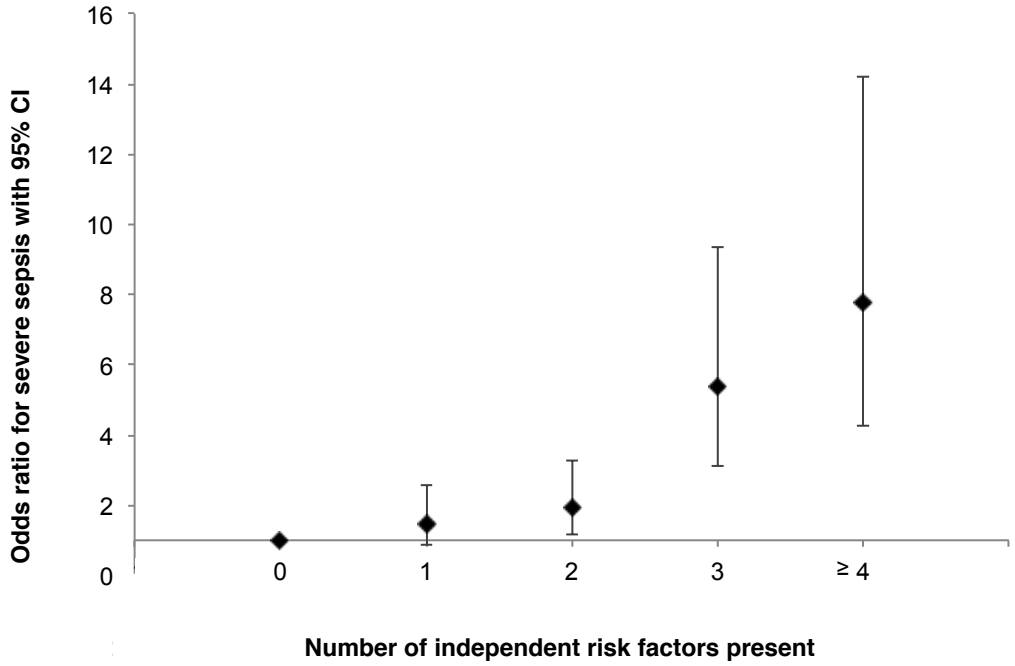


Figure 14. Odds of severe sepsis as a function of the number of risk factors.

5.3.5 Risk factors for septic shock

A priori sociodemographic, infection and delivery characteristics amongst woman who had septic shock, and compared to women with severe sepsis but not septic shock are described in Figure 15 and Table 16. After adjustment for all *a priori* and infection factors in the model, multiple pregnancy and group A streptococcus as the causative organism were significantly associated with an increase in the odds of progression from severe sepsis to septic shock. Before adjustment for group A streptococcal infection, spontaneous vaginal delivery (aOR=3.85; 95% CI 1.35-10.96) and operative vaginal delivery (aOR=3.12; 95% CI 1.03-9.57) were significantly associated with an over three-fold increase in the odds of progression to septic shock.

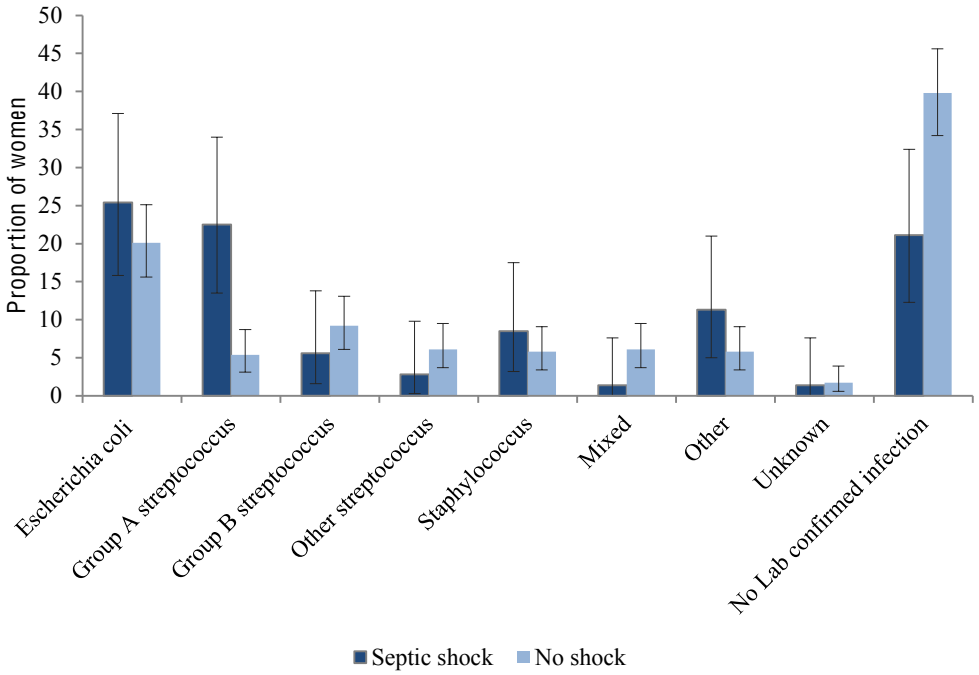


Figure 15. Distribution of causative organism according to septic shock.

5.3.6 Severe genital-tract sepsis

When the logistic models were re-run specifically including only cases with genital-tract infection (n=113) compared to controls, women who were of black or from another minority ethnic group (aOR=2.08; 95% CI 1.27-3.40), had a multiple pregnancy (aOR=5.29 95% CI 1.31-21.44) or had a febrile illness or were taking antibiotics in the two weeks prior to delivery (aOR=11.70; 95% CI 6.83-20.07) had significantly increased odds of severe sepsis. After adjusting for *a priori* factors, compared to women who had a spontaneous vaginal delivery, and controlling for illness prior to delivery, women who had a pre-labour caesarean section (aOR=2.67; 95% CI 1.16-6.14), caesarean section after the onset of labour (aOR=6.91; 95% CI 2.96-16.13) or who had a complication of delivery (aOR=2.10; 95% CI 1.09-4.05) had significantly increased odds of severe sepsis. Of women with severe genital tract sepsis, 23.9% (n=27) developed septic shock. Infection with group A streptococcus (aOR=3.30; 95% CI 1.03-10.53) was the single factor associated with an increased odds of septic shock.

Table 16. Unadjusted and adjusted odds for progression to septic shock, comparing cases of septic shock with cases of severe sepsis without septic shock.

	Septic shock n (%)	Severe sepsis without shock n (%)	P-value	uOR (95% CI)	aOR* 95% CI
	n=71	n=294			
***A priori* sociodemographic and infection factors**					
Age (years)			0·011		
<25	16 (22·5)	101 (34·6)		1	1
25-34	35 (49·3)	151 (51·4)		1·46 (0·77-2·78)	1·25 (0·60-2·58)
≥35	20 (28·2)	42 (14·3)		3·01 (1·42-6·36)	2·24 (0·94-5·30)
Ethnic group			0·608		
White	45 (63·4)	176 (60·1)		1	1
Black and other minority	26 (36·6)	117 (39·9)		0·87 (0·51-1·48)	0·77 (0·42-1·38)
Socio-economic group			0·677		
Employed	12 (16·9)	56 (19·1)		1	1
Unemployed	59 (83·1)	238 (81·0)		1·16 (0·58-2·30)	0·93 (0·51-1·72)
Febrile illness or antibiotics in 2 wks before delivery			0·637		
Yes	43 (60·6)	169 (57·5)		0·88 (0·52-1·49)	0·85 (0·47-1·51)
No	28 (39·4)	125 (42·5)		1	1
Parity			0·002		
0	26 (37·1)	171 (58·2)		1	1
≥1	44 (62·9)	123 (41·8)		2·35 (1·37-4·03)	1·7 (0·94-3·10)
Multiple pregnancy			0·012		
Yes	5 (7·1)	5 (1·7)		4·45 (1·25-15·81)	5·75 (1·54-21·45)
No	65 (92·9)	289 (98·3)		1	1

Table 16. Continued

	Septic shock n (%) n=71	Severe sepsis without shock n (%) n=294	P-value	uOR (95% CI)	aOR 95% CI
Postpartum			0·255		
Yes	62 (87·3)	240 (81·6)		1·55 (0·73-3·31)	1·02 (0·45-2·33)
No	9 (12·7)	54 (18·4)		1	1
Organism*			<0·001		
Escherichia coli	18 (25·4)	59 (20·1)		1	
Group A streptococcus	16 (22·5)	16 (5·4)		3·28 (1·37-7·83)	
Group B streptococcus	4 (5·6)	27 (9·2)		0·49 (0·15-1·57)	
Other streptococcus	2 (2·8)	18 (6·1)		0·36 (0·08-1·72)	
Staphylococcus	6 (8·5)	17 (5·8)		1·16 (0·40-3·37)	
Mixed	1 (1·4)	18 (6·1)		0·18 (0·02-1·46)	
Other	8 (11·3)	17 (5·8)		1·54 (0·57-4·16)	
Unknown	1 (1·4)	5 (1·7)		0·66 (0·07-5·98)	
No laboratory confirmed infection	15 (21·1)	117 (39·8)		0·42 (0·20-0·89)	
Group A streptococcus organism			<0·001		
Yes	16 (22·5)	16 (5·4)		5·05 (2·39-10·71)	4·84 (2·17-10·78)
No	55 (77·5)	278 (94·6)		1	1

* Not included in the adjusted model; only group A streptococcus as a dichotomous variable was included

Table 16. Continued

	Septic shock n (%) n=71	Severe sepsis without shock n (%) n=294	P-value	uOR (95% CI)	aOR 95% CI
Delivery factors (postpartum only)					
Mode of delivery**			<0·001		
Spontaneous vaginal	21 (29·5)	36 (12·3)		5·06 (2·16-11·86)	2·49 (0·81-7·65)
Operative vaginal	8 (11·3)	31 (10·6)		2·43 (0·88-6·76)	2·89 (0·92-9·09)
Pre-labour caesarean	9 (12·7)	58 (19·9)		1·76 (0·66-4·69)	1·12 (0·37-3·42)
Caesarean after labour onset	9 (12·7)	99 (33·9)		1	1
No delivery***	24 (33·8)	68 (23·3)			
Delivery complications			0·123		
Yes	15 (21·1)	88 (29·9)		0·71 (0·36-1·37)	0·67 (0·33-1·39)
No	32 (45·1)	138 (46·9)		1	1
No delivery***	24 (33·8)	68 (23·3)			
Woman readmitted			0·08		
Yes	23 (32·4)	87 (29·6)		1·42 (0·76-2·66)	0·93 (0·33-1·39)
No	24 (33·8)	139 (47·3)		1	1
No delivery***	24 (33·8)	68 (23·3)			

** Before adjustment for group A streptococcus: Spontaneous vaginal aOR=3·85 (1·35-10·96); Operative vaginal aOR=3·12 (1·03-9·57)

***Antepartum cases and 1st/2nd trimester loss not included in the model assessing delivery factors

5.4 Discussion

5.4.1 Summary

This was the first national population-based study of severe maternal sepsis morbidity in the UK. For each maternal death from sepsis, approximately 50 women have life-threatening morbidity from sepsis and onset of severe sepsis from SIRS occurs very rapidly. Genital tract and urinary tract infections are the predominant sources of infection; all modes of operative delivery carry significant risks for severe sepsis; risk factors are significantly cumulative; whilst the largest proportion of cases of severe sepsis is caused by *E.coli*, outcomes are significantly worse for women with group A streptococcal infection; and women with group A streptococcal infection progressed more rapidly to severe sepsis than women with other organisms.

5.4.2 Strengths and limitations

Strengths of this study include (1) the robust design and system of data collection, (2) participation of 100% of all UK maternity units, and (3) the rigorous case definition based on clinical criteria. As this study represented all maternity units in the UK, many limitations and biases concerning regional differences and sample size were minimised. Hospital-based studies and even regional studies, such as that conducted in Aberdeen (Chapter 4) or the previous Waterstone et al study (Waterstone et al., 2001), are particularly prone to this because of population characteristics. In this study however, 100% participation from all maternity units in the UK reduced the risk of a selection bias.

A limitation of this study was the proportion of women with a clinical diagnosis of sepsis, but no identified organism. This is, however, to be expected and is a relative limitation given that there is currently no other UK study which has elucidated the distribution of causative organisms for severe maternal sepsis, and a large proportion of patients in the general population who are diagnosed with severe sepsis and septic shock have no causative organism identified (Kinasewitz et al., 2004; Astiz & Rackow, 1998). In this study there was also a potential for a case ascertainment bias (a form of selection bias); it is possible that a number of antepartum women with non-obstetric sepsis and postpartum women who were discharged after delivery and later developed severe postpartum (puerperal) sepsis, however were not readmitted to the maternity unit, were treated in another hospital unit such as intensive care and therefore were not captured by UKOSS. Lastly, data on medical co-morbidities such as asthma was collected using a general question, "did the woman have any other medical problems," and also included self-report. This may limit the accuracy of the medical co-morbidity data and hence findings should be interpreted with caution.

5.4.3 Comparison of methods and findings to other studies

5.4.3.1 Methods

The methods used by Waterstone and colleagues were discussed in detail in Chapter 4, and will therefore not be discussed here. Another study that is also comparable to the present one was carried out in the Netherlands by Kramer and colleagues (Kramer et al., 2009). The study used morbidity data from the National study of Ethnic determinants of Maternal Morbidity in the Netherlands (LEMMoN) study from 2004-2006. Results of the full morbidity study were published separately (Zwart et al., 2008). Similar to the

present study, the LEMMoN study also utilised data from all 98 maternity units in The Netherlands. However, as with the full LEMMoN study, Kramer and colleagues were not able to explore possible risk factors in an adjusted analysis because the comparison data were aggregated national reference data. Thus the authors were not able to make any comment on the role of confounding. For example, maternal age ≥35 years was reported as a possible risk factor, however maternal age is likely to be confounded by caesarean section as indicated by the significant Cochran-Mantel-Haenszel test in this study. Multiple pregnancy, also identified by Kramer and colleagues as a possible risk factor, may also be prone to confounding; in the present study multiple pregnancy was significantly associated with severe sepsis in unadjusted analyses, however the association disappeared after adjusting for age and mode of delivery.

Another important finding from the Kramer et al study was the rapidity with which severe sepsis occurs in the maternal population; 39% of women with obstetric sepsis in The Netherlands had less than 24 hours between the first symptom of sepsis and severe sepsis. Whilst the authors highlight the important role of group A *streptococcus* (38% (N=14) of women who were cultured had the organism), the time course of sepsis for women with this organism was not reported. Building on the methods used by Kramer and colleagues, risk factors for severe sepsis in adjusted analyses and the time course sepsis caused by group A *streptococcus* were explored in the present study. This included analyses on time course and mode of delivery in women with group A streptococcal infection, in an effort to elucidate possible aetiologies of infection with this organism and subsequent maternal outcomes.

5.4.3.2 Findings

The incidence rate and risk factors identified concur with previous studies of severe maternal sepsis (Cantwell et al., 2011; Acosta et al., 2013; Waterstone et al., 2001; Acosta et al., 2012; Kramer et al., 2009) and the results are likely to be generalisable to other high resource setting such as the US and The Netherlands, which have experienced similar increases in severe maternal morbidity and mortality from sepsis (Schutte et al., 2010; Acosta et al., 2013). Waterstone and colleagues (Waterstone et al., 2001) reported an incidence of 4.0 (95% CI 2.0-6.0) per 10,000 maternities in southwest England during the period from 1997 to 1998. The incidence of 4.7 (95% CI 4.2-5.2) per 10,000 maternities identified in this study, although not a statistically significant increase, represents a 15% increase, which corresponds to the increase in maternal deaths from sepsis in the UK over this period (0.85 to 1.13 per 100,000 maternities (Cantwell et al., 2011)). An incidence of 4.7 (95% CI 4.2-5.2) is also within the range of other population-based studies of severe maternal sepsis, most recently 2.1 (95% CI 1.7-2.6) per 10,000 in The Netherlands (Kramer et al., 2009), 2.1 (95% CI 2.0-5.0) per 10,000 in Scotland (Chapter 4) (Acosta et al., 2012), and 4.9 per 10,000 live birth maternities in California (Acosta et al., 2013).

Black or other minority ethnic status as a risk factor for severe sepsis is consistent with other morbidity studies (Bryant et al., 2010). Other well established risk factors for sepsis supported by the study findings were primiparity, multiple pregnancy, and caesarean section (Maharaj, 2007). Black or minority ethnic status, primiparity and caesarean section are all common in the UK, and must not be forgotten in the context of sepsis in light of the finding that the odds of severe sepsis increases with the increasing number of risk factors by up to nearly eight-fold in the presence of four or more.

Obesity was not identified as a risk factor in this study, however this may be the result of improved obstetric care for women with a high BMI since the Aberdeen study period.

5.4.4 Rapid progression of sepsis

As sepsis progresses along a spectrum of severity, the occurrence of life-threatening sepsis represents the severest end short of a maternal death, and therefore only the 'tip of the iceberg' of serious maternal morbidity. Failure to recognise the severity of an infection is a ubiquitous factor in the progression to severe sepsis (Cantwell et al., 2011; Sriskandan, 2011; Appelboam et al., 2010). Intensivists have the most training in sepsis management, however initial presentation is often to general practitioners or to accident and emergency staff with less awareness of the signs and symptoms of sepsis, or of the rapidity with which it may progress to severe sepsis in the obstetric population (Senior, 2012). For most women with severe sepsis in this study there was less than 24 hours between the first sign of SIRS and the diagnosis of severe sepsis, and for most women with a group A streptococcal infection there was less than 9 hours between the first sign of SIRS and severe sepsis with half having less than 2 hours between the first signs and diagnosis. In addition, 42% of women with severe sepsis had a febrile illness or were taking antibiotics prior to presentation, which suggests that at least a proportion were not adequately diagnosed, treated or followed up.

5.4.5 Modes of operative delivery

A challenge in all previous studies of maternal sepsis has been to assess the temporality of mode of delivery in relation to infection and sepsis. The present study shows that

after controlling for illness before delivery, as well as clinical risk factors such as premature rupture of membranes, all modes of operative delivery (operative vaginal, pre-labour caesarean and caesarean after the onset of labour) were independent risk factors for severe sepsis. Corresponding with the findings from the Aberdeen study, 5% of controls still did not receive antibiotics despite a recent move to offering antibiotics to all women undergoing a caesarean section since 2004 under the UK National Institute for Health and Clinical Excellence (NICE) guidelines (National Institute for Clinical Health Excellence, 2011). In addition, although maternity units are now giving antibiotics prior to elective caesarean sections with ample time for administration, prophylactic antibiotics in emergency caesarean situations must be prioritised. For women who have emergency caesarean sections, antibiotics could be given at the time of decision to perform a caesarean section to maximize their preventive efficacy. The risk associated with operative vaginal delivery confirms findings from a previous study, (Acosta et al., 2012) and implies that there may be a need to test the efficacy of prophylactic antibiotics at operative vaginal delivery in a randomised control trial, as well as the need for stringent attention to infection control measures for these deliveries.

5.4.6 Causative organisms

Although severe sepsis as a result of *E.coli* and following caesarean delivery are more common, women delivering vaginally are at heightened risk of group A streptococcal infection, and those that are infected with group A *streptococcus* are at significantly increased risk of progression to septic shock compared with being infected with another organism. These results are consistent with the recent trend in maternal sepsis deaths in the UK; 50% of direct genital-tract sepsis deaths in the most recent Confidential Enquiry into Maternal Deaths (2006-2008) were caused by group A streptococcus

(Cantwell et al., 2011). Correspondingly, 50% of proven group A streptococcal infections in the study population led to septic shock with very rapid progression from the first sign of SIRS. This has a direct implication for decisions about the availability of rapid antigen diagnostic tests for group A *streptococcus* in obstetrics.

Whilst culture remains the gold standard for confirmation of group A *streptococcus*, it takes one to two days to obtain results, which is significantly longer than the time course from the first signs of SIRS to septic shock for most women. In the absence of rapid diagnostics, a positive culture for group A *streptococcus* should be reported urgently by telephone as soon as it is discovered in the laboratory, and prior to this a clinical suspicion of group A *streptococcus* should be regarded as a red flag for urgent action and very close monitoring. In addition, training about group A streptococcal infection and the Surviving Sepsis Campaign (SSC) intervention bundles should be routinely included in all obstetric emergency training courses; currently, the 'resuscitation bundle' and 'management bundle' are recommended for obstetric patients in the UK (Royal College of Obstetricians and Gynaecologists, 2011).

5.5 Conclusion

This study was designed to answer for the first time in the UK, the questions: how many women are affected by severe maternal sepsis, what are the main causative organisms, what are the main sources of infection, and what are the risk factors for severe sepsis and poor outcomes such as septic shock on a national level. This study also emphasises that both primary and secondary care practitioners should remain aware that pregnant or recently pregnant women with suspected infection need closer attention than women

who are not pregnant. Antibiotic prescription does not necessarily prevent progression to severe sepsis, and women should be followed up to ensure recovery. The rapid progression to severe sepsis highlights the importance of administration of high dose intravenous antibiotics within one hour of admission to hospital. Signs of severe sepsis, particularly with confirmed or suspected group A streptococcal infection, should be regarded as an obstetric emergency and should be routinely included in obstetric emergency training courses. This study also emphasises the importance of on-going initiatives to reduce caesarean delivery rates. In addition, consideration could be given to a change of timing of prophylactic antibiotics to administration at time of decision for emergency caesarean section, and vigilant infection control at vaginal delivery should be maintained, with a potential role for prophylactic antibiotics at operative vaginal delivery. Future research should assess the efficacy of rapid antigen diagnostic tests for group A streptococcus in obstetrics.

A key question that remained after this study was whether or not a bias was present caused by identification of cases through maternity units. One way to address this question was to conduct a national level cohort study of critical care admissions for severe maternal sepsis, and compare the results with this study.

Chapter 6

Severe Maternal Sepsis within the First 24 Hours of Critical Care Admission in the UK: A National Cohort Study

6.1 Background

The last chapter presented the incidence, described the causative organisms and sources of infection, and identified risk factors for severe maternal sepsis in the UK on a national level. The study, however, had the potential for a case ascertainment bias with regards to women who may have been discharged from maternity units before developing postpartum sepsis and readmitted to another service without having come to the attention of the UKOSS reporter. So an important question stemming from that study was if the results would differ from a national cohort study of all maternal sepsis admissions to critical care in the UK. The assumption for this comparison was that any woman with severe life-threatening postpartum sepsis would almost certainly be treated in a critical care setting. Of the UKOSS cases, 78.4% (N=286) were admitted to either level 2 or 3 (high-dependency or critical care) units, with 31.2% (N=114) of cases admitted to level 3 critical care.

In addition, as discussed in Chapter 2 there have been seven population-based studies of severe obstetric sepsis morbidity in high-resource countries. Each used a different strategy to identify cases of severe 'near-miss' sepsis. The Waterstone et al (Waterstone et al., 2001) study from the UK was limited to one geographic region, as was the study in Aberdeen (Acosta et al., 2012) (Chapter 4). Due to these issues, a second study was needed to assess the UKOSS study findings, as well as the extent of organ dysfunction or septic shock, which may not have been diagnosed amongst a proportion of UKOSS cases at the time of their initial reporting.

6.1.1 Study objectives

The objectives of this study were to describe the characteristics of pregnant or postpartum women who had severe sepsis within the first 24 hours following critical care admission in the UK, and to evaluate the risk factors for both severe sepsis morbidity and mortality on a national population level. A secondary objective was to compare the results of this study to those of the UKOSS study in order to assess the case ascertainment through the UKOSS mechanism, as well as to assess the replication of findings in order to draw possible inferences on causality.

6.2 Methods

6.2.1 Data sources

6.2.1.1 Primary data

This study was conducted using data about women admitted to critical care units from the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme (CMP) database. The CMP is the national clinical audit for adult critical care units (including intensive care and combined intensive care and high-dependency units) in England, Wales and Northern Ireland, and is coordinated by ICNARC. The CMP database contains pooled case-mix data, collected during the first 24 hours following admission to a critical care unit, and outcome data on consecutive admissions to units participating in the CMP (McLennan et al., 2011; Harrison et al., 2004). The CMP database has been independently assessed to be of high quality (Harrison et al., 2007). Data validation procedures and variable definitions have been described in previous studies (Office for National Statistics, 2012; Harrison et al., 2004; Harrison et al., 2006).

Index of multiple deprivation (IMD) in the CPM database was calculated according to IMD 2010 (England) (Harrison et al., 2004; McLennan et al., 2011) and WIMD 2008 (Wales). Data on IMD were not available for Northern Ireland. Women were assigned to a quintile of the relevant IMD based on their postcode at the time of admission to the critical care unit (1=least deprived and 5=most deprived). Ethnicity was recorded according to current UK Census ethnicity codes, and then regrouped to white/ non-white for this analysis. Gestation of a current pregnancy was either recorded directly or calculated as 274 days plus the difference between the date of admission to the critical care unit and the expected date of delivery of the current pregnancy. Gestation of a recent pregnancy was recorded directly from delivery or pregnancy end-date information. All data used in this study were validated and from units that had been reporting to the CMP for at least six months.

6.2.1.2 National comparison data

Routinely available national statistics and hospital episode statistics data were used for comparison with CMP data in this study. Data on maternal age, Index of Multiple Deprivation (IMD), multiple births and stillbirths were obtained from the Office for National Statistics for England and Wales (Harrison et al., 2004; Office for National Statistics, 2012; Harrison et al., 2006), and the Northern Ireland Statistics and Research Agency (Northern Ireland Statistics and Research Agency, 2012a). Data on ethnic group were obtained from the Office for National Statistics for England and Wales and extrapolated for Northern Ireland based on the reported ethnic population distribution in the region (Northern Ireland Statistics and Research Agency, 2012b; Central Statistics Office, 2012). Data on mode of delivery were obtained from Hospital Episode Statistics (Hospital Episode Statistics, 2012), StatWales (StatsWales, 2012) and extrapolated for

Northern Ireland based on published rates of mode of delivery in the region (Black, 2011; Secondary Care Directorate, 2012).

6.2.1.3 Data not included

Scottish critical care units do not participate in the CMP and therefore data from Scotland are not included in the study. Scotland accounts for approximately 6% of all UK maternal critical care admissions, 2% of maternal sepsis critical care admissions (Scotland, 2010) and 7.3% of all maternities (Information Services Division, 2012).

6.2.2 Study design

This was a cohort study of all pregnant and postpartum women who were reported in the CMP from 2008 to 2010, and who were either admitted with or developed severe sepsis within the first 24 hours of admission.

6.2.3 Definitions

6.2.3.1 Case definition

Pregnant women were still pregnant on admission to critical care. Postpartum women were defined as having been pregnant within 42 days of admission to the critical care unit regardless of how the pregnancy ended (live birth, stillbirth, miscarriage or termination). Severe sepsis was defined according to a modified version of the PROWESS clinical trial definition (Table 17) (Padkin et al., 2003). Septic shock was defined as severe sepsis with cardiovascular organ system dysfunction (Parker et al., 1984). Readmissions of women to critical care during the same hospital stay were excluded.

Table 17. Severe Sepsis Case Definition*.

Criteria for SIRS, infection, and organ dysfunction used in the CMP database analysis. Severe sepsis was considered to be present if all three components (a-c) were present in the first 24 hours following critical care admission.

a) SIRS - three or more of the following to be present within the first 24 hours following admission to the critical care unit:	
Temperature	Central temperature > 38.0°C or < 36.0°C. If only non-central temperature available, 0.5°C added to measured value. Hypothermia must be confirmed by a central temperature.
Cardiovascular	Heart rate >90 beats min^{-1}, or heart block or myxedema recorded as primary or secondary reason for admission.
Respiratory	Respiratory rate >20 breaths min^{-1} or $PaCO_2$ <32 mm Hg in a non-ventilated admission or mechanical ventilation in the first 24h in an admission not previously receiving home ventilation.
White blood count	>12,000 mm^{-3} or <4,000 mm^{-3}.
b) Diagnosis of Infection - Diagnosis of infection as primary or secondary reason for critical care admission	
c) Organ dysfunction - one or more of the following to be present during the first 24 hours following admission to the critical care unit:	
Cardiovascular	SBP <90 mm Hg or MAP <70 mm Hg.
Respiratory	PaO_2/FiO_2 ratio <250 mm Hg. If the lung is the sole organ meeting an organ dysfunction criterion and primary/secondary reason for critical care admission indicated lung infection, PaO_2/FiO_2 must be <200 mm Hg.
Renal	Average hourly urine output for first 24h <0.5 ml kg-1 h-1 (assumed body weight = 70kg) without requirement for chronic dialysis.
Metabolic	Base deficit (calculated from arterial blood gas and haemoglobin) <5.0 mmol l-1.
Haematological	Platelet count <80,000 mm^{-3}.

* Based on the modified version of the PROWESS clinical trial definition (Padkin et al., 2003).

6.2.3.2 Definition of maternal sepsis mortality

Mortality was estimated using death at ultimate discharge from the acute hospital, irrespective of direct or indirect causes. This differs from the UK Confidential Enquiry into Maternal Deaths (2006-2008) methodology, which used the definition of 'genital-tract sepsis' encompassing causes directly related to pregnancy. In this study, deaths from 'all-cause maternal sepsis' including both direct and indirect causes of sepsis such as respiratory infection were included. Respiratory infection in particular has been traditionally regarded as an illness coincidental to pregnancy and therefore an indirect cause of maternal sepsis morbidity and mortality. However, since severe sepsis/ septic shock is an end-stage condition for which resuscitation and immediate management is not dependent on source of infection (direct or indirect causes), it was considered clinically and epidemiologically relevant to evaluate the total burden of severe maternal sepsis morbidity as well as mortality.

6.2.4 Sample size

The sample size of this study was determined by the rate of critical care unit reporting coverage during the study period. In 2008, 2009 and 2010, coverage of the database was 65.0%, 75.2% and 80.2% of critical care units in England, Wales and Northern Ireland reported to the CMP, respectively, with a total of 198 critical care units contributing data at some stage during this time.

6.2.5 Statistical analyses

6.2.5.1 Incidence rates

The total number of maternal critical care admissions with severe sepsis was estimated based on the number of severe maternal sepsis admissions observed in the CMP

database each year, the CMP reporting coverage rate for each year, and the total number of adult general critical care units in England, Wales and Northern Ireland. The absolute risk or incidence of morbidity and mortality were calculated by dividing extrapolated numbers (to allow for incomplete coverage) by the total number of maternities obtained from Office for National Statistics for England and Wales (Office for National Statistics, 2012) and Northern Ireland Statistics and Research Agency (Northern Ireland Statistics and Research Agency, 2012a).

6.2.5.2 Univariable analyses

Frequencies of demographic, clinical and delivery characteristics were tabulated for all cases. Continuous data are summarised as mean and standard deviation (SD) when normally distributed, and as median and inter-quartile range (IQR) for skewed data; categorical data are presented as frequency and percentage. Rates were compared with nationally available data where possible. Using all maternities in England, Wales and Northern Ireland as the comparison group, the relative risk (RR) with 95% confidence interval (CI) for maternal critical care admission with severe sepsis was calculated for each variable. Adjusted analysis of risk factors for severe maternal sepsis morbidity was not possible since only aggregated national data were available.

Characteristics of cohort survivors were compared to non-survivors in a univariable logistic regression model. Odds ratios (OR) with 95% CIs were estimated. The reference group for each categorical variable was determined by ease of interpretation or by the largest group.

6.2.5.3 Multivariable logistic regression

For the maternal mortality analysis, variables were modelled using unconditional multivariable logistic regression based on previous literature, factors found to be significant in univariable analysis and plausible confounders. Since the sample size of women who died was (fortunately) very small (N=29), a parsimonious approach was used in order to avoid over adjustment using the backward stepwise approach as discussed in detail in Chapter 4. Specific organ system dysfunctions were included in the model, however, the number of organ system dysfunctions and acute severity of illness scores (APACHE II Score(Knaus et al., 1985) and ICNARC Physiology Score (Harrison et al., 2007)) were excluded since these were derived from the same physiology data and thus inclusion would have lead to substantial over adjustment.

Multivariable regression results were adjusted for calendar time and all other factors in the model. In addition, a possible hospital clustering effect was controlled for by using robust standard errors. Continuous variables were tested for departure from linearity by adding a first-order fractional polynomial to the multivariable model with subsequent likelihood ratio testing. There was no evidence of departure from linearity for age, therefore it was treated as a continuous linear term in the analysis, but presented as a categorical variable in the results table for ease of interpretation. For BMI there was evidence of a non-linear relationship and there was a large amount of missing data; it was subsequently treated as a categorical variable in the regression model.

6.2.5.4 Missing data

Missing data for BMI (N=312; 48.3%) were dealt with by creating a variable for 'unknown BMI'. The distribution of all demographic and clinical factors were compared

between ‘unknown BMI’ and ‘known BMI’ using χ^2 tests and multivariable logistic regression to ascertain whether there was an over-representation of particular characteristics amongst either group. There were no significant differences in survival or the distribution of characteristics between groups, indicating a high probability that these data were missing at random and there was minimal systematic reporting bias. Additionally, the ‘unknown BMI’ variable was retained in all regression models so that these observations would not be dropped. After accounting for missing BMI data, complete case analyses were used, as levels of missing data were very low for all other variables. Results are reported as unadjusted and adjusted ORs with 95% CIs.

6.2.5.5 Post model checking procedures

Plausible interactions between variables were tested in the final model using likelihood ratio tests with a significance level of $P<0.01$. Interactions were tested between the following variables: age and organ system dysfunction; BMI and organ system dysfunction; ethnic group and low socioeconomic status. Goodness-of-fit was also assessed for the final model using the Hosmer-Lemeshow's goodness-of-fit test with a significance level of $P<0.05$. No interactions were detected in the final model and the Hosmer-Lemeshow test had a P-value of >0.05 indicating a good fit.

6.2.6 Statistical power

For the multivariable logistic regression analysis comparing survivors with non-survivors, and assuming a prevalence of exposure of at least 15% amongst survivors, the model had 80% power at $P<0.05$ (two-sided) to detect a statistically significant OR of 3.5 or greater.

6.2.7 Sensitivity Analysis

A sensitivity analysis was performed using the obstetric specific SIRS criteria defined by Waterstone and colleagues (Waterstone et al., 2001): elevated heart rate defined as >100 beats per minute (compared to >90) and an elevated white blood cell count defined as >17,000 cells per microliter (compared to >12,000). This was done in order to assess whether the more rigorous criteria used in the UKOSS analysis were significantly associated with greater severity of sepsis or a different pattern of maternal characteristics. As discussed in Chapter 2, with the increased incidence of maternal sepsis, confusion has arisen over the use of the non-obstetric definition for SIRS in pregnant and peripartum women, since it is accepted that the clinical signs and symptoms of SIRS can be physiologically normal in this population. Differences in the distribution of case characteristics and sources of infection were assessed using χ^2 tests with a significance level of $P<0.05$.

6.2.8 Assessment of UKOSS study case ascertainment

This study was used to assess the level of case ascertainment in the UKOSS study (discussed in the previous chapter), by comparing the 2010 incidence rates and distribution of infection sources of women admitted to critical care using obstetric SIRS criteria in this study with the rate of critical care admission in the UKOSS study.

6.2.9 Statistical software

Stata statistical software 11 (StataCorp, College Station, TX) was used for all analyses.

6.2.10 Data management

Data were received as an anonymised Stata file. The CMP has a query system in place to detect internal inconsistencies, however the data were also checked by the author (CA) for any inconsistencies and for missing data through tabulation of the variables.

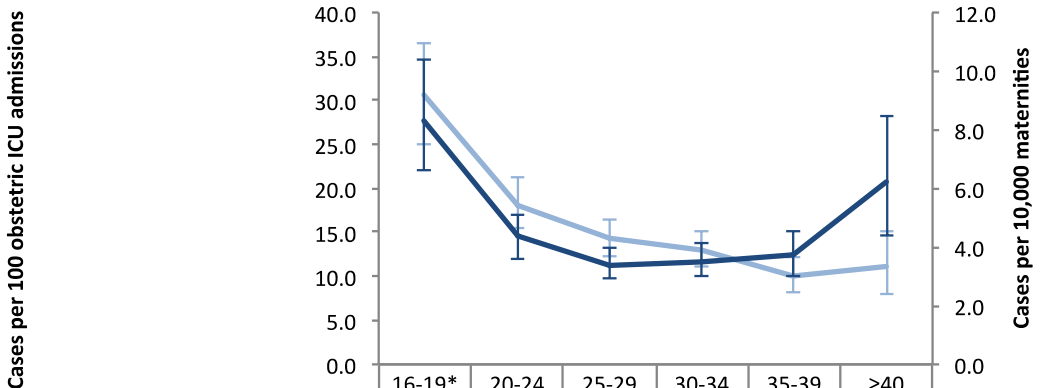
6.2.11 Research ethics

Support for the collection and use of patient-identifiable data without consent by ICNARC was obtained under Section 251 of the NHS Act 2006 (approval number PIAG 2–10(f)/2005). Research ethics committee approval for use of anonymised data was not required. Approval of the research protocol was obtained from ICNARC prior to data extraction. The protocol for the study can be found in Appendix 7.

6.3 Results

6.3.1 Incidence rates

In the CMP database between 2008 and 2010, there were 646 pregnant or postpartum women who met the case definition for severe sepsis, which represented 14.4% (one in seven) of maternal critical care unit admissions; 10.6% (N=474) had septic shock (one in nine). Taking into account the incomplete participation in the ICNARC CMP it was estimated that 873 women in England, Wales and Northern Ireland had severe sepsis requiring critical care over the three-year period, and 642 were estimated to have had septic shock. The estimate of absolute risk of maternal critical care admission with severe sepsis based on extrapolated figures was 4.1 (95% CI 2.9-5.6) per 10,000 maternities. The remainder of the analyses in this study, however, are based on ICNARC data and not extrapolated figures except where specified. Sepsis admission rates were the highest amongst women aged 16 to 19 years (Figure 16). One in three pregnant or postpartum women in this age category admitted to critical care had severe sepsis.



	16-19*	20-24	25-29	30-34	35-39	≥40
Proportion of severe sepsis among maternal critical care admissions	30.6	18.2	14.4	12.9	10.0	11.2
Rate of severe sepsis per 10,000 maternities	8.3	4.3	3.4	3.5	3.7	6.2

*** Five-year age bands**

Figure 16. Rate of severe sepsis amongst maternal critical care admissions and maternities by five-year age bands from 2008-2010.

6.3.2 Characteristics of pregnant and postpartum cases

Characteristics of the cohort are listed in Tables 18-19. National statistics are only listed where data were available. Women had a significantly increased risk of admission to critical care with severe sepsis if they were aged <20 years or ≥40 years compared to women aged 25-29 years. Increased risk of severe sepsis was also significantly and progressively associated with increasing deprivation (Figure 17). Of women who delivered by caesarean section (N=242), 33.1% (N=80) were admitted directly from theatre for an emergency indication; 1.7% (N=4) were admitted after elective surgery. The relative risk of admission to critical care units with severe sepsis for women who had a caesarean section compared with a vaginal delivery was 6.2 (95% CI 4.9-7.8); it was not possible to discern from the data, however, whether this was a cause or a response to antenatal sepsis. Compared to all maternities in this period, women with severe sepsis were significantly more likely to have had a stillbirth. There was also a higher frequency of multiple gestation births amongst women with severe sepsis compared to all other maternities; the majority of these births were by caesarean section (67.9% N=19). Being from a Black or other minority ethnic group was not a risk factor for admission to critical care with severe sepsis.

Table 18. Characteristics and relative risks of severe sepsis amongst pregnant and postpartum women admitted to critical care units compared with all maternities in England, Wales and Northern Ireland from 2008-2010.

	Critical care admissions with sepsis (*n*=**646**)	**All maternities** (*n*=**2186818**)	**RR (95% CI)**
Postpartum women	413 (63.9)	N/A	
Maternal age years (mean; SD)	28.3 (6.9)	29.0 (--)*	
<20	80 (12.4)	129167 (5.9)	2.5 (1.9-3.3)
20-24	133 (20.6)	419944 (19.2)	1.3 (1.0-1.6)
25-29	148 (23.0)	602716 (27.6)	1
30-34	153 (23.7)	600694 (27.5)	1.0 (0.8-1.3)
35-39	95 (14.7)	352364 (16.1)	1.1 (0.9-1.4)
≥40	36 (5.6)	81933 (3.7)	1.8 (1.2-2.6)
Black and other minority ethnic groups	154 (23.8)	609250 (27.9)	0.9 (0.8-1.0)
Index of multiple deprivation (quintiles)**	623 (96.4)	2137412 (97.7)	
1 (least deprived)***	63 (10.1)	589784 (27.6)	1
2	75 (12.0)	475573 (22.2)	1.5 (1.1-2.1)
3	109 (17.5)	395137 (18.5)	2.6 (1.9-3.5)
4	148 (23.8)	346002 (16.2)	4.0 (3.0-5.4)
5 (most deprived)	228 (36.6)	330916 (15.5)	6.5 (4.9-8.5)
BMI (Median; IQR) (missing=312)	26 (22-30)	N/A	
History of immunosupression	15 (2.3)	N/A	
Weeks gestation		N/A	
Antenatal diagnosis (Median; IQR)	26 (20-31)		
Postnatal diagnosis (Median; IQR)	38 (31-41)		

N/A=data not available

* SD could not be calculated with aggregate data

** Figures (including denominators) are for England and Wales only

*** Denominators are total data available for IMD

Continuous data are summarised as mean and standard deviation (SD) when normally distributed, and as median and inter-quartile range (IQR) for skewed data; categorical data are presented as frequency and percentage.

Table 19. Characteristics and relative risks of severe sepsis amongst postpartum women only compared with all maternities, admitted to critical care units in England, Wales and Northern Ireland from 2008-2010.

	Critical care admissions with sepsis (*n*=**413**)	**All maternities** (*n*=**2186818**)	**RR (95% CI)**
Parity*		N/A	
0	193 (48.4)		
1	96 (24.1)		
≥2	110 (27.6)		
Assisted conception*	24 (8.1)	N/A	
Mode of delivery**			
Spontaneous vaginal	98 (25.9)	1334242 (61.0)	1
Assisted vaginal	28 (7.4)	273340 (12.5)	1.4 (0.9-2.1)
Caesarean section	242 (64.0)	535999 (24.5)	6.2 (4.9-7.8)
Unknown	10 (2.7)		
All multiple births***	28 (7.6)	34663 (1.6)	4.4 (3.1-6.3)
Pregnancy Outcomes			
Live births	321 (77.7)	N/A	
Stillbirths	47 (11.4)	11697 (0.5)	21.3 (16.3-27.9)
1st/2nd trimester loss	25 (6.1)	N/A	
Ectopic pregnancy	10 (2.4)	N/A	
Other******	2 (0.5)	N/A	
Unknown	10 (2.4)	N/A	
Hysterectomy*	20 (5.4)	N/A	
Days since delivery (Median; IQR)	3 (0-8)	N/A	

N/A=data not available

* Individuals with complete data

** National rates are total deliveries

*** Live births and stillbirths

**** Two women each had one live birth and one stillbirth from the most recent pregnancy

Skewed data are summarised as median and inter-quartile range (IQR); categorical data are presented as frequency and percentage.

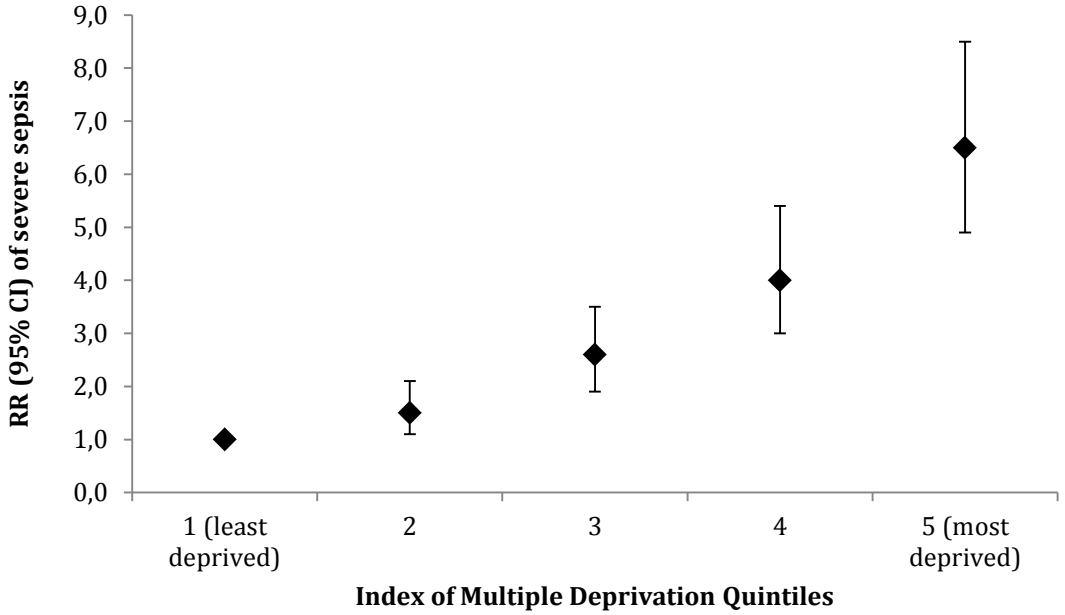


Figure 17. Relative risk of severe sepsis by deprivation quintiles (Reference group = 1st IMD quintile).

6.3.2.1 Caesarean section and deprivation

In assessing whether the rate of caesarean section may have contributed to the social gradient associated with the risk of severe sepsis (since there was significant association between the proportion of deliveries by caesarean section and deprivation within the cohort), it was found that compared to affluent women (IMD quintiles 1-2), deprived women (IMD quintiles 4-5) had a 1.9 (95% CI 1.2-3.1) times higher odds of caesarean section, although it is difficult to know what this means since it was not known whether caesarean section was a cause or an outcome of severe sepsis; of all women in the cohort who had a caesarean section, 64.3% (N=151) were deprived compared to 19.2% (N=45) who were affluent. Results of exploratory stratification of deprivation level and mode of delivery by other factors are shown in Table 20. There was a significantly greater proportion of black or other ethnic minority women were from a deprived area

(IMD quintile 4-5) (P<0.001). There was also a significantly greater proportion of women from deprived areas who had a caesarean section compared to a vaginal delivery (P=0.01) and a significantly greater proportion of primiparous women who had a caesarean section compared to a vaginal delivery (P<0.001).

Table 20. Exploratory stratification of deprivation status and mode of delivery by other factors.

	High deprivation* (N=376)	Low deprivation* (N=138)	P-value**	Caesarean section*** (N=242)	Vaginal delivery*** (N=98)	P-value**
Age <20	48 (12.8)	11 (8.0)	0.1	23 (9.5)	11 (11.2)	0.6
Age ≥40	24 (6.4)	9 (6.5)	1.0	17 (7.0)	5 (5.1)	0.5
High deprivation*	--	--	--	151 (62.4)	46 (46.9)	0.01
Black or other minority ethnic group	98 (27.2)	17 (12.7)	<0.01	52 (22.1)	25 (26.9)	0.4
BMI≥30	49 (13.0)	20 (14.5)	0.7	35 (14.5)	10 (10.2)	0.3
Primiparous***	102 (45.1)	45 (49.5)	0.5	129 (54.2)	33 (34.0)	<0.01

* High deprivation=IMD Quintile 4-5; Low deprivation=IMD Quintile 1-2
** Comparisons were made using $\chi 2$ tests with a significance level of P<0.05
*** Postpartum women only

6.3.3 Source of infection and illness severity

The source of infection could be identified from the primary reason for admission to the critical care unit for 598 women (92.6%). Frequencies of the reported source of infection and severity of illness amongst women admitted with severe sepsis are shown Table 21. The most common source of infection was pneumonia/ respiratory infection (n=257; 39.8%) (Figures 18-19). Of these, 27 were identified as laboratory confirmed cases of AH1N1 influenza; 2009 and 2010 were AH1N1 influenza pandemic years. There was no significant difference in severity of illness (APACHE II score) between sources of infection, however women with pneumonia or respiratory infection had a significantly longer critical care unit length of stay compared with other causes (median length of stay 4 days IQR 2-9 days compared with median length of stay 2 days IQR 1-5 days, respectively; $P<0.001$). There was a significantly different distribution of sources of infection between pregnant and postpartum women ($P<0.001$) (Figure 19). A significantly greater proportion of pregnant women had pneumonia ($P<0.001$), urinary tract infection/pyelonephritis ($P<0.001$), or appendicitis ($P=0.04$). In contrast, a significantly greater proportion of postpartum women had a genital tract infection ($P<0.001$), an infection arising from surgical trauma ($P=0.02$), or septicaemia ($P<0.05$).

Table 21. Source of infection and illness severity amongst pregnant and postpartum women admitted to critical care units with severe sepsis in England, Wales and Northern Ireland from 2008-2010.

	Pregnant critical care admissions with sepsis (*n*=233)	**Postpartum critical care admissions with sepsis (*n*=413)**	**Total critical care admissions with sepsis (*n*=646)**	**P-value***
Source of infection				<0.001
Pneumonia/ respiratory infection	138 (59.2)	119 (28.8)	257 (39.8)	
Genital tract	9 (3.9)	148 (35.8)	157 (24.3)	
UTI/ Pyelonephritis	42 (18.0)	17 (4.1)	59 (9.1)	
Surgical trauma	3 (1.3)	21 (5.1)	24 (3.7)	
Septicaemia with unknown primary source	3 (1.3)	17 (4.1)	20 (3.1)	
Appendicitis	11 (4.7)	8 (1.9)	19 (3.0)	
Other infection	17 (7.3)	45 (10.9)	62 (9.6)	
Unknown	10 (4.3)	38 (9.2)	48 (7.4)	
Number of organ system dysfunctions				0.008
1	63 (27.2)	159 (38.5)	222 (34.4)	
2	99 (42.7)	135 (32.7)	234 (36.3)	
≥3	70 (30.2)	119 (28.8)	189 (29.3)	

Figures are N (%) unless otherwise stated

* Comparisons made using $\chi 2$ and Wilcoxon rank-sum tests with a significance level of P<0.05

Table 21. Continued.

	Pregnant critical care admissions with sepsis (*n*=**233**)	**Postpartum critical care admissions with sepsis** (*n*=**413**)	**Total critical care admissions with sepsis** (*n*=**646**)	**P-value***
Organ system dysfunctions**				
Cardiovascular	178 (76.7)	297 (71.9)	475 (73.5)	0.16
Respiratory	141 (60.8)	240 (58.1)	381 (59.0)	0.51
Metabolic acidosis	139 (59.9)	206 (49.9)	345 (53.4)	0.014
Renal	13 (5.6)	37 (9.0)	50 (7.7)	0.13
Haematological	8 (3.5)	57 (13.8)	65 (10.1)	<0.001
ICNARC Physiology Score (Median; IQR)	13 (9-18)	14 (10-20)	14 (10-20)	0.005
APACHE II Score (Median; IQR)	13 (10-16)	12 (10-16)	12 (10-16)	0.30
Days in ICU (Median; IQR)	2.8 (1.5-5.1)	2.7 (1.2-6.0)	2.8 (1.3-5.7)	0.37
Deaths	7 (3.1)	22 (5.4)	29 (4.6)	0.18

Figures are N (%) unless otherwise stated

* Comparisons made using $\chi 2$ and Wilcoxon rank-sum tests with a significance level of $P<0.05$

** Organ system dysfunctions are not mutually exclusive

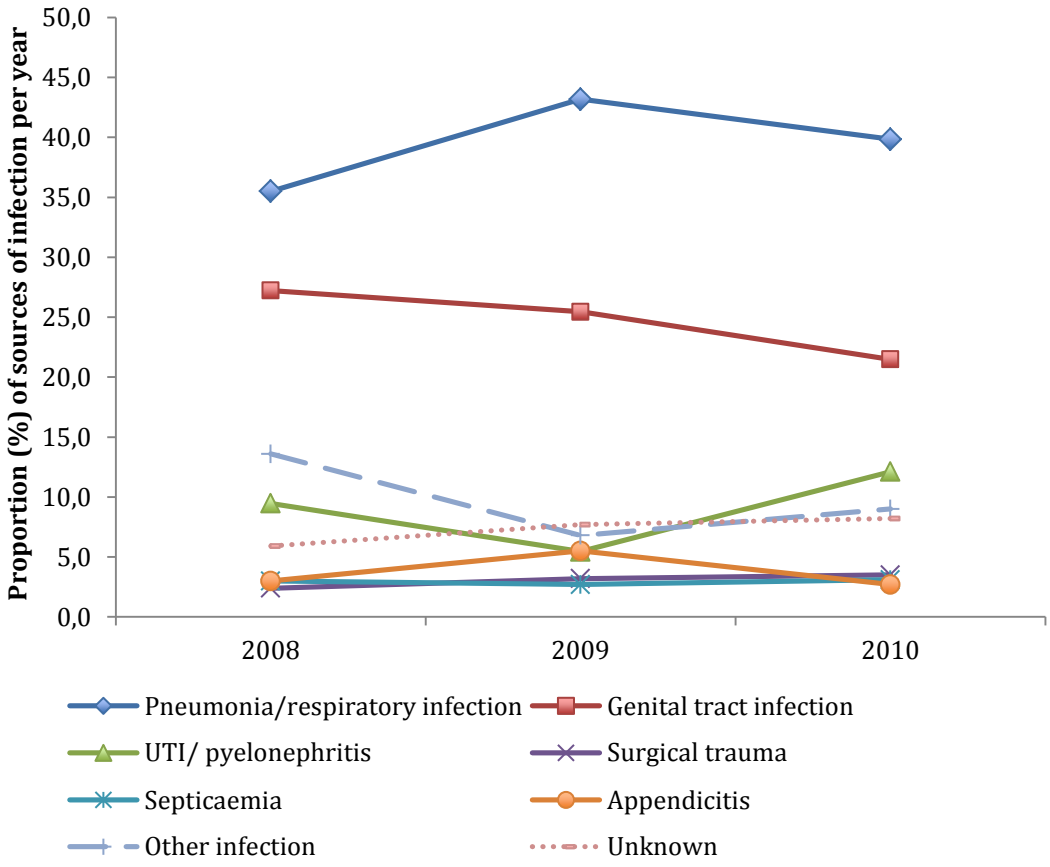


Figure 18. Proportion of sources of infection by year.

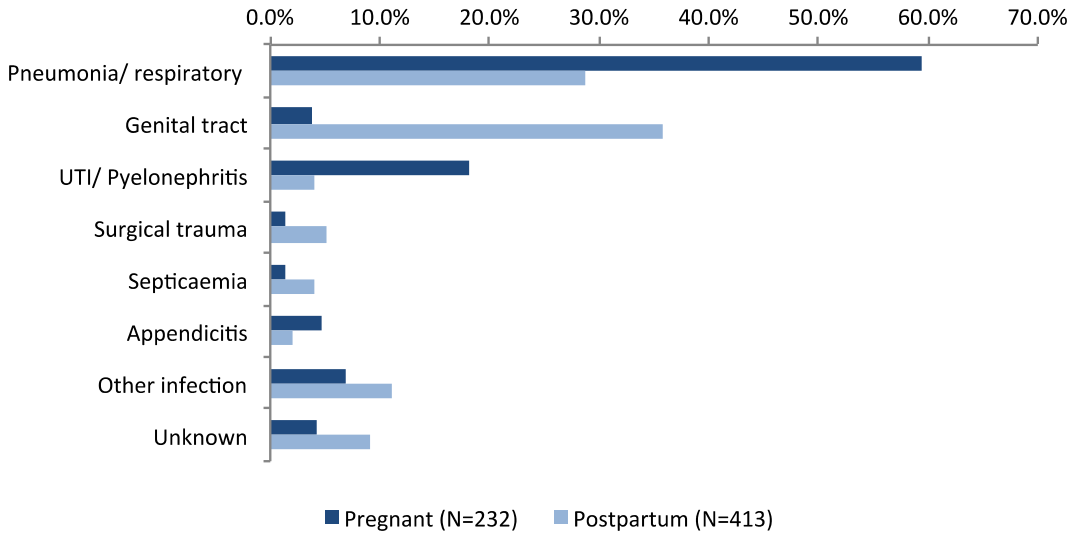
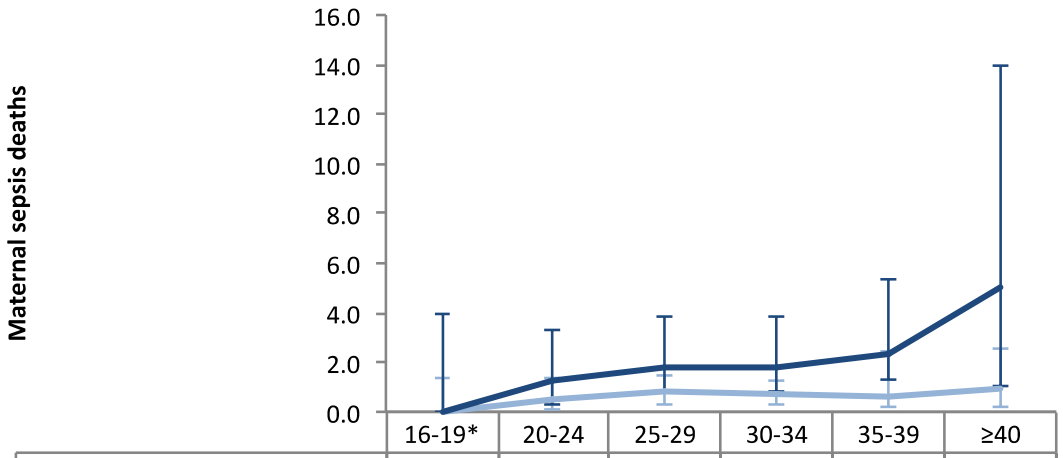


Figure 19. Source of infection amongst pregnant and postpartum critical care admissions with severe sepsis from 2008-2010.

6.3.4 Incidence of maternal mortality

Of all women admitted with maternal sepsis, 4.6% (N=29) died. The absolute risk of acute hospital mortality of women admitted was 1.8 (95% CI 1.1-2.8) per 100,000 maternities. Mortality rates by five-year age bands are shown in Figure 20. Mortality rates were the highest amongst women aged 40 or older. Out of 330 total maternal critical care admissions in this age category, three women died of severe sepsis. The absolute risk of mortality for women in this age category was 5.0 (95% CI 1.04-14.7) per 100,000 maternities. Pneumonia/ respiratory infection was the most common source of sepsis amongst women who died (N=12; 41.4%). It was not possible to ascertain from the data if these were women who died of AH1N1 influenza because disaggregated information on AH1N1 influenza was not included in the dataset.



	16-19*	20-24	25-29	30-34	35-39	≥40
Proportion of severe sepsis deaths among maternal critical care admissions	0.0	0.5	0.8	0.7	0.6	0.9
Rate of severe sepsis death per 100,000 maternities	0.0	1.3	1.8	1.8	2.3	5.0

*** Five-year age bands**

Figure 20. Rate of severe sepsis mortality amongst maternal critical care admissions and maternities by five-year age bands from 2008-2010.

6.3.5 Risk factors for maternal mortality

Survivors were compared with women who died in order to identify factors associated with mortality (Table 22). In the unadjusted model, when maternal age was evaluated as a continuous variable, the odds of dying increased significantly by 10% with each additional year of age (OR=1.1, 95% CI 1.0-1.1, p=0.03). After adjustment for *a priori* factors identified in the literature and changes over time, deprivation, being overweight or obese, respiratory dysfunction and haematological dysfunction were significant independent risk factors for mortality. Age ≥35 years and renal dysfunction were significant in univariable regression but were not significant when adjusted for other factors; however, it was not possible to exclude these as possible risk factors given the low power and that the adjusted odds could be as high as 11.2 for age ≥35 and as high as 9.3 for renal dysfunction. Black or other ethnic minority ethnic group was not significant in either univariable or multivariable regression.

Table 22. Clinical characteristics of survivors and non-survivors of severe maternal sepsis following critical care admission. Figures are numbers (%) of women.

	n (%) **Severe sepsis survivors** (*n*=**610**)	*n* (%) **Severe sepsis deaths** (*n*=**29**)	**uOR (95% CI)**	**aOR (95% CI)**
Recently pregnant	387 (63·4)	22 (75·9)	1·8 (0·76-4·3)	1·1 (0·42-3·0)
Maternal age				
<25	234 (38·4)	5 (17·2)	1	1
25-34	254 (41·7)	15 (51·7)	2·8 (0·99-7·7)	2·2 (0·71-7·0)
≥35	121 (19·9)	9 (31·0)	3·5 (1·1-10·6)	3·3 (0·94-11·2)
Black and other minority ethnic groups	147 (24·1)	7 (24·1)	0·98 (0·39-2·5)	0·59 (0·21-1·6)
IMD quintiles 4&5	354 (58·1)	17 (58·6)	1·02 (0·48-2·2)	2·6 (1·03-6·7)
BMI				
Unknown	317 (52·1)	13 (44·8)	0·78 (0·17-3·7)	1·2 (0·15-9·1)
<25	126 (20·7)	3 (10·3)	1	1
≥25 <30	90 (14·8)	7 (24·1)	3·3 (0·8-13·3)	5·2 (1·4-18·9)
≥30	76 (12·5)	6 (20·7)	3·5 (0·9-14·6)	6·3 (1·5-27·0)
History of immunosupression	13 (2·1)	2 (6·9)	3·3 (0·73-15·7)	
Source of infection*				
Pneumonia (chest infection)	216 (35·4)	12 (41·4)	1·3 (0·60-2·7)	
Intrauterine infection	69 (11·3)	2 (6·9)	0·58 (0·13-2·5)	
Pelvic infection	47 (7·7)	0 (0·0)	--	
UTI/ Pyelonephritis	43 (7·1)	0 (0·0)	--	

'--' Indicates no comparison group, i.e. zero incidence in either case or control group

* Known sources of infection with >5% frequency

Table 22. Continued

	n (%) **Severe sepsis survivors** (*n*=**610**)	*n* (%) **Severe sepsis deaths** (*n*=**29**)	**uOR (95% CI)**	**aOR (95% CI)**
Number of organ system dysfunctions				
1	221 (36·2)	2 (6·9)	1	
2	224 (36·7)	8 (27·6)	3·9 (0·83-18·7)	
≥3	165 (27·1)	19 (65·5)	12·7 (2·9-55·1)	
Organ system dysfunction**				
Cardiovascular	444 (72·8)	24 (82·8)	1·8 (0·68-4·8)	
Respiratory	349 (57·2)	26 (89·7)	6·5 (1·9-21·6)	8·1 (1·8-36·0)
Metabolic acidosis	322 (52·8)	18 (62·1)	1·5 (0·68-3·1)	
Renal	39 (6·4)	8 (27·6)	5·6 (2·3-13·4)	2·9 (0·94-9·3)
Haematological	52 (8·5)	11 (37·9)	6·5 (2·9-14·6)	5·7 (2·0-16·0)
Recently pregnant women only:				
Parity				
0	183 (48·9)	9 (42·9)	1	
1	88 (23·5)	7 (33·3)	1·6 (0·58-4·5)	
≥2	103 (27·5)	5 (23·8)	1·0 (0·32-3·0)	

'--' Indicates no comparison group, i.e. zero incidence in either case or control group

** Organ system dysfunctions not mutually exclusive

Table 22. Continued

	n (%) **Severe sepsis survivors** (*n*=**610**)	*n* (%) **Severe sepsis deaths** (*n*=**29**)	**uOR (95% CI)**	**aOR (95% CI)**
Assisted conception	24 (8·7)	0 (0·0)	--	
Mode of delivery				
Spontaneous vaginal	89 (23·6)	8 (36·4)	1	
Assisted vaginal	28 (7·4)	0 (0·0)	--	
Caesarean section	227 (60·2)	12 (54·6)	0·59 (0·23-1·5)	
Termination	23 (6·1)	2 (9·1)	0·97 (0·19-4·9)	
Ectopic	10 (2·7)	0 (0·0)	--	
All multiple births	24 (7·0)	3 (15·0)	2·3 (0·64-8·6)	
Stillbirth(s)	42 (21·9)	4 (33·3)	1·8 (0·5-6·2)	
Hysterectomy	16 (4·6)	3 (15·0)	3·6 (0·96-13·7)	
<24 hours since delivery	104 (27·6)	8 (36·4)	1·5 (0·61-3·7)	

'--' Indicates no comparison group, i.e. zero incidence in either case or control group

6.3.6 Sensitivity analysis

In a sensitivity analysis using the obstetric specific SIRS criteria defined by Waterstone and colleagues (Waterstone et al., 2001), 77 (11.9%) women did not meet the more rigorous criteria, however there were no significant changes in the distribution of case characteristics, sources of infection or significance of adjusted risk factors for mortality. In the absence of any significant differences, the PROWESS definition of cases was retained so that cases would not be unnecessarily excluded.

6.3.7 UKOSS case ascertainment

As a measure of case ascertainment, the number of critical care (level 3) admissions were compared between the ICNARC and UKOSS cohorts, and results are summarised in Table 23. ICNARC estimates (extrapolated figures) from 2010 were used for the comparison, as this was the closest year to the UKOSS study. Extrapolated figures of the total number of maternal critical care unit admissions for severe sepsis in the UK were used instead of the actual figures reported to ICNARC because of the incomplete coverage of the database.

As discussed further in the discussion section 6.4.6, it is likely that a number of high-dependency care (level 2) admissions in the UKOSS study were also captured in the ICNARC database, as this database includes information on intensive care and combined intensive care/high-dependency care units. Of all additional women admitted to level 2 care units in the UKOSS study (N=171), 161 came from combined intensive care/high-dependency care units and thus could have been reported to ICNARC; the remaining 10 women were from stand-alone level 2 units that could not have been

reported to ICNARC. Since the UKOSS data were anonymous, it was not possible to discern which women came from these units.

Using these estimates, between 54% (114 level 3 UKOSS cases only) and 100% (all 114 level 3 plus a number of level 2 UKOSS cases) of the total extrapolated number of maternal critical care unit admissions (N=212) were captured in the UKOSS study. The lower number of pneumonia/respiratory cases in the UKOSS study compared to the ICNARC study (11 to 19 versus 57 cases, respectively) suggests that the actual case ascertainment was somewhere in between 54% and 100%, and that a large proportion of cases not captured by UKOSS were respiratory cases.

Table 23. Comparison of ICNARC and UKOSS cases admitted for critical care.

	Number of maternal critical care unit admissions with severe sepsis reported to ICNARC in 2010*	Extrapolated number of total maternal ciritical care unit admissions for severe sepsis in the UK in 2010**	Number of UKOSS critical care unit (level 3 only) admissions	Number of UKOSS high dependency and critical care unit (level 2&3) admissions	Total UKOSS cases
Genital tract	49	55	33	93	113
UTI	28	31	24	60	72
Wound	9	10	9	25	33
Respiratory	51	57	11	19	20
Other infection	34	38	12	24	32
Unknown	18	20	25	65	95
Total	**189**	**212**	**114**	**286**	**365**

* Cases who met the Waterstone SIRS criteria, which was used in the UKOSS study.

** 2010 figures extrapolated using methods described in section 6.2.5. For respiratory infection, 2008 rates were used since 2009-2010 were H1N1 pandemic influenza years.

6.4 Discussion

6.4.1 Summary

This was the first national cohort study of maternal critical care admissions for severe sepsis in the UK. This study demonstrated that severe sepsis and septic shock morbidity are common amongst pregnant and postpartum women admitted to critical care (one in seven and one in nine respectively). Additionally, the rate of maternal death from 'all-cause' maternal sepsis was substantially higher than for genital tract sepsis alone (1.8 (95% CI 1.1-2.8) per 100,000 vs. 1.1 (95% CI 0.8–1.7) per 100,000 maternities) (Cantwell et al., 2011). The findings highlighted several important clinical and healthcare policy implications: namely that pneumonia/ respiratory infection is a leading source of sepsis irrespective of epidemic influenza periods; there are major significant disparities in deprivation and the risk of severe sepsis; and deprivation, increased BMI, respiratory and haematological organ system dysfunctions are significant independent risk factors for death from sepsis despite admission to critical care. This study also supports previous studies that caesarean section is a risk factor for severe sepsis. It is important to note, however, that the temporality of infection, whether the infection occurred after the caesarean section or if the woman had a caesarean section as a result of antepartum or intapartum infectious morbidity, could not be determined from these data. Each scenario has significant causal implications.

6.4.2 Pneumonia and respiratory infection

Forty percent of women admitted to critical care with severe sepsis had pneumonia/respiratory infection as the source of sepsis. A significantly larger proportion of pregnant women had pneumonia/respiratory infection as the source of

sepsis compared to postpartum women. In addition, women with pneumonia/respiratory infection had a significantly longer length of critical care unit stay compared with all other causes, and the absolute risk of maternal mortality was the largest compared with all other causes, comprising 41% of women who died from severe sepsis. Despite the significant influenza epidemic, which occurred from 2009 to 2010, only 10.5% (27/257) of pneumonia/ respiratory infection cases were identified as being due to the pandemic AH1N1 strain, although reporting is likely to have been incomplete. The incidence of primary pneumonia (bacterial and viral) is known to increase during seasonal and epidemic influenza periods (Morens et al., 2008), which is reflected in the increased proportion of severe sepsis from respiratory infection from 2009-2010 (Figure 18). However, in the pre-epidemic year of 2008, respiratory infection was also the largest cause of severe maternal sepsis.

These results indicate that in addition to genital tract infection, respiratory infection is a major source of severe maternal sepsis irrespective of an influenza epidemic. This should be considered in the context that pregnant and peripartum women are at greater risk of developing respiratory infection (Poulakou et al., 2012) and an increased incidence of invasive streptococcal infections (caused by *Streptococcus pneumoniae* and *Streptococcus pyogenes* (group A streptococcus) occurring through community-acquired respiratory transmission, has also been recently recorded in the UK (Zakikhany et al., 2011). Immediate implications are that in addition to precautions for genital tract sepsis (Cantwell et al., 2011), there is clearly a need to improve timely recognition of severe and progressive respiratory tract infection particularly in pregnant women. Most maternal deaths and critical illnesses from severe sepsis occur due to delay in recognition and diagnosis (Cantwell et al., 2011). Obstetric and front-line clinicians

should therefore maintain a high index of suspicion and remain alert to the possibility of progression. They should also alert pregnant and postpartum women to the possible severity of any infection, in particular the clinical symptoms of respiratory and genital tract infection and the dangers of delay in seeking medical care. From an economic perspective, an improvement in recognition and prompt treatment before the onset of severe infection would have a substantial effect on intensive care resource utilisation.

6.4.3 Deprivation

In addition to the risk of severe maternal sepsis associated with respiratory infection, there was a clear dose response relationship in the risk of severe sepsis associated with increasing deprivation. Importantly, a significant proportion of women who had a caesarean section (a well-established risk factor for severe sepsis) were IMD 4 and 5 (64.3%). It is unlikely, however, that rates of caesarean section were simply higher amongst more deprived women in the population. In a cohort study of all women delivering in English hospitals, Alves and colleagues found that the most affluent women had a significantly higher odds of caesarean section compared with women who were most deprived (Alves & Sheikh, 2005). The deprivation gradient in the risk of severe maternal sepsis appears to be consistent with an overall deprivation gradient in health outcomes that exists in the UK and other advanced-economy countries (Marmot & Bell, 2012). Whilst the mechanism behind this finding is unknown, women in more deprived geographic areas are known to have higher rates of poor underlying health (Marmot & Bell, 2012) and decreased uptake and continuity of maternity care (Hemingway et al., 1997), which is yet another health inequality experienced by the more deprived section of the population.

6.4.4 Agreement with previous studies

Known risk factors for maternal sepsis morbidity supported by this study were: younger (Acosta et al., 2012) and older age (Kramer et al., 2009), multiple gestation birth (Kramer et al., 2009) and caesarean section (Kramer et al., 2009; Acosta et al., 2012; Waterstone et al., 2001). Additionally, the significantly higher rate of stillbirth in this cohort is likely to be primarily an outcome of severe maternal infection, although in some cases stillbirth can also be a cause of sepsis.

6.4.5 Risk factors for mortality

Risk of maternal death from severe sepsis associated with increased BMI supports findings from the UK Confidential Enquiries into Maternal Deaths in 2006-2008 (Confidential Enquiry into Maternal and Child Health CEMACH, 2008). Importantly however, the Confidential Enquiry finding, although widely cited and used as the basis for inclusion in national UK Obstetric guidelines (Royal College of Obstetricians and Gynaecologists, 2012a; Royal College of Obstetricians and Gynaecologists, 2012b), did not have control data (a comparison group) to estimate effect sizes. From the present study it is possible to ascertain the effect size of the risk of dying amongst mothers with severe sepsis who are obese compared to mothers who are normal weight. Adjusting for confounders, women who are obese have more than six times the odds of dying of severe sepsis compared to normal weight women. Additionally, the risk of dying amongst overweight women was also more than five times the adjusted odds of normal weight women. The overlapping confidence intervals between the overweight and obese categories indicate that the increased risk of dying is not statistically different between these two groups.

In light of the clear dose response relationship between increasing deprivation and severe sepsis, the more than two-fold increased risk in the odds of dying amongst women who are in a high deprivation index has strong implications for policies surrounding health services provision in the UK. Although age was not found to be significant in the adjusted analysis, this is likely due to low power since the odds ratios did not change appreciably from the unadjusted model and the CIs for age ≥35 were compatible with an 11.2 fold increase in the odds of sepsis death; similarly the CIs for renal dysfunction were compatible with a 9.3 fold increase in the odds. It is therefore not possible to exclude the possibility of chance with these two factors, and that real findings are higher than an odds of one.

6.4.6 Comparison with UKOSS data

The ICNARC CMP includes data from combined intensive care and high-dependency (level 2) units. In many of these units the level of care (level 2 or 3) is determined by the bed within the unit. ICNARC has no mechanism of auditing the proportion of women reported from these combined units that were given level 2 care. In the UKOSS study, of all additional women admitted to level 2 care units (N=171), 161 women were admitted to combined intensive care/high-dependency care units, and thus could have been reported to ICNARC. In the scenario that only data on women cared for in level 3 beds were reported to ICNARC, the case ascertainment of UKOSS would be 54%. In another scenario whereby data on women cared for in both level 2 and level 3 beds were included in ICNARC, case ascertainment in the UKOSS study would be as high as 100%.

It is not possible to determine where on this spectrum the true level of case ascertainment lies, however several factors suggest that the true ascertainment is somewhere in between these two estimates. The significantly lower number of pneumonia/respiratory cases in the UKOSS study compared to the ICNARC study (11 to 19 versus 57 cases, respectively) suggests that the UKOSS case ascertainment was lower than 100%. In contrast, given that 34% (N=24) of women who had septic shock in the UKOSS study (the severest of end of the sepsis severity spectrum before death) were admitted to level 2 care, it is likely that these cases would have received critical-level care and would have been reported to ICNARC; in this case the UKOSS case ascertainment would likely be significantly higher than 54%.

As there were more cases of severe sepsis in the UKOSS study than the total extrapolated number of critical care unit admissions for one year in the ICNARC study (365 versus 212, respectively), clearly there are a number of women who meet the clinical criteria for severe sepsis, but are not captured through ICNARC. This indicates that there is a total population of women in the UK who have severe maternal sepsis, and that each system (UKOSS and ICNARC) captures an overlapping sample of these women, and together the systems likely capture nearly all cases of severe maternal sepsis in the UK. Those cases not captured in the respective systems are largely due to the limits of the data collection systems. UKOSS is best suited to identify peripartum morbidity cases, whereas ICNARC would only capture those peripartum cases that were admitted to critical care, as well as those women that presented to another service other than a maternity unit and that were not in the immediate period of labour and delivery. For example, in the present study, 60% of respiratory cases were amongst antepartum

women, indicating that a large proportion of cases not captured by UKOSS were antepartum respiratory sepsis cases, who would not usually be identified by UKOSS.

The total distribution of sources of infection in the ICNARC and UKOSS cohorts are shown in Table 24. It is clear that the distribution of infection sources amongst the two populations differed significantly (P<0.001), with a significantly larger proportion of women in the ICNARC cohort having had a pneumonia/ respiratory infection as the source of sepsis (Table 24). This further highlights that pregnant and postpartum women outside the immediate period labour and delivery are at particular risk of respiratory-tract sepsis.

Source of infection	ICNARC (N=646)	UKOSS (N=365)
Pneumonia/ respiratory infection	257 (39.8)	20 (5.5)
Genital tract	157 (24.3)	113 (31.0)
UTI/ Pyelonephritis	59 (9.1)	72 (19.7)
Surgical trauma	24 (3.7)	33 (9.0)
Other	101 (15.6)	32 (8.8)
Unknown	48 (7.4)	95 (26.0)

Table 24. Distribution of infection sources amongst all severe sepsis cases in the ICNARC and UKOSS cohorts.

An important question, however, is whether the difference in the sources of infection between the two cohorts leads to a disparity in the characteristics of each case population. In order to assess this, the distribution of characteristics was compared between the two case groups and is summarised below.

Similarities between ICNARC and UKOSS cohorts

- The age distribution was nearly identical between the ICNARC and UKOSS cohorts: mean age 28 years for both (33% vs. 32% of women <25 years,

respectively; χ^2 P=0.83). In both studies there was a significantly larger proportion of younger women compared to the total maternal and control populations respectively. Younger age was also a risk factor for severe sepsis in unadjusted risk factor analyses in both studies.

- Accordingly, parity did not differ significantly between the ICNARC and UKOSS groups (32% vs. 35%, respectively; P=0.25).

- Median BMI was similar between the ICNARC and UKOSS cohorts: 26 (IQR 22-30) vs. 25 (IQR 22-29), respectively.

- Using the denominator of all postpartum cases, there was no significant difference in the proportions of women who had a multiple gestation pregnancy in the ICNARC cohort compared to UKOSS: 7% (95% CI 4.6-9.6) vs. 4% (95% CI 2.1-7.8), respectively (χ^2 P=0.30).

- The proportion of caesarean section deliveries was also not significantly different between the ICNARC and UKOSS cohorts (64% vs. 60%, respectively; χ^2 P=0.39). The rate of operative vaginal delivery was lower in the ICNARC cohort (7% vs. 16% in UKOSS; χ^2 P=0.03), however, it is possible that the proportion of unknown mode of delivery may have contributed to this difference.

Differences between ICNARC and UKOSS cohorts

- The proportion of black or other ethnic minority groups was significantly smaller in the ICNARC cohort compared to UKOSS (24% (95% CI 20.6-27.3) vs. 39% (95% CI 34.1-44.4), respectively; χ^2 P<0.001). This difference,

however, may have been due to how the UK Census Coding for ethnic groups was interpreted, particularly for women of mixed white and black or other ethnic minority groups, when aggregated respectively in the ICNARC CMP or reported by UKOSS clinicians.

Indicators of socioeconomic status could not be compared between the two studies because each study used a different indicator; employment classification (an individual level indicator) was used in the UKOSS study, whilst IMD (an area level indicator) was used in the present ICNARC study.

In summary, the distributions of the population characteristics age, parity, BMI, multiple pregnancy and mode of delivery, did not differ significantly between the ICNARC and UKOSS cases populations. The two populations appeared to differ in the distribution of ethnic groups, however the possibility that this difference arose as a result of coding scheme interpretation cannot be ruled out. These results suggest that together the two systems likely capture nearly all cases of severe maternal sepsis in the UK. In addition, the respective studies capture complementary information, particularly regarding infection source. The lack of significant differences in characteristics between the two cases populations provides further evidence that there is significant overlap between the UKOSS and ICNARC cohorts, suggesting good ascertainment by UKOSS. In the future, linkage between the two data collection systems would provide a valuable means to definitively assess the total burden of severe sepsis in the obstetric population across the entire spectrum of pregnancy and the postpartum period.

6.4.7 Strengths and limitations

Irrespective of how the case definition may have differed from UKOSS, major strengths of this study were that it (1) utilised nationally representative data from England Wales and Northern Ireland, (2) data were obtained through a robust and validated data collection system, and (3) the study had a robust case definition. These factors ensured that in the present study potential population biases were minimised, and that the study had a high degree of sensitivity (that the cases included were correctly identified). This was further tested in sensitivity analyses using the obstetric-specific SIRS criteria, which demonstrated that use of the stricter criteria would not have significantly changed the conclusions drawn from the study (or in other words, that non-use of the stricter criteria did not bias the results).

As also discussed in the Chapter 5, previous studies have been prone to possible population bias. For example, in the Waterstone et al study it was not possible to know whether the significance of factors such as race, social exclusion and potentially even smoking were influenced by overall population characteristics. Similarly, in the Aberdeen study (Chapter 4) there may have been regional specificities in clinical practice and demographics, such as antibiotic usage and a relatively homogenous population. With the potential for population bias minimised in the present study, the external validity of the study is high. Results are also arguably generalisable to other high resource settings, particularly those that have experienced similar increases in severe maternal morbidity and mortality from sepsis, although differences in population characteristics and risk factors need to be considered (Schutte et al., 2010; Acosta et al., 2013; Bauer et al., 2013).

Although the results in this study were extrapolated to the entire UK, it cannot be ruled out that rates and risk factors for severe sepsis may differ in Scotland. Comparison of cohort data with aggregated national data precluded multivariable risk modelling for the outcome of morbidity. Additionally, since the number of deaths in the cohort was (fortunately) small, results of the logistic regression models for mortality should be interpreted cautiously. Whilst some strong predictors of mortality were identified, the absence of statistically significant findings for other potential risk factors including age cannot exclude that true effects may exist, but there was insufficient power to exclude the role of chance in the findings.

6.5 Conclusions

The burden of severe sepsis for pregnant and peripartum women admitted to critical care is significant. The finding that pneumonia/respiratory infection caused the largest proportion of severe sepsis cases and maternal sepsis deaths, irrespective of epidemic influenza indicates a critical need to improve timely recognition of severe respiratory tract infection, in addition to genital tract infection, in the obstetric population. Comparison of UKOSS and ICNARC cohorts suggests that the overall burden of severe sepsis may be greater than previous studies from a single clinical care setting have indicated. Studies presented in Chapters 4-6 represent a comprehensive exploration of the incidence and risk factors for severe maternal sepsis in the UK. However, questions remain about what the risk factors are for progression in maternal sepsis severity, and whether the trends observed in the UK are present in other countries with advanced healthcare systems. Further exploration of these questions is presented in the next chapter.

Chapter 7

The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study

7.1 Introduction

The last three chapters have reported studies designed to explore the incidence, causes and risk factors for severe maternal sepsis in the UK. However important questions arising from that research are (1) whether or not the rate of severe maternal sepsis is also increasing in other countries with advanced healthcare systems, and (2) what the risk factors are for progression in sepsis severity.

At the time of this research there was already some evidence of increasing rates of maternal sepsis from studies carried out in The Netherlands, however, this trend had not been established in the USA. In the USA, whilst the absolute risk of maternal death from sepsis is low (0.60 per 100,000 live births; extrapolated from Berg et al (Berg et al., 2010)), the risk of severe sepsis morbidity is substantially higher (20.9 per 100,000 deliveries; extrapolated from Callaghan et al (Callaghan et al., 2008). At the time of this research, a population-based study examining the risk factors and outcomes of maternal sepsis morbidity in the USA had not been carried out.

As described in Chapter 6, the risk factors for dying of sepsis differ from the risk factors for severe morbidity. Although maternal sepsis, severe sepsis, septic shock and maternal death from sepsis have been studied in isolation from one another, there has not been a study assessing how risk associated with these factors changes with the progression of severity. An understanding of the risk factors along the continuum of sepsis morbidity from uncomplicated sepsis to severe sepsis at the population level is important for targeting preventive strategies that could be implemented to prevent maternal deaths.

7.1.1 Study objectives

The aim of this study was to investigate the incidence and risk factors of uncomplicated maternal sepsis, severe sepsis and septic shock as well as the probability of progression to severe sepsis, amongst all live birth maternities from 2005 to 2007 in California, where there are 507,746 births per year (Hamilton et al., 2013), representing approximately one in eight American births. The advantage of using the California dataset to investigate these objectives was its large size and therefore power to look at progression issues.

7.2 Methods

7.2.1 Data source

This study was conducted using data linked from the California Vital Statistics records to statewide hospital discharge data from the Office of State Wide Planning and Development (OSHPD). These data were obtained from the California Perinatal Quality Care Collaborative network database. This linked dataset contains comprehensive demographic and clinical information including mode of delivery and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes from the birth hospitalisation of all inpatient live births in California. Data were linked using a probabilistic matching algorithm for large public health data sets as described by Jaro and colleagues (Jaro, 1995; Herrchen et al., 1997). The linkage was performed by the California Perinatal Quality Care Collaborative under grant support from the March of Dimes. Quality assurance of the linkage is through

validation (Lyndon et al., 2012). For the study presented, hospital and patient identifiers were masked in order to anonymise the data.

7.2.2 Study design and outcome variables

This was a cohort study of administratively collected data about maternal sepsis amongst all in-hospital live birth maternities in California between 2005 and 2007. A cohort design was used because both outcome and exposure data were available on the entire population of women who gave birth in California over the time period. Outcome variables were: uncomplicated sepsis, severe sepsis and septic shock.

7.2.3 Case definitions

Cases of uncomplicated sepsis were defined as those with an ICD-9-CM code for septicaemia (038.1-038.9) or sepsis (995.91). Cases of severe sepsis were those with an ICD-9-CM code for severe sepsis (995.92), or a sepsis code plus the management indicators: length-of-stay ≥90th percentile for mode of delivery (at least three days), or a postpartum transfer to intensive care (Callaghan et al., 2008; Lyndon et al., 2012) or if the woman died. These management criteria for severe sepsis were adopted in order to account for potential misclassification of sepsis severity (Callaghan et al., 2008), since it was noted that a proportion of women with codes for septicaemia or sepsis and no other severe morbidity had a long length-of-stay, other management indicators of severe morbidity, or were either transferred or died thus indicating that the ICD-9-CM code for a more severe form of sepsis might not have been used since clearly these women had management indicators for severe morbidity, but only the disease classification code for sepsis recorded. These management criteria have been established in other morbidity studies (Callaghan et al., 2008; Lyndon et al., 2012), as administrative datasets do not

usually contain clinical information (such as heart rate, respiratory rate, white blood cell count, etc.), which would otherwise be used as clinical indicators of severity. Sepsis was also regarded as severe if it was complicated by other acute co-morbidity and the woman had the criteria for severe sepsis (as defined above). Cases of septic shock were those with an ICD-9-CM code for septic shock (785.52).

7.2.3.1 Maternal deaths

Maternal deaths were identified from OSHPD disposition data and Vital Statistics records. These data however did not include the actual cause of death; these were women who had sepsis but could have died from other causes, therefore case fatality rates and risk factors for direct maternal death from sepsis could not be assessed in this study.

7.2.4 Case groups

Women were grouped according to the most severe outcome including women with multiple codes. For example women with uncomplicated sepsis and severe sepsis codes were categorised as having severe sepsis, and women with uncomplicated or severe sepsis and septic shock codes were categorised as having septic shock. Final outcome groups were thus mutually exclusive. This was necessary in order to avoid double counting of cases in each case group since the aim was to assess the adjusted odds of progression to the more severe stages of sepsis. Therefore (as described in further detail in the statistical analysis section) significant differences in risk factors between case groups needed to be evaluated.

7.2.5 Risk factors

Potential risk factors examined included demographic and clinical factors, other acute co-morbidities as well as management-based indicators of severe morbidity (Kuklina, Meikle, et al., 2009b). In the US, race and ethnicity are categorised separately, which differs from the UK. According to the US Census Bureau, individuals can belong to one of two ethnic groups (Hispanic or non-Hispanic) in addition to a specific racial group (White, Black, Asian, multi-race or other) (Humes et al., 2011). Accordingly, ethnicity and race were analysed as separate risk factors in this study. When payor status was analysed, public health insurance (Medi-Cal; California Medicaid) was grouped together with no insurance in order to avoid under-reporting, because previous studies have found that up to 20% of women in California are uninsured during the first trimester of pregnancy before being later enrolled in a public program (Egerter et al., 2002). Adequacy of prenatal care was defined according to the Kotelchuck Adequacy of Prenatal Care Utilisation Index: adequate prenatal care was defined as initiation of prenatal care within the first four months of pregnancy, and receipt of at least 80% of the expected number of prenatal care visits based on the American Congress of Obstetricians and Gynaecologists (ACOG) prenatal care visitation standards for uncomplicated pregnancies (Kotelchuck, 1994; Lyndon et al., 2012). Other significant morbidities were identified by ICD-9-CM diagnostic and procedure codes in addition to birth certificate diagnosis codes (Lyndon et al., 2012). Co-morbidities evaluated were diabetes and chronic hypertension. These conditions were identified by ICD-9-CM codes for diabetes type I or II (diabetes mellitus) or gestational diabetes (ICD-9-CM codes 648.01-648.04 and 648.80-648.84), and chronic/pre-existing hypertension (essential hypertension, excluding preeclampsia/ eclampsia) (ICD-9-CM codes 401-405).

7.2.6 Sample size

The sample size of this study was represented by the population incidence of maternal sepsis amongst virtually all hospitals in California; military hospitals and freestanding birth centres do not report discharge data (which comprised 1.9% (n=31,884) of live births) and data from these births were therefore excluded. Similarly, this study did not include data from home births, which occurs infrequently in California (0.5% of all births (Hamilton et al., 2013). Since the denominator of interest was live birth maternities (still births were not included in the dataset), only one record was retained for women who had a multiple birth; the original dataset contained a record for each birth, however these were identified according to hospital record numbers and duplicate records were dropped. Separate birth events, for example if a woman had two children over the three-year study period, were retained in the dataset. The final analysis included the 1,622,474 live birth maternities with reported discharge data. In the progression of severity model, with 783 cases of severe sepsis/ septic shock compared to 815 cases of uncomplicated sepsis, and assuming a prevalence of exposure of at least 5.0% amongst women with uncomplicated sepsis, the analysis had 90% power at $P<0.05$ (two-sided) to detect a statistically significant odds ratio of 1.95 or greater.

7.2.7 Statistical Analyses

7.2.7.1 Incidence

The absolute risks of developing uncomplicated sepsis and severe sepsis were calculated by dividing the total number of cases by the total number of live birth maternities during the study period. Frequencies of demographic and clinical variables and other significant morbidities were tabulated for uncomplicated sepsis, severe sepsis and septic shock case groups, and each group was compared to the immediately less severe group

in the morbidity continuum (Geller et al., 2004); uncomplicated sepsis was compared with all other women who gave birth in California without a sepsis code, severe sepsis was compared with uncomplicated sepsis and septic shock was compared with severe sepsis.

7.2.7.2 Univariable analyses

Proportions were compared using Pearson's chi-square test and Fisher's exact test where there were ≤5 observations in a single cell. Additionally to make comparisons between continuous data, the Wilcoxon rank-sum (Mann-Whitney) test was used. The rank-sum test was also used for the variable age because the distribution of age in the population was positively skewed. In order to test for possible outliers due to spurious data, a scatter plot of the variable and box plots of the age categories were used, however these revealed no obvious outliers.

At the first stage of the analysis it was shown that there were no statistically significant differences in the proportion of *a priori* demographic and clinical factors (all factors except for mode of delivery) between severe sepsis and septic shock, and given that women with septic shock would have progressed through the severe sepsis stage, women with either of these outcomes were grouped together into a severe sepsis/ septic shock outcome category. In order to evaluate the initial risk for developing sepsis, women with uncomplicated sepsis were compared with all other women who gave birth in California without a sepsis code. And in order to evaluate the risk for progression of sepsis severity, women with severe sepsis/ septic shock were compared with women who had uncomplicated sepsis. All factors were initially compared using univariable

logistic regression. Unadjusted odds ratios (uOR) with 95% confidence intervals (CIs) were estimated.

7.2.7.3 Multivariable logistic regression

Factors were then modelled using multivariable logistic regression. Both multivariable models (for sepsis and severe sepsis/ septic shock, respectively) were constructed based on risk factors identified in previous literature and plausible confounding. The stepwise approach for multivariable modelling was not used in this study because of the large sample size (N=1,622,474). Therefore there was sufficient power to use a Bayesian approach, similar to that used in the UKOSS study in Chapter 5. This approach, as opposed to a purely statistical one, allowed for the inclusion of most variables thereby reducing the risk of residual confounding.

All demographic and clinical factors were included in the models with the exception of metropolitan statistical area (MSA) and body mass index (BMI). Metropolitan statistical area was not included since it was found to be collinear with hospital volume. Body mass index was also not included since these data were only collected for one year and therefore available for only one-third of the study population. The morbidities or management indicators: wound complication, coagulation disorder, organ system failures, blood transfusion, hysterectomy, and ventilation were not included because these factors are likely to be on the causal pathway of sepsis. Episiotomy, 3rd or 4th degree laceration and pelvic trauma were included in initial model iterations, but were removed because they were not significant in either univariable or multivariable regression, and did not affect the relationship between other predictor variables and the outcomes.

In addition, both models were re-run with the 'public/ uninsured' health insurance group disaggregated to test for any significant effects on the risk associated with other predictor variables (such as prenatal care) and the outcomes; no significant effects were detected. Adjusted odds ratios (aOR) with 95% CIs are reported. Since all variables with the exception of those discussed above were included in the adjusted models, only results of the multivariable analysis are shown in the chapter, however the full tables are provided in Appendix 10. Differences in rates reported in the text are all statistically significant.

7.2.7.4 Adjustment for clustering effect

Since this was a very large dataset comprising all live birth maternities over a three-year period in California, the effects of clustering needed to be taken into consideration. This was because the clusters of women delivering in a given hospital were large. For example, some tertiary care hospitals in the major cities such as San Francisco or Los Angeles had over 6,000 births per year. Therefore, the possibility of interclass correlation between these clusters of women would have been high. Interclass correlation would have been particularly evident amongst sociodemographic characteristics such as race, ethnicity, education level and health insurance, depending on the geographical location of the hospital. The final models were adjusted for possible hospital clustering effect by using robust standard errors. Robust standard errors were used instead of multilevel modelling (an alternative way to handle clustering effect) for ease of interpretation, since the logistic regression analysis itself does not change using this technique.

7.2.7.5 Post modelling checking procedures

Plausible interactions between variables were tested in the final models using likelihood ratio tests with a significance level of $P<0.01$. Interactions were tested between age and prenatal care, age and education, and level of health insurance and prenatal care. No significant interactions were identified. Goodness-of-fit was also assessed for the final models using the Hosmer-Lemeshow's goodness-of-fit test with a significance level of $P<0.05$; all models had a P-value >0.05 indicating that all of the models fit the data well.

7.2.7.6 Multiple risk factors

The absolute risks for uncomplicated and severe sepsis in groups of women with multiple risk factors were also calculated. This was done by dividing the total number of cases by the total number of live birth maternities in each group. Groups were defined according to the number of *a priori* risk factors. Additionally as carried out in the UKOSS data, cumulative risk was calculated in order to understand the relationship between an increasing number of risk factors, the risk of sepsis and progression to severe sepsis. This was done because many women in this study had multiple risk factors identified as statistically significant in the analyses. For this analysis, the number of significant adjusted risk factors was counted for each case and non-case. Cases and non-cases were then compared using univariable logistic regression with 'zero risk factors' as the reference group. Thus an estimate was derived of how much the odds of sepsis and progression to severe sepsis increased with each additional risk factor compared to women without any known risk factors.

7.2.8 Statistical software

SAS 9.2 (SAS Institute, Cary, NC) and Stata SE statistical software 12.1 (StataCorp, College Station, TX) was used for the analyses.

7.2.9 Data management

Data were initially received as a SAS file and kept on a secure cloud network owned by the University of California San Francisco. SAS was used to initially exclude data from military hospitals and freestanding birth centres (as these did not report discharge data) as well as linked data on neonatal outcomes. This was done in order to reduce the size of the dataset so that it could be exported to Stata. Once the data was in Stata format, it was cleaned in particular for duplicate entries. For example if a woman was readmitted, two records (one for each admission) were contained in the dataset. A large amount of coding was subsequently necessary in order to derive the variables eventually used in the study. This was because all of the variables comprised of multiple ICD-9 codes, vital statistics, birth certificate and OSHPD codes.

The master file of the dataset, a copy 'working-file', and all Stata Do-files were kept on the cloud. No variables were changed or re-coded in either data file. Re-coding of the variables for analyses, however, was written into the Stata Do-file. The author did not have access to download any of these files, so all analyses were performed on the cloud.

7.2.10 Research ethics approval

Institutional Review Board approval was obtained from Stanford University and the University of California San Francisco. The study protocol can be found in Appendix 7.

7.3 Results

7.3.1 Incidence

During the study period from 2005 to 2007, there were 1,622,474 maternities resulting in a live birth in California of which 1598 mothers developed sepsis. The absolute risk of developing sepsis was 10 per 10,000 live birth maternities (95% CI 9.4-10.3). Of all women who had sepsis, 807 had uncomplicated sepsis, 735 had severe sepsis, and 56 had septic shock. The absolute risk of all severe sepsis including septic shock was 4.9 per 10,000 live birth maternities (95% CI 4.5-5.2). Of all inpatient maternal deaths, 14 mothers had severe sepsis/ septic shock (11.5% of all inpatient maternal deaths over the study period).

7.3.2 Demographic and clinical characteristics

The distributions of demographic and clinical characteristics amongst the non-sepsis obstetric population and the three sepsis outcome groups are shown in Tables 25-26 respectively. There were significant differences in the distribution of demographic and clinical characteristics between women with uncomplicated sepsis and the non-sepsis obstetric population. Compared to the obstetric population without sepsis, women with uncomplicated sepsis were slightly older (P=0.001), and there was a larger proportion of women that were of non-Hispanic ethnicity (P=0.03), with less education (P<0.001), diabetes (P=0.01), and who had a primary or repeat caesarean section (P<0.001).

There were also significant differences in the distribution of demographic and clinical characteristics between women with severe sepsis compared to those with uncomplicated sepsis. Compared to women with uncomplicated sepsis, amongst women

with severe sepsis there was a larger proportion of women of black race (P=0.02), Hispanic ethnicity (P<0.05), who had public or no health insurance (P<0.005), were multiparous (P<0.01), had a multiple gestation pregnancy (P<0.001), had diabetes (<0.001), had chronic hypertension (P<0.001), and had a primary or repeat caesarean section (P<0.001).

Only the proportions of mode of delivery differed between women with septic shock compared to severe sepsis, with higher caesarean rate for septic shock cases (P=0.006). It was not possible from the data available to distinguish the temporality of these two events.

Table 25. Demographic characteristics of the non-sepsis obstetric population, women with uncomplicated sepsis, severe sepsis, and septic shock in California (2005-2007). Figures are numbers (%) of women.

	Obstetric population without sepsis	P-value*	Uncomplicated sepsis	P-value*	Severe sepsis	P-value*	Septic shock
	n=1620876		n=807		n=735		n=56
Maternal age							
Median years (IQR)	28 (23-33)	0.001**	29 (24-33)	0.826**	29 (24-34)	0.423**	32 (22.5-35)
Race		0.055		0.017		0.26	
White	1265843 (78.1)		645 (79.9)		556 (75.7)		41 (73.2)
Black	86093 (5.3)		43 (5.3)		70 (9.5)		5 (8.9)
Asian	186749 (11.5)		70 (8.7)		66 (9.0)		9 (16.1)
Other/ Multirace	82191 (5.1)		49 (6.1)		43 (5.9)		1 (1.8)
Ethnicity		0.032		0.049		0.768	
Non-Hispanic	750807 (47.0)		403 (50.8)		329 (45.7)		24 (43.6)
Hispanic	848365 (53.1)		391 (49.2)		391 (54.3)		31 (56.4)
Education		<0.0001		0.152		0.884	
Highschool or less	875186 (55.6)		491 (62.8)		427 (60.8)		29 (58.0)
Some college	556303 (35.4)		225 (28.8)		229 (32.6)		18 (36.0)
Some post-graduate	141612 (9.0)		66 (8.4)		46 (6.6)		3 (6.0)
Health insurance		0.761		0.005		0.313	
Private	767519 (47.5)		375 (46.5)		280 (38.4)		27 (48.2)
Military/ Other government	49426 (3.1)		24 (3.0)		25 (3.4)		1 (1.8)
Public/ uninsured	798983 (49.4)		407 (50.5)		425 (58.2)		28 (50.0)

Categories are mutually exclusive

*Difference in distribution between groups; χ^2 test; Fisher's exact test for <5 observations. Comparison groups are: obstetric population without sepsis and uncomplicated sepsis, uncomplicated sepsis and severe sepsis, severe sepsis and septic shock.

** Wilcoxon rank-sum (Mann-Whitney) test

Table 25. Continued

	Obstetric population without sepsis	P-value*	Uncomplicated sepsis	P-value*	Severe sepsis	P-value*	Septic shock
	n=1620876		n=807		n=735		n=56
Hospital volume (deliveries per year)		0.081		0.857		0.808	
<1000	116195 (7.2)		54 (6.7)		53 (7.2)		5 (8.9)
1000-3000	717022 (44.2)		332 (41.1)		303 (41.2)		21 (37.5)
≥3000	787659 (48.6)		421 (52.2)		379 (51.6)		30 (53.6)
Metropolitan statistical area population		0.727		0.127		0.679	
Small (<250,000)	80856 (5.0)		44 (5.4)		28 (3.8)		3 (5.4)
Medium (250,000<1 million)	381495 (23.6)		183 (22.7)		146 (19.9)		13 (23.2)
Large (>1 million)	1157311 (71.5)		580 (71.9)		561 (76.3)		40 (71.4)

Categories are mutually exclusive

*Difference in distribution between groups; χ^2 test; Fisher's exact test for <5 observations. Comparison groups are: obstetric population without sepsis and uncomplicated sepsis, uncomplicated sepsis and severe sepsis, severe sepsis and septic shock.

Table 26. Clinical characteristics of the non-sepsis obstetric population, women with uncomplicated sepsis, severe sepsis, and septic shock in California (2005-2007). Figures are numbers (%) of women.

	Obstetric population without sepsis	P-value*	Uncomplicated sepsis	P-value*	Severe sepsis	P-value*	Septic shock
	n=1620876		n=807		n=735		n=56
Prenatal care		0.13		0.593		0.292	
Adequate	1299448 (80.2)		630 (78.1)		582 (79.2)		41 (73.2)
Inadequate	321428 (19.8)		177 (21.9)		153 (20.8)		15 (26.8)
Parity		0.216		<0.0001		0.575	
Primiparous	625377 (38.6)		293 (36.5)		349 (47.6)		24 (43.6)
Multiparous	994185 (61.4)		510 (63.5)		385 (52.4)		31 (56.4)
Multiple pregnancy		0.626		<0.0001		0.66	
Singleton	1571423 (96.9)		780 (96.7)		657 (89.4)		49 (87.5)
Multiple	49453 (3.1)		27 (3.4)		78 (10.6)		7 (12.5)
Chronic Co-Morbidities							
Diabetes	113014 (7.0)	0.014	74 (9.2)	<0.0001	112 (15.2)	0.381	11 (19.6)
Chronic hypertension	15850 (1.0)	0.266	11 (1.4)	<0.0001	37 (5.0)	1.00	2 (3.6)
Mode of delivery**		<0.0001		0.001		0.006	
Spontaneous vaginal	1037472 (64.0)		425 (52.7)		314 (42.7)		17 (30.4)
Primary caesarean	292114 (18.0)		232 (28.8)		272 (37.0)		34 (60.7)
Repeat caesarean	216915 (13.4)		120 (14.9)		123 (16.7)		4 (7.1)
Operative vaginal	74375 (4.6)		30 (3.7)		26 (3.5)		1 (1.8)
BMI (2007 only)	*n=481994*		*n=250*		*n=211*		n=17
Median (IQR)	24.3 (21.5-28.3)	0.642***	24.5 (21.8-28.7)	0.298***	25.6 (22.1-29.3)	0.379***	24.2 (19.4-29.2)

* Difference in distribution between groups; $\chi 2$ test; Fisher's exact test for <5 observations. Comparison groups are: obstetric population without sepsis and uncomplicated sepsis, uncomplicated sepsis and severe sepsis, severe sepsis and septic shock.

**Data on elective versus emergency caesarean section was not available; operative delivery includes forceps or vacuum extraction.

*** Wilcoxon rank-sum (Mann-Whitney) test

7.3.3 Other significant morbidities and maternal death

The distributions of other significant morbidities and maternal death amongst the non-sepsis obstetric population and the three sepsis outcome groups are shown in Table 27. The median length of postpartum hospital stay was progressively longer with increasing sepsis severity. The median length-of-stay for severely septic women without other acute co-morbidity was five days (IQR=4-10). Compared to women with uncomplicated sepsis, a larger proportion of women with severe sepsis had preeclampsia, postpartum haemorrhage and wound complications. The rate of preeclampsia was also more than three times higher amongst women with septic shock compared to women with severe sepsis (37.5% vs. 10.2% respectively; $p<0.0001$). The proportion of morbidities and management indicators of severe morbidity, which may occur along the causal pathway of sepsis (wound complication, coagulation disorder, organ system failures, blood transfusion, hysterectomy, and ventilation) increased significantly with increasing sepsis severity. Unsurprisingly, nearly all wound complications across the spectrum of sepsis severity were amongst women who had a caesarean section. The case fatality rate for severe sepsis was 0.8% (95% CI 0.3-1.8), and for septic shock was 14.3% (95% CI 6.4-26.2).

Table 27. Other serious morbidity and maternal death amongst the non-sepsis obstetric population, women with uncomplicated sepsis, severe sepsis, and septic shock in California (2005-2007). Figures are numbers (%) of women.

	Obstetric population without sepsis	P-value*	Uncomplicated sepsis	P-value*	Severe sepsis	P-value*	Septic shock
	n=1620876		n=807		n=735		n=56
Postpartum LOS (median days; IQR)							
Median days (IQR)	2 (2-3)	1.00**	2 (2-3)	<0.0001**	5 (4-10)	0.0003**	9.5 (5-18.5)
Other serious morbidity							
Preeclampsia	101575 (6.3)	0.252	57 (7.1)	<0.0001	155 (21.1)	0.491	14 (25.0)
Postpartum haemorrhage	45969 (2.8)	0.85	22 (2.7)	<0.0001	75 (10.2)	<0.0001	21 (37.5)
Wound complication	6031 (0.4)	0.562	2 (0.3)	<0.0001	68 (9.3)	0.219	2 (3.6)
Caesarean section	5093 (84.6)***		2 (100.0)***		65 (95.6)***		2 (100.0)***
3rd or 4th degree laceration	37915 (2.3)	0.977	19 (2.4)	0.313	12 (1.6)	1.00	1 (1.8)
Pelvic trauma	51080 (3.2)	0.931	25 (3.1)	0.24	31 (4.2)	0.72	1 (1.8)
Coagulation disorder	2087 (0.1)	1.00	1 (0.1)	<0.0001	40 (5.4)	<0.0001	16 (28.6)
Respiratory failure	1107 (0.1)	0.019	3 (0.4)	<0.0001	77 (10.5)	<0.0001	32 (57.1)
Renal failure	437 (0.03)	1.00	0 (0.0)	<0.0001	30 (4.1)	<0.0001	16 (28.6)
Heart failure	5007 (0.3)	1.00	2 (0.3)	0.001	18 (2.5)	<0.0001	11 (19.6)

*Difference in distribution between groups; $\chi 2$ test; Fisher's exact test for <5 observations, Comparison groups are: obstetric population without sepsis and uncomplicated sepsis, uncomplicated sepsis and severe sepsis, severe sepsis and septic shock.

** Wilcoxon rank-sum (Mann-Whitney) test

*** Proportion of women who had a wound complication who had a cesarean section

Incidence <0.1% in obstetric population and women with sepsis for: phlebitis or thrombophlebitis, pulmonary embolism, uterine rupture, anesthetic complications, dilation and curettage, and cerebrovascular disorders.

Table 27. Continued

	Obstetric population without sepsis	P-value*	Uncomplicated sepsis	P-value*	Severe sepsis	P-value*	Septic shock
	n=1620876		n=807		n=735		n=56
Management Indicators							
Episiotomy	214552 (13.2)	<0.0001	66 (8.2)	0.119	45 (6.1)	0.329	2 (3.6)
Blood transfusion	11472 (0.7)	0.337	8 (1.0)	<0.0001	98 (13.3)	<0.0001	29 (51.8)
Hysterectomy	1344 (0.1)	0.488	1 (0.1)	<0.0001	14 (1.9)	<0.0001	6 (10.7)
Ventilation	762 (0.1)	0.009	3 (0.4)	<0.0001	56 (7.6)	<0.0001	29 (51.8)
Materal death	108 (0.01)	1.00	0 (0.0)	0.012	6 (0.8)	<0.0001	8 (14.3)

*Difference in distribution between groups; χ2 test; Fisher's exact test for <5 observations, Comparison groups are: obstetric population without sepsis and uncomplicated sepsis, uncomplicated sepsis and severe sepsis, severe sepsis and septic shock.

7.3.4 Risk factors for sepsis

In assessing the risk of developing uncomplicated sepsis without progression to severe sepsis, after adjustment and compared to the general obstetric population, women who were ≥25 years, who had only a high school or lower level of education, or who had public or no health insurance were at significantly greater risk of developing uncomplicated sepsis (Table 28). Primary and repeat caesarean section were also associated with uncomplicated sepsis however the temporality in relation to uncomplicated sepsis could not be determined.

In assessing the risk of progression from uncomplicated sepsis to severe sepsis/ septic shock, women who were of Black or Asian race, Hispanic ethnicity, who had public or no health insurance, diabetes, chronic hypertension, who delivered in low volume hospitals (<1,000 births per year), were primiparous or had a multiple pregnancy were at significantly increased risk of progression to severe sepsis. Women who progressed to severe sepsis/ septic shock also had significantly higher odds of the acute co-morbidities preeclampsia and postpartum haemorrhage compared to women with uncomplicated sepsis.

The effect sizes for progression were large in the cases of the risk factors: multiple pregnancy (aOR=3.5; 95% CI 2.1-5.9), chronic hypertension (aOR=8.51; 95% CI 1.8-38.0), preeclampsia (aOR=3.72; 95% CI 2.5-5.4) and postpartum haemorrhage (aOR=4.18; 95% CI 2.5-7.1). The number of women with chronic hypertension was small, which is evident in the wide confidence interval of the aOR; the high degree of uncertainty therefore makes it difficult to interpret the true effects of this factor. Caesarean section was also of borderline significance in the adjusted model. The lack of

statistical significance of this factor, however, may be the effect of controlling for preeclampsia and postpartum haemorrhage, for which caesarean section is a strongly associated factor (Magann et al., 2005; Silver et al., 2006; Wang et al., 2013).

Table 28. Adjusted odds ratios for factors associated with development of uncomplicated sepsis and with progression from uncomplicated sepsis to severe sepsis/ septic shock.

	Uncomplicated sepsis vs. no sepsis			Severe sepsis/ shock vs. uncomplicated sepsis		
	aOR*	95% CI	P-value	aOR*	95% CI	P-value
Maternal age						
<18	0.94	(0.59-1.50)	0.805	1.2	(0.61-2.35)	0.594
18-24	1			1		
25-34	1.29	(1.08-1.54)	0.005	0.89	(0.68-1.18)	0.425
≥35	1.41	(1.12-1.78)	0.003	1.00	(0.71-1.40)	0.978
Race						
White	1			1		
Black	0.78	(0.55-1.09)	0.148	2.09	(1.34-2.26)	0.001
Asian	0.61	(0.47-0.79)	<0.0001	1.59	(1.07-2.37)	0.023
Other/ Multirace	1.1	(0.77-1.52)	0.659	0.73	(0.43-1.23)	0.237
Ethnicity						
Hispanic	0.73	(0.61-0.88)	0.001	1.42	(1.09-1.83)	0.008
Non-Hispanic	1					
Education level						
Highschool or less	1.63	(1.35-1.97)	<0.001	0.79	(0.60-1.04)	0.089
More than highschool	1			1		
Health Insurance						
Private	1			1		
Military/ Other government	1.02	(0.67-1.56)	0.933	1.52	(0.85-2.72)	0.162
Public/ uninsured	1.22	(1.02-1.46)	0.03	1.52	(1.19-1.94)	0.001
Hospital volume (deliveries per year)						
<1000	0.78	(0.58-1.04)	0.093	1.93	(1.15-3.23)	0.013
1000-3000	0.84	(0.72-0.98)	0.024	1.07	(0.85-1.35)	0.58
≥3000	1			1		
Inadequate prenatal care						
Yes	1.12	(0.94-1.33)	0.197	1.01	(0.78-1.30)	0.956
No	1					
Primiparous						
Yes	0.84	(0.71-1.00)	0.044	2.03	(1.56-2.63)	<0.0001
No	1			1		

*Results adjusted for hospital clustering and for all factors listed in the table.

Table 28. Continued

	Uncomplicated sepsis vs. no sepsis			Severe sepsis/ shock vs. uncomplicated sepsis		
	aOR*	95% CI	P-value	aOR*	95% CI	P-value
Multiple pregnancy						
Yes	0.76	(0.51-1.12)	0.169	3.5	(2.09-5.85)	<0.0001
No	1			1		
Diabetes						
Yes	1.22	(0.95-1.56)	0.124	1.47	(1.04-2.09)	0.014
No	1					
Chronic hypertension						
Yes	1.23	(0.61-2.07)	0.491	8.51	(1.92-37.7)	0.005
No	1			1		
Mode of Delivery						
Spontaneous vaginal	1			1		
Primary caesarean	1.99	(1.68-2.34)	<0.0001	1.24	(0.97-1.59)	0.086
Repeat caesarean	1.25	(1.02-1.54)	0.035	1.33	(0.97-1.81)	0.076
Operative vaginal**	0.96	(0.66-1.41)	0.844	1.08	(0.62-1.90)	0.782
Preeclampsia						
Yes	0.99	(0.75-1.29)	0.921	3.72	(2.52-5.44)	<0.0001
No	1			1		
Postpartum haemorrhage						
Yes	1.00	(0.67-1.53)	0.967	4.18	(2.46-7.11)	<0.0001
No	1			1		

*Results adjusted for hospital clustering and for all factors listed in the table.
** Forceps or vacuum extraction

7.3.5 Cumulative risk

The odds associated with *a priori* demographic and clinical factors was significantly cumulative; compared to women without sepsis, for every additional factor, the odds of uncomplicated sepsis which did not progress to severe sepsis/septic shock increased by 25% (OR=1.246; 95% CI 1.174-1.323; P<0.0001), and odds of progression to severe sepsis/ septic shock increased by 57% (OR=1.567; 95% CI 1.408-1.744). The absolute risks for uncomplicated and severe sepsis in groups of women with multiple risk factors are shown in Figure 21.

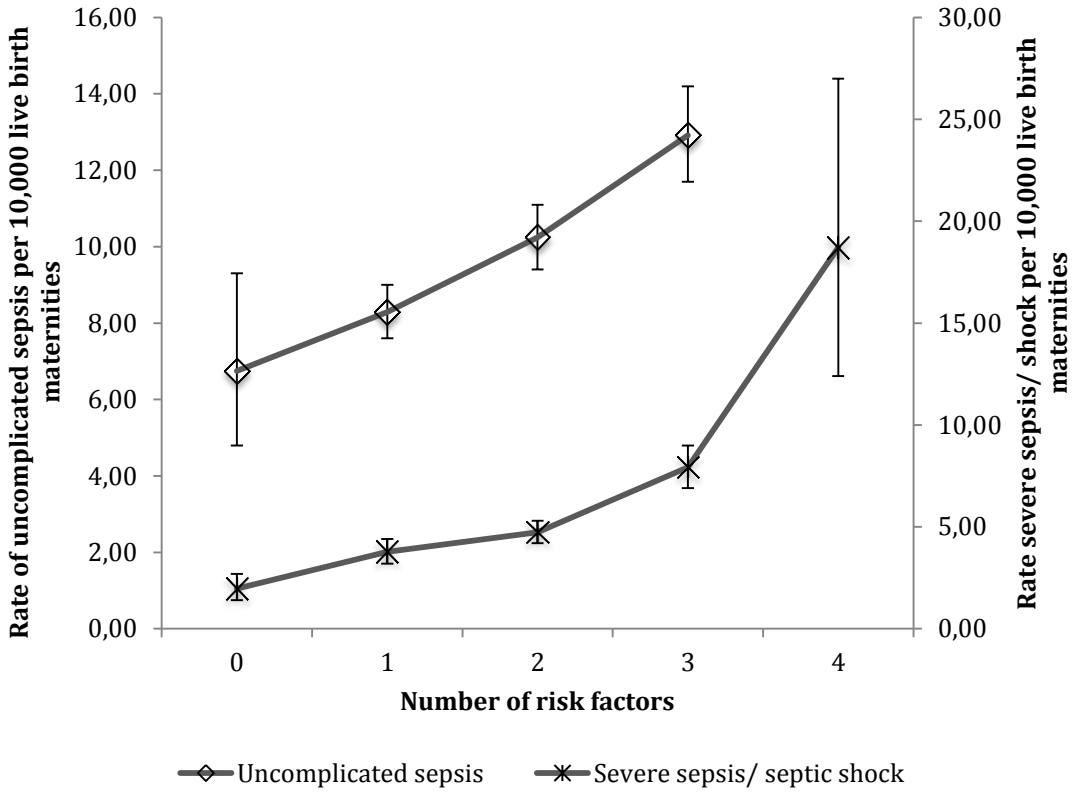


Figure 21. Rate of uncomplicated sepsis and severe sepsis/ septic shock

7.4 Discussion

7.4.1 Summary

At the time this analysis was carried out, this was the first population-based cohort study in the US to examine the incidence and risk factors for developing sepsis as well as progression from uncomplicated to severe sepsis. The rate of severe sepsis was more than twice the previously estimated national rate (Callaghan et al., 2008), and significant socioeconomic disparities exist amongst women who develop sepsis compared to those who do not. In addition to known clinical risk factors including primiparity and multiple gestation pregnancy, having public or no health insurance, being of a racial or ethnic minority, giving birth in hospitals with low hospital birth volume, having diabetes and chronic hypertension were all identified as playing a role in the risk of progression from uncomplicated to severe sepsis/septic shock, and that the risks associated with these factors are significantly cumulative.

7.4.2 Incidence

Callaghan and colleagues, in their study of severe morbidity during delivery hospitalisations in the US from 1991-2003 using the National Hospital Discharge Survey, found that the rate of all severe morbidity was 5.1 per 1,000 deliveries, of which sepsis accounted for 4.1% (Callaghan et al., 2008); this extrapolates to a severe sepsis rate of 2.1 per 10,000 deliveries (20.9 per 100,000 deliveries). Using identical severity criteria, the rate of all severe sepsis including septic shock in California from 2005 to 2007 was 4.7 per 10,000 live birth maternities. Factors that may explain this significantly higher estimate are that this study utilised population-based cohort data as opposed to sample data, and in addition to the ICD-9-CM code for septicaemia, included ICD-9-CM codes for sepsis, severe sepsis and septic shock; in the California data the additional sepsis codes accounted for 12.3% of severe cases. However, even without these cases included, and taking into account all live births and the 0.6% national rate of stillbirths (American Congress of Obstetricians and Gynecologists, 2009) (included in the 'deliveries' denominator), the severe sepsis rate from the present study would be approximately 100% higher than the national estimate. An alternative explanation is that these results indicate an increase in the rate of severe sepsis in the obstetric population. It is not clear whether there has been an increase in California specifically due to the lack of previous sepsis studies, however there has nevertheless been a significant increase in the overall rate of severe maternal morbidity (Lyndon et al., 2012) and maternal death in California (California Department of Public Health, 2011), indicating a likely increase in the rate of severe sepsis morbidity as well. Additionally, national rates of hospitalisation for sepsis have more than doubled since 2000 (M. J. Hall et al., 2011), which is consistent with the findings of the analysis presented here.

7.4.3 Risk factors

7.4.3.1 Socioeconomic status

In assessing risk factors and after adjustment, women with public or no health insurance had a 22% increased odds of developing uncomplicated sepsis which did not progress compared to the general obstetric population, and a further 52% increased odds of progressing to severe sepsis compared to women with uncomplicated sepsis. Health insurance status was also the only *a priori* factor to be significantly evident throughout the continuum of severity. This finding is consistent with morbidity studies in the US that have demonstrated a relationship between under-insurance and poorer health outcomes compared to individuals who are privately insured (Vitale et al., 2005). It has been postulated that this trend might be underpinned by poorer general health associated with lower socioeconomic status. However, considering that half of the California obstetric population had either public or no insurance, and that the association with sepsis was significant after controlling for demographics, clinical factors and co-morbidities, it appears that other factors such as access to care, delay in recognition or treatment of infection may play a role. Additionally, more than half of the population of cases had a low level of education and had a 63% increased odds of developing sepsis compared to women with a higher education. The mechanism of this risk factor is unclear, however it is likely tied to similar socioeconomic issues as that of low level of insurance.

7.4.3.2 Racial and ethnic disparity

In addition to public or no health insurance, ethnic and racial minority groups were at significantly higher risk of progression to severe sepsis. Women of Black, Asian and Hispanic groups all had increased odds compared to White and non-Hispanic groups,

with Black women having more than twice the odds of progression to severe sepsis. This finding is consistent with the distressing disparity observed in other studies of severe morbidity and mortality rates amongst Black mothers in California and the US in general (Miniño et al., 2011; California Department of Public Health, 2011; M. J. Tucker et al., 2007; Bryant et al., 2010). Bryant et al found that medical care and social circumstances were the strongest risk factors for maternal mortality amongst Black women (Bryant et al., 2010; Main, 2010). When considering severe infection and sepsis specifically, the prevalence of sickle cell disease amongst Black women resulting in poor splenic function and higher incidence of anaemia and infection may also be a contributing factor (Cantwell et al., 2011). However these factors do not explain the increased risk to other racial and minority groups who have not been found to be at increased risk of death (California Department of Public Health, 2011) after controlling for health insurance coverage, entry into prenatal care, and other clinical factors.

7.4.3.3 Hospital volume

Women delivering in low volume hospitals had 93% greater odds of progressing to severe sepsis compared to women delivering in high volume hospitals. Consistent with other morbidity studies (Lyndon et al., 2012; Birkmeyer et al., 2002), it has been suggested that resource limitations combined with insufficient time for transfer to a higher level of care may underlie this trend. Considering that low volume was highly correlated with low population density (indicating rural areas) in this study, and that sepsis can quickly progress in severity, this is a possible explanation.

7.4.3.4 Diabetes

Women with diabetes are at increased risk of death from maternal sepsis (Cantwell et al., 2011), however their risk of severe sepsis morbidity had not been quantified before at the population level. Diabetic women had 47% increased odds of progressing from uncomplicated sepsis to severe sepsis compared to septic women without diabetes. This result is in keeping with previous findings that diabetic compared to non-diabetic women are at increased risk of infection during pregnancy and postpartum (Stamler et al., 1990; Takoudes et al., 2004) as are all diabetics in general.

7.4.3.5 Preeclampsia

The association between preeclampsia and certain types of infection, particularly urinary tract infection, has been well established, however the mechanism of the association in still unclear (Conde-Agudelo et al., 2008). Several studies suggest that infection plays a key role in initiation of preeclampsia via uteroplacental atherosis or ischaemia (Conde-Agudelo et al., 2008) with subsequent up-regulation of antiangiogenic factors resulting in hypertension and other clinical signs of preeclampsia (Young et al., 2010), or by enhancing the systemic inflammatory response leading to a similar pathway (Herrera et al., 2001; Dadelszen & Magee, 2002). Results of this study indicate a strong association between the inflammatory process of sepsis and preeclampsia although the temporal relationship between the two could not be established. Over 21% of all women with severe sepsis in this cohort also had preeclampsia, and women with severe sepsis had a 372% increased odds of preeclampsia compared to women without severe sepsis. These results reflect a similar distribution as the study in North Scotland (Acosta et al., 2012).

7.4.3.6 Chronic hypertension

Interestingly, chronic (pre-existing) hypertension, independent of preeclampsia, was found to be a strong risk factor for progression to severe sepsis (aOR=8.61). Chronic hypertension had not been identified as a risk factor for maternal sepsis in previous studies. The association found in the present study may be attributed to the significant increase in chronic hypertension in the obstetric population (Kuklina, Ayala, et al., 2009a), although the prevalence was still very low. Unlike preeclampsia, it was clear that chronic hypertension was an *a priori* condition and thus preceded the development of sepsis. Although sparsely described for the obstetric population, the pathogenesis of severe sepsis and septic shock can differ between normotensive and hypertensive women (Schmidt & Mandel, 2012). A sign of severe sepsis is hypoperfusion which is marked by hypotension, however women with chronic hypertension may develop critical hypoperfusion at a higher blood pressure, and therefore earlier, than normotensive women (Schmidt & Mandel, 2012). This puts them at greater risk for failure of clinical staff to recognise the severity of their condition.

7.4.4 Agreement with previous studies

Established risk factors for developing sepsis supported by this study include older maternal age and caesarean section (Kramer et al., 2009; Maharaj, 2007). Given that prophylactic antibiotics should have been in general use during the study period, it is possible that a proportion of women undergoing a caesarean section may have had an infection prior to delivery, although there was also a strong association between caesarean section and wound complication indicating postoperative infection as well. Changes in recommendations for the timing of prophylactic antibiotic administration to pre-incision, as apposed to intraoperative, were recomended in 2010 by the American

Congress of Obstetricians and Gynaecologists (ACOG); this is the standard practice in non-obstetric surgery as it has been demonstrated to reduce the rate of postoperative infection (The American College of Obstetricians Gynecologists, 2010). Primiparity, multiple births and postpartum haemorrhage were all associated with progression to severe sepsis and have also been identified as risk factors for severe sepsis in previous studies (Kramer et al., 2009; Waterstone et al., 2001).

7.4.5 Strengths and limitations

Major strengths of this study were its size and comprehensiveness. The large study size, including the entire birth population of California, minimised the risk of selection biases that exist amongst smaller hospital-based studies. In addition, linked data provided insights into possible risk factors that would not normally be captured in routine databases. Results should be considered in light of several limitations. First, data used in this study are subject to possible inaccuracies inherent in administrative datasets. Although it was impossible to audit potential misclassification, it is likely that the large sample size mitigates random errors, whilst adjustment for hospital clustering would have accounted for systematic reporting errors at the hospital level. We used management criteria to additionally define severe sepsis; some misclassification may thus have been introduced if these women had additional morbidity to account for the presence of these codes. Additionally, given the size of the dataset, random noise in the data would not have had a significant effect and would have been adjusted for by the robust standard errors.

As body mass index was only available for one year, it was not possible to adjust for the potential confounding effect of obesity (Acosta et al., 2012), particularly with regards to

diabetes and hypertension. Additionally, it was not possible to assess the temporality of factors such as mode of delivery and acute comorbidities with respect to sepsis. There was also insufficient power to exclude the role of chance in the association between maternal age ≥35 and mode of delivery with the odds of progression to severe sepsis. It was not possible to determine from these data whether women progressed to severe sepsis whilst hospitalised for delivery, or if they presented with an advanced infection or sepsis before delivery. This temporality issue is key to understanding whether underlying differences in health status, or access (including language barriers) and quality of care are determinant factors in progression to severe sepsis. Lastly, elements such as Hispanic ethnicity may not be representative of the wider US population.

7.5 Conclusion

This study analysis was undertaken in order to ascertain whether the rate of severe maternal sepsis is also increasing in other countries with advanced healthcare systems, and to explore whether the risk factors are comparable to those found in the UK. From this study, and three additional studies from the USA published in the same year (discussed in Chapter 2, Part 2), it can be concluded that rates of severe maternal sepsis are increasing the USA. Several risk factors corresponded to those found in the UK, such as low socioeconomic status and mode of delivery. Additionally, this study identified further clinical risk factors that were not possible to confirm in other studies due to smaller sample sizes, such as diabetes and hypertension, and risk factors for progression from uncomplicated to severe sepsis. Findings from this study have important implications for strategies that could be implemented to prevent maternal deaths from severe sepsis.

Chapter 8

Discussion and conclusion

8.1 What was done in this research

The aim of this research was to advance the understanding of the epidemiology of severe maternal sepsis, in order to inform strategies to improve outcomes for mothers and their babies. In order to address this aim, the research was first put into current context through a review of maternal sepsis mortality in the UK and other countries. In addition, a structured review of the current literature on severe maternal morbidity from sepsis was carried out. Those reviews were then used to inform the research questions for four population-based epidemiological studies of maternal sepsis. The first was a study of uncomplicated sepsis and severe maternal sepsis in the North NHS region of Scotland (Aberdeen) over a 23-year period using a case-control design. The second was a study of the incidence, risk factors, causative organisms, sources of infection and outcomes for women with severe maternal sepsis in the UK using a national case-control design. The third was a study of women with severe maternal sepsis in the first 24 hours of critical care unit admission in the UK using a national cohort design. And the last was a study of women with uncomplicated sepsis and severe maternal sepsis who delivered in the state of California, USA over a three-year period using a cohort design, which enabled exploration of the risk factors for progression from uncomplicated to severe sepsis.

8.2 Why this research was undertaken

In the UK the incidence of maternal sepsis mortality has nearly tripled over the last two decades (Cantwell et al., 2011), and was the leading cause of direct maternal death in 2006-2008. Although it is clear that maternal death as a result of sepsis is rare, even small increases are likely to represent an increase in serious morbidity, the cases for

which are more numerous. In countries that have relatively low maternal mortality rates, identification of risk factors for severe morbidity is critical to target points of intervention before progression to more serious outcomes. The risk factors for severe maternal sepsis identified in the UK, however, have been inconsistent, most likely due to the scarcity of population-based studies. A challenge to synthesising an accurate picture of the burden of severe maternal sepsis and the contributing risk factors in the UK has been the limitations in study population sizes with geographical and data availability differences. Added to this are variations in case definitions, and subsequent inconsistent conclusions.

8.3 What was known before embarking on this research

8.3.1 Consistent level of evidence

Before embarking on this research, there was only a partial picture of the burden of maternal sepsis in the UK and related epidemiological determinants. Due to the accuracy and consistency of the UK Confidential Enquiries into Maternal Deaths, there was good evidence showing that, in stark contrast to the steep and steady decline in overall maternal mortality in the latter part of the twentieth century, the rate of maternal death from genital tract sepsis began to increase in the mid 1980s. Since causative organisms are recorded by the Confidential Enquiries, there was also good evidence showing an increase in Group A *streptococcus* as a major causative organism in maternal genital tract sepsis deaths. The increased incidence of maternal sepsis deaths also corresponded to an increase in overall population mortality due to group A *streptococcus*.

From clinical accounts in both high and low resource countries and epidemiological literature, there were several studies reporting that various factors were associated with maternal sepsis. However the temporality of these factors in relation to sepsis was unknown. Therefore only partial evidence of their role as true risk factors existed. This was also an issue in the Aberdeen, ICNARC and California datasets in the present research (Chapters 4, 6, and 7).

8.3.2 Partial evidence

Caesarean section and particularly emergency caesarean section was the most definitively known factor associated with infectious morbidity at the start of this research (Smaill & Gyte, 2010; Lucas et al., 2012). However, no study had been able to estimate the risk of sepsis associated with caesarean section taking into account the temporality of the association i.e. whether the caesarean section was a cause or consequence of the sepsis, and controlling for illness prior to delivery. An infection can occur after a caesarean section for example from a wound infection; or if the woman had a caesarean section as a result of antepartum infectious morbidity; or if the woman had a caesarean section after labouring as in the example of prolonged or obstructed labour, which increases the risk for infection due to prolonged rupture of membranes. Clearly, a study (UKOSS) controlling for these factors was necessary in order to understand the independent role of caesarean section as a risk factor for sepsis and vice versa.

Other frequently cited risk factors were: prolonged rupture of membranes, retained products of conception, early labour, multiple vaginal examinations, and anaemia. Although intuitive as risk factors, the actual evidence for this was inconsistent,

particularly in reports from countries with advanced healthcare systems (Maharaj, 2007; Royal College of Obstetricians and Gynaecologists, 2006; Lucas et al., 2012). This was largely because of the reasons discussed above, such as small sample sizes, data availability differences, and differences in cases definitions. It should be noted that risk factors cited in current guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) are based on those factors identified in the Confidential Enquiries into Maternal Deaths (Royal College of Obstetricians and Gynaecologists, 2012a; Royal College of Obstetricians and Gynaecologists, 2012b). Although it should be noted that evidence for these factors is also inconsistent due to the (fortunately) small number of maternal deaths due to sepsis and the general lack of comparator data in a confidential enquiry.

The epidemiological determinants contributing to the increasing trend in maternal mortality from sepsis were also unclear. One possible determinant identified at the start of this research was the increasing rate of invasive streptococcal disease in the general population. In particular the rate of group A *streptococcus*, which is generally accepted to be the causative pathogen of historical epidemics of maternal sepsis, had increased. Other interrelated determinants include increased travel and population movement that may have contributed to circulation of pathogens and shifting strains of group A *streptococcus*. Other possible determinants were the increasing rates of invasive delivery including caesarean section and operative vaginal delivery, as well as increasing rates of obesity, which is a known risk factor for maternal morbidity and when associated with diabetes increases susceptibility to infection.

8.3.3 Key information gaps

At the start of this research there were key information gaps in the understanding of severe maternal sepsis. These gaps were an understanding of the following at the UK national population level:

1. The incidence of severe maternal sepsis;
2. The risk factors for severe maternal sepsis;
3. The main causative organisms;
4. How severe maternal sepsis is managed;
5. The outcomes of severe sepsis;
6. The factors that are associated with poor outcomes; and
7. If this trend is similarly occurring in other countries and risk factors associated with progression to severe sepsis.

8.4 What was learned during the course of this research

8.4.1 Incidence of severe maternal sepsis morbidity and mortality

Before this research was undertaken, the only other population-based study of severe obstetric morbidity in the UK was by Waterstone and colleagues (Waterstone et al., 2001). Waterstone et al estimated the incidence of severe maternal sepsis as 4.0 (95% CI 2.0-6.0) per 10,000 deliveries. This study, however, had been conducted over a decade ago in 1997-1998. From the UKOSS study (Chapter 5), the incidence of severe maternal sepsis was estimated as 4.7 (95% CI 4.2-5.2) per 10,000 maternities although the increase in incidence was not statistically significant. The increase in incidence of severe morbidity since the Waterstone et al study corresponds with the increase in

maternal deaths from sepsis since the late 1990s. From the ICNARC study of intensive care unit admissions with severe sepsis (Chapter 6), the extrapolated incidence of maternal critical care admission with severe sepsis was 4.1 (95% CI 2.9-5.6) per 10,000 maternities. Lastly, it was found that the incidence of maternal death from 'all-cause' maternal sepsis was substantially higher than genital tract sepsis alone from 2008-2010 (1.8 (95% CI 1.1-2.8) per 100,000 vs. 1.1 (95% CI 0.8–1.7) per 100,000 maternities) (Cantwell et al., 2011; J. Hall et al., 2005).

8.4.2 Risk factors for severe maternal sepsis identified in this research

Before this research was undertaken, there had been no national population-based study of the risk factors associated with severe maternal sepsis in the UK. It must be noted, however, that in the study in northern Scotland, the size of the severe sepsis group was very small. Thus, results of the adjusted analysis for severe sepsis could only be interpreted as exploratory. And because in the ICNARC study only aggregated data for the comparison of risk factors were available, adjustment for other possible confounding factors could not be carried out. Conclusions regarding the risk factors for severe maternal sepsis identified over the course of this research are, therefore, best drawn from the UKOSS study. Agreement with the other studies and the previous UK regional study (Waterstone et al., 2001) are indicated in parentheses in Table 29.

Table 29. Risk factors and effect sizes for severe maternal sepsis identified in this research.

Risk factor	Effect size aOR (95% CI)
Black or other minority ethnic status (agreement with Waterstone et al., 2001)	1.8 (1.3-2.5)
Primiparity	1.6 (1.2-2.2)
Pre-existing medical problems*	1.4 (1.01-1.9)
Febrile illness or antibiotics in the 2 weeks before delivery	12.1 (8.1-18.0)
Operative vaginal delivery (agreement with Northern Scotland study)	2.5 (1.3-4.7)
Pre-labour caesarean section	3.8 (2.2-6.6)
Caesarean after the onset of labour (agreement with Waterstone et al., 2001)	8.1 (4.7-14.0)

All caesarean section was also found to be a risk factor in Northern Scotland and ICNARC studies.

* Major pre-existing medical problems include: asthma, endocrine disorders, haematological disorders, mental health/ psychiatric disorders, and renal disorders.

** Identified as risk factors for septic shock

After controlling for illness before delivery, all forms of operative delivery (operative vaginal, pre-labour caesarean section, and caesarean after the onset of labour) were significant risk factors for severe sepsis. Importantly, it was also clear that risk factors were significantly cumulative. This finding was supported by the analysis of the California data. Black or minority ethnic status, primiparity, caesarean section and operative vaginal delivery are all common in the UK; which has important implications in light of the finding that the odds of severe sepsis increases with the increasing number of risk factors by up to nearly eight-fold in the presence of four or more.

8.4.3 Main sources of infection and causative organisms

Conventionally, the focus in relation to maternal sepsis has been on genital tract sepsis, however, this inevitably excludes a substantial number of cases of sepsis. It is well established that pregnant and peripartum women are more susceptible to infection, particularly respiratory infection (Poulakou et al., 2012), however before this research was undertaken, there was no estimate of the total burden or associated risk factors for 'all cause' sepsis in the UK obstetric population. An understanding of this epidemiology, however, has important implications particularly for general practice and front-line clinical care. Many women likely initially present in these settings, however the severity or the rapidity with which an infection could progress to severe sepsis may be unrecognised by clinical staff, particularly in cases of non-genital-tract infections that are not immediately related to labour and delivery.

As with incidence and population-level risk factors, before this research was undertaken there had been no other study elucidating the distribution of causative organisms for all causes of severe maternal sepsis in the UK. In the UKOSS study amongst all women with severe maternal sepsis, the largest proportion of cases was due to genital tract infection (31.0%). Had the focus of study only been on genital tract sepsis, two-thirds of the total cases would have been missed. Similarly, in the ICNARC study genital-tract sepsis accounted for only 24% of cases, whilst respiratory tract sepsis accounted for 40%.

In the UKOSS study, the most common organism causing infection was *Escherichia coli* (*E. coli*) (21.1%) followed by group A *streptococcus* (8.8%) (Table 30). Although it was not possible to identify what organisms may have been the cause of the respiratory

sepsis cases in the ICNARC study, two likely candidates are *Streptococcus pneumoniae* and group A *streptococcus*, given the noted recent increase in community acquired respiratory infections caused by these organisms in the UK (Bauer et al., 2013; Zakikhany et al., 2011).

Table 30. Source of infection and causative organism in women with severe sepsis in the UK from the UKOSS and ICNARC studies.

	All maternity unit severe sepsis cases in the UK (UKOSS) n (%)	Critical care unit severe maternal sepsis cases in the UK (ICNARC)* n (%)
Source of infection		
Genital tract	113 (31.0)	55 (21.5)
Urinary tract	72 (19.7)	31 (12.1)
Wound	33 (9.0)	9 (3.5)
Respiratory	20 (5.5)	102 (39.8)
Other	32 (8.8)	38 (14.8)
Unknown	95 (26.0)	21 (8.2)
Organism		
Escherichia coli	77 (21.1)	
Group A streptococcus	32 (8.8)	
Group B streptococcus	30 (8.2)	
Other streptococcus	21 (5.7)	
Staphylococcus	23 (6.3)	
Mixed organisms	19 (5.2)	
Other	25 (6.9)	
Unknown	6 (1.6)	
No laboratory confirmed infection	132 (36.2)	

*Actual (not extrapolated) figures

8.4.4 Management of severe maternal sepsis

As identified in the UKOSS study, 78% of women with severe maternal sepsis were admitted to level-two or level three critical care. It was also found in this study that 42% of women had a febrile illness or were taking antibiotics prior to presentation, which

suggests that at least a proportion were not adequately diagnosed and managed in the early stages of infection; a failure to recognise the severity of illness and deterioration was a common theme in the last UK Confidential Enquiry into Maternal Deaths. Additionally, in the ICNARC study it was found that 40% of women admitted to critical care with severe sepsis had pneumonia/respiratory infection as the source of sepsis. This suggests that important opportunities for recognising severe respiratory tract infection in pregnant and peripartum women are being missed. Implications of these findings for management and clinical practice are further discussed in section 8.7.

8.4.5 Outcomes of severe sepsis

In the Scottish regional study severe sepsis accounted for approximately 14% of all maternal sepsis cases. However, previous literature indicates that this may be an underestimate. In the only multinational study of maternal sepsis morbidity in western and northern Europe (Mothers Mortality and Severe Morbidity (MOMS) study (Modder & Fitzsimons, 2010; Zhang et al., 2005)) it was found that the incidence of all maternal sepsis was 8.0 (95% CI 7.0-9.0) per 10,000 deliveries. Taking into account the overall increase in sepsis rates since the mid 1990s when the study was conducted, a severe sepsis incidence rate in the UK of 4.7 (95% CI 4.2-5.2) per 10,000 maternities would indicate that approximately 50% of all sepsis cases are severe. This estimate is supported by the US data in which severe sepsis accounted for nearly 50% of all sepsis cases.

From the UKOSS study it was found that of all severe sepsis cases in the UK, approximately 20% of women progress to septic shock and 1.4% (95% CI 0.4-3.2) of women die (0.64 (0.21-1.5) per 100,000 maternities). Comparison of UKOSS mortality

rates with those from the UK Confidential Enquiries into Maternal Deaths (1.1 (95% CI 0.8–1.7) per 100,000 maternities) and the ICNARC study (1.8 (95% CI 1.1-2.8) per 100,000 maternities) suggest that this may be an underestimate. However it must be noted that the UKOSS estimate was based on one year of data and therefore has wider confidence intervals. Furthermore, as all of the confidence intervals overlap and the differences are therefore not statistically significant, the next Confidential Enquiries report will be critical for determining whether the maternal mortality rate from sepsis has decreased since 2006-2008.

8.4.6 Factors associated with poor outcomes

Although the UK Confidential Enquiry into Maternal Deaths are more comprehensive in describing why women die of sepsis, it is not possible to measure an effect size of potential risk factors identified due to the lack of a comparison population. Therefore, the UKOSS study and the ICNARC study specifically investigated risk factors associated with septic shock and maternal sepsis mortality, respectively. The distributions of the population characteristics (age, parity, BMI, multiple pregnancy and mode of delivery) did not differ significantly between the ICNARC and UKOSS case populations, indicating that the two data collection systems sampled from the same population and that neither sample was likely to be a biased sub-section of the overall case population. Results from the respective studies, therefore, are likely to be generalizable to the entire UK and thus risk factors for poor outcomes of sepsis (septic shock or maternal death) identified in both studies are listed in Table 31.

Table 31. Risk factors for poor outcomes (septic shock or death) from maternal sepsis.

Risk factor	Effect size aOR (95% CI)
Multiple pregnancy (UKOSS study)	5.8 (1.5-21.5)
Infection with Group A streptococcus (UKOSS study)	4.8 (2.2-10.8)
Deprivation (ICNARC study with partial agreement from the UKOSS study)	2.6 (1.03-6.7)
Obesity (ICNARC study with agreement from the Scottish study)	6.3 (1.5-27.0)
Respiratory organ system dysfunction (ICNARC study)	8.1 (1.8-36.0)
Haematological organ system dysfunction (ICNARC study)	5.7 (2.0-16.0)

8.4.7 Comparison with other country settings

From literature that was published during the time of this research as well as the California cohort study, it is clear that the incidence of maternal mortality and severe morbidity from sepsis have similarly increased in the USA. Risk factors identified in the California study that support findings from the UK are listed in Table 32.

Table 32. Agreement of risk factors for severe maternal sepsis from the California study.

Risk factor	Effect size aOR (95% CI)
Black or other minority ethnic group (Bauer et al., 2013)	2.1 (1.3-2.3)
Low socioeconomic status (public or no health insurance) (Bauer et al., 2013)	1.5 (1.2-1.9)
Primiparity	2.0 (1.6-2.6)
Multiple pregnancy (Bauer et al., 2013)	3.5 (2.1-5.9)
Diabetes	1.5 (1.04-2.1)

Primary and repeat caesarean section were identified as risk factors for uncomplicated sepsis, but were not significant risk factors for the progression to severe sepsis in the California data. Chronic hypertension and delivery in low volume hospitals (<1,000 births per year) were also found to be risk factors. Another California cohort study of all severe morbidity agreed with these findings (Lyndon et al., 2012). However, a national USA study published during this time by Bauer and colleagues (Bauer et al., 2013) did not concur; caesarean section and chronic hypertension were not evaluated in adjusted analyses in that study, and small volume hospitals (used as the reference group) demonstrated decreased risk compared with larger centres. This could possibly indicate regional specificity. The sampling methods used in the Bauer study could also explain lack of agreement in relation to the risk associated with hospital volume. The dataset used in that study was a 20% sample of acute care hospitals in USA. Acute care hospitals are typically larger hospitals in the USA, thus the sample may have excluded a representative number of smaller volume hospitals.

8.5 Contribution to the epidemiological picture of maternal sepsis

With new information gathered during this research and put into context of other recent literature, how has the picture of the causes and consequences of maternal sepsis changed since the beginning of this work? Several gaps in the understanding of severe maternal sepsis have been addressed with regards to incidence and both distal and proximal determinants, allowing a more complete picture of severe maternal sepsis in the UK to be formed. Before this research, there was strong evidence that the rate of maternal mortality from sepsis had increased. It is now clear that compared to the 1990s (Waterstone et al., 2001), the rate of severe morbidity has proportionally increased.

8.5.1 Epidemiological determinants of increasing trends

As discussed in the background, epidemiological investigation can elucidate the risk factors for severe maternal sepsis morbidity and mortality. This in turn can further the understanding of how changes in those risk factors may have precipitated and contribute to the current trends in maternal mortality and severe morbidity from sepsis. Possible determinants include the role of Group A *streptococcus*, and increasing rates of caesarean section (particularly emergency caesarean section), operative vaginal delivery and obesity. In the course of this research, Group A *streptococcus* was specifically identified as a risk factor for septic shock controlling for other factors. Additionally, all forms of caesarean section and operative vaginal delivery were identified as risk factors with a large effect size for severe morbidity after controlling for illness before delivery and other factors. Obesity was also found to be a risk factor for sepsis mortality and for uncomplicated sepsis in the Scottish data controlling for other factors. Interestingly, obesity was not identified as an independent risk factor in the national UKOSS study for

severe sepsis. This could be explained by the fact that different factors were controlled for in the respective studies. Additionally, one might speculate that this may be due to an improvement in obstetric care for obese women, as the rate of obesity has increased amongst the UK obstetric population and guidelines for care introduced as a consequence of the high number of deaths amongst obese women reported by the Confidential Enquiries (Modder & Fitzsimons, 2010). Given that group A streptococcus, all forms of operative delivery and obesity have been found to be patient-level risk factors for severe maternal sepsis (through the course of this research and other studies), it may be likely that increasing rates of these factors in the population have, at least in part, led to the increase in maternal sepsis deaths and severe morbidity in the UK.

8.5.2 Overall risk factors for severe maternal sepsis

Taking into consideration all four studies conducted during this research, the epidemiological determinants discussed in section 8.5.1, the UK Confidential Enquiries into Maternal Deaths, the previous population-based study from the UK (Waterstone et al., 2001) and the recent national population-based study from the USA (Bauer et al., 2013), risk factors can be categorised into: 1) those with consistent evidence and specific to the UK, 2) those identified by the UK Confidential Enquiries into Maternal Deaths and other published population-based studies outside the UK, and 3) additional risk factors that have only been cited by the Confidential Enquiries, but not any other population-based source. This categorisation is shown in Table 33.

Table 33. Risk factors for severe maternal sepsis in the UK according to consistency of evidence.

Risk factor	Effect size aOR (95% CI)	Effect size reference study
Consistent level of evidence supporting a role as a risk factor in the UK*		
Deprivation/ low socioeconomic status**	2.6 (1.03-6.7)	ICNARC
Black or other minority ethnic status	1.8 (1.3-2.5)	UKOSS
Primiparity	1.6 (1.2-2.2)	UKOSS
Obesity	2.4 (1.5-4.0)	Northern Scotland
Anaemia	3.4 (1.9–6.1)	Northern Scotland
Multiple pregnancy**	5.8 (1.5-21.5)	UKOSS
Febrile illness or antibiotics in the 2 weeks before delivery***	12.1 (8.1-18.0)	UKOSS
Pre-labour caesarean section	3.8 (2.2-6.6)	UKOSS
Caesarean after the onset of labour	8.1 (4.7-14.0)	UKOSS
Operative vaginal delivery	2.5 (1.3-4.7)	UKOSS
Infection with Group A streptococcus**	4.8 (2.2-10.8)	UKOSS
Identified by the UK Confidential Enquiries into Maternal Deaths and other sources outside the UK		
Diabetes	1.5 (1.04-2.1)	California
Preterm premature rupture of membranes	2.5 (1.8–3.5)	Bauer et al
Retained products of conception	4.5 (2.8–7.4)	Bauer et al
Cervical cerclage	3.4 (1.8–6.2)	Bauer et al
Impaired immunity/immunosuppressant medication	3.2 (1.3–7.6)	Bauer et al
Only identified by the UK Confidential Enquiry into Maternal Deaths as possible risk factors		
Vaginal discharge	No effect size because no comparison group	
History of pelvic infection		
Amniocentesis and other invasive procedures		

* Risk factor identified in 2 or more population-based studies including the UK Confidential Enquiries into Maternal Deaths

** Effect size is for poor outcome of sepsis

*** Risk factor only identified in the UKOSS study, however with a very large effect size

Note: Additional risk factors identified in only one study were: pre-existing medical problems, respiratory organ system dysfunction, and haematological organ system dysfunction (the latter two were specifically identified as risk factors for maternal mortality).

Risk factors with very large effect sizes for severe maternal sepsis were: if the woman was ill before delivery (had a febrile illness or was taking antibiotics in the two weeks prior to delivery), had a caesarean section after the onset of labour, had a multiple gestation pregnancy, or had retained products of conception. Particularly, women who were ill before delivery had more than 12 times the adjusted odds of severe sepsis compared to women who were not ill; 42% of all women with severe sepsis in the UKOSS study had a febrile illness or were taking antibiotics in the two weeks prior to delivery. The effect size of infection with group A *streptococcus* was also very large; women infected with this organism had nearly 5 times the adjusted odds of progression to septic shock compared to women infected with other organisms. Implications of these findings will be further discussed in section 8.7.

8.5.3 Proximal to distal risk factors

Drawing inferences on causality of associations in epidemiology is controversial (Rothman & Greenland, 2005). Whilst an explanation of the controversy is beyond the scope of this discussion, risk factors identified may be explored in terms of biological plausibility (Hill, 1965). For example, low socioeconomic status would not directly lead to severe sepsis, but might help to facilitate other more proximal risk factors such as poor underlying health or decreased uptake and continuity of maternity care (section 6.5.3). Likewise, obesity itself would not cause sepsis, but might play a role in immunosuppression (section 2.6) or diabetes (section 4.5.3), and thereby further place a woman at risk of infection. Based on analyses and discussion in respective chapters of risk factors with strong evidence of association with severe sepsis in the UK, a conceptual model of how these factors might be ordered in terms of proximity to disease is shown in Figure 22.

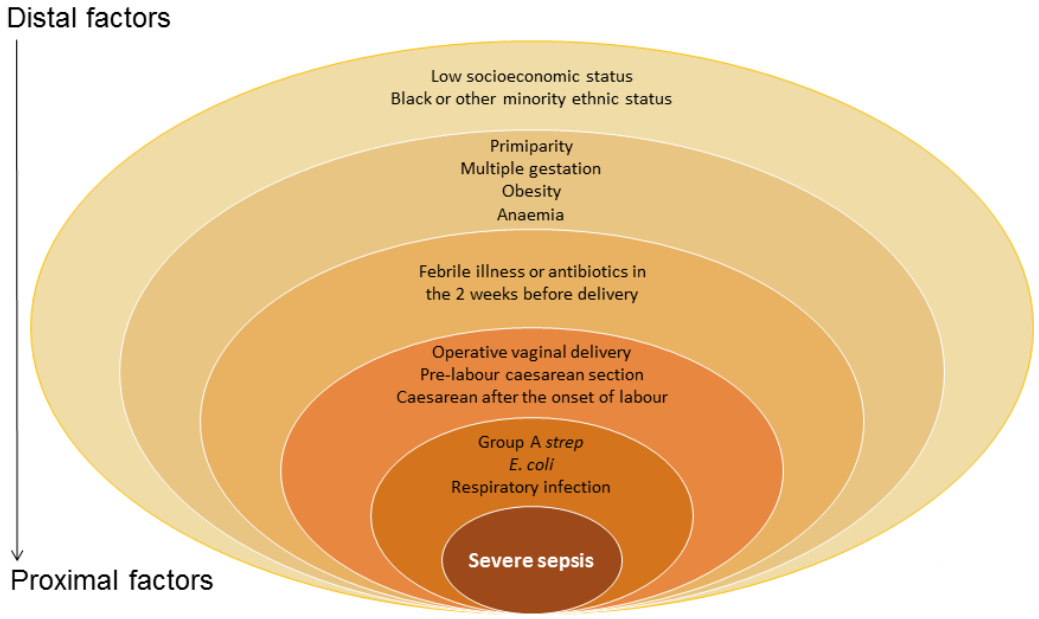


Figure 22. Conceptual model of proximal and distal risk factors associated with severe maternal sepsis in the UK.

8.6 Strengths and limitations of this research

8.6.1 Summary of study strengths and limitations

In the Scottish study, major strengths were that is was population-based using a comprehensive and robust dataset with information on a relatively stable population. From this study it was possible to gain significant insights into the incidence trends over several decades, which was not possible in the other studies. Major limitations were that it was geographically limited to one area of the UK and risk factors identified for severe sepsis could only be interpreted as exploratory due to a very small sample size. In the UKOSS study, major strengths were its robust design capturing information not previously collected in other studies, and participation of 100% of all UK maternity units. Major limitations were the proportion of women without an identified infectious organism, and the likely under-ascertainment of respiratory-sepsis cases. In the

ICNARC study, major strengths were that it utilised comprehensive and nationally representative data on critical care admissions. However lack of available national comparison data precluded multivariable risk modelling for factors associated with severe morbidity. Finally, the major strength of the California cohort study was the size and comprehensiveness of the dataset, which allowed for detailed examination of not only risk factors for sepsis, but also risk factors for progression to severe sepsis. The major limitation was that the study was geographically limited to one state; although California is the most populous state in the USA, factors such as Hispanic ethnicity may not have been representative of the wider USA population. In addition, information about the temporality of serious morbidity as well as mode of delivery in relation to sepsis would have provided extremely insightful information about the causal pathway of sepsis, however routine databases very rarely include this information and was the case in this instance. The Bauer and Callaghan studies of severe sepsis in the USA were similarly not able to assess temporality information using routine data sources (Callaghan et al., 2008; Bauer et al., 2013).

8.6.2 Strengths and limitations of the overall research

At the start of this research scarcity of population-based studies and varying case definitions used in smaller studies led to inconsistent conclusions. Most of the existing studies were hospital-based, and thus subject to inherent biases such as case selection, sociodemographic as well as hospital policy and practice specificities. These issues in combination with differing cases definitions rendered it difficult to draw accurate conclusions about incidence rates and risk factors. It was found over the course of this research that although it was also not possible to use the same case definition

throughout, that the scale and scope of the respective studies greatly mitigated this potential limitation, and additionally allowed further information to be gleaned.

Although it was not possible to link the ICNARC and UKOSS anonymised datasets (the two largest datasets) the overlapping scope of data allowed for the mutual identification of several risk factors such as multiple pregnancy and caesarean section. Where the data did not overlap, further analyses were possible. For example, the estimation of the burden of respiratory tract sepsis and risk factors for maternal sepsis mortality could be carried out using the ICNARC data.

8.6.2.1 Sources of bias

The research presented in this thesis addressed the problem of population representativeness by using national cohorts for the UKOSS and ICNARC studies. Although these two sources of data were the most comprehensive available in the UK, there was not complete population data in either, as indicated in the case ascertainment analysis. This was a result of the limits of the data collection systems. All women in the immediate period of labour and delivery are likely to have been captured by UKOSS, whilst women who had been discharged from maternity units (postpartum cases) or had not yet presented (antepartum cases) would have been captured by ICNARC and not necessarily by UKOSS. Thus there was a risk that both cohorts experienced a degree of selection bias. This would have rendered the respective studies prone to the very problem they aimed to mitigate, that being different conclusions made based on different populations. Complicating this issue was the use of different case definitions.

It was possible, however, to assess the extent of both of these potential selection (ascertainment) biases that were due to (1) differing clinical care settings and (2) differing cases definitions. To address the first, the distributions of case characteristics were compared between the two study cohorts. A lack of significant differences in the majority of characteristics (which collectively differed from the general obstetric/control population) indicated that the case populations, and thus the underlying risk factors, were unlikely to be biased.

Concerning the case definitions, it must be first noted that the two studies had comprehensive case definitions, which utilised clinical criteria. Thus there was little possibility for incorrectly identified cases within the respective national cohorts (maternity units and critical care units). To assess the effect of the different case definitions on the comparability of the findings, a sensitivity analysis was performed on the ICNARC data using the Waterstone SIRS criteria, which were also used in the UKOSS study. The absence of any significant differences in the distribution of sources of infection or risk factors indicated that a change in the clinical SIRS criteria would not have affected the comparability of the findings with those of the UKOSS study. Thus it was concluded that it was not necessary to exclude cases from the ICNARC cohort to meet the more rigorous definition. Statistical power was thus retained. In addition, utilisation of the Waterstone et al SIRS criteria for the UKOSS case definition, allowed for the comparison of results, including incidence rates, with the previous study. Changes in morbidity incidence rates over time could then be accurately assessed. Risk factors could also be compared with the previous study, however the low power of the Waterstone et al study made this comparison unreliable.

Potential non-response bias posed by incomplete reporting in both studies was also considered. In the ICNARC data there was incomplete reporting with about 20% of critical care units in the UK not participating in the CMP, and in the UKOSS data 10% of the data collection forms were not returned. Although it was not possible to audit the characteristics of non-participating units in ICNARC, the database is widely used and previous studies have found the distribution of non-participating units to be random, and the level of critical care unit participation to be representative of the UK (Harrison et al., 2004). In the UKOSS data, missing data collection forms were not found to be clustered from a specific hospital, and therefore appeared to be randomly distributed. Clustered or systematic non-response in either the ICNARC or UKOSS data would introduce a reporting bias (for example if critical care units with particular sociodemographic characteristics did not report). However the apparent random distribution of non-responders, and the relatively low level of non-response particularly in the UKOSS study, indicated that the risk of bias was low.

As with any observational study, there was the possibility of residual confounding since it was not possible to control for all variables that may play a role in the risk of maternal sepsis. Additionally, it is possible that some of the very small effect sizes observed may have been due to residual confounding. However given the comprehensiveness of the data and given that the major plausible confounders were controlled for, residual confounding was unlikely to be a major source of bias, particularly in the UKOSS and California studies.

8.6.2.3 Power issues

In common with any study of a rare outcome, these component analyses are subject to the limitations of small numbers and hence limited study power. This restricts ability to detect interactions as statistically significant.

8.6.2.3 Strengths and limitations conclusion

Collection of data in different clinical care settings may have been the largest limitation of this research. However this lack of consistency arose from the nature of large datasets collected for different purposes; the effect of these differences was measured and found not to significantly affect the comparability of the results. The size and scope of the datasets with higher power than previous studies were in turn the major strength of the research, which also enabled complimentary analyses to be carried out.

8.7 Implications and recommendations for clinical practice

The implications and recommendations from this research are summarised in Table 34.

Table 34. Summary of clinical implications and recommendations

- Infection prior to delivery, even if the woman appears to be well, should be a marker for very close monitoring, and suspicion of group A *streptococcus* should be regarded as an obstetric emergency.
- All modes of operative delivery carry significant risks for severe sepsis, and there is a need for further investigation of a potential role for prophylactic antibiotics at operative vaginal delivery, in addition to on-going initiatives to reduce caesarean delivery rates.
- There is a critical need to improve timely recognition of severe respiratory tract infection, in addition to genital tract infection in the obstetric population; a high index of suspicion amongst general and emergency medical staff must be emphasised.

- Sepsis and severe sepsis progress very rapidly, highlighting the importance of administration of high dose intravenous antibiotics within one hour of admission to hospital or diagnosis for inpatients (Dellinger et al., 2013); initiation of Surviving Sepsis Campaign resuscitation and management bundles should be implemented as soon as severe sepsis in suspected.

- Social disparities in maternal healthcare and utilisation must be addressed by public health policy.

8.7.1 Infection control and recognition of deterioration

Sepsis can progress rapidly along the severity continuum. The implications of the UKOSS study for clinical practice are the need to consider a change of timing of prophylactic antibiotics to administration at time of decision for emergency caesarean section, and to maintain vigilant infection control at vaginal delivery. The study in Scotland also underscored the need for prophylactic antibiotics to be given at caesarean section. The fact that there was much higher antibiotic usage amongst controls that had a caesarean section prior to discharge compared to cases supports the need for antibiotic prophylaxis at caesarean section. There is also a potential role for prophylactic antibiotics at operative vaginal delivery, particularly given the similar findings of the UKOSS and Scottish studies. A randomised clinical trial to investigate whether prophylactic antibiotics offer protection at operative vaginal delivery would answer this question conclusively.

Additionally, given that 42% of severe sepsis cases in the UKOSS study had a febrile illness or were taking antibiotics prior to presentation suggests that there is much room for improvement in maintaining a high index of suspicion for infection in this population, as well as performing adequate follow-up of those women who are diagnosed. Signs of severe sepsis, particularly with confirmed or suspected group A

streptococcal infection, should be regarded as an obstetric emergency and should be routinely included in obstetric emergency training courses. Pneumonia/ respiratory infection was identified as a leading source of severe sepsis irrespective of epidemic influenza periods in the ICNARC study, indicating a critical need to improve timely recognition of severe respiratory tract infection and deterioration, in addition to genital tract infection, in the obstetric population.

8.7.2 Clinical and reporting guidelines

Clinical risk factors such as primiparity, multiple birth, diabetes and caesarean section have been incorporated into obstetric guidelines for sepsis in the UK (Zhang et al., 2005; Waterstone et al., 2001; Royal College of Obstetricians and Gynaecologists, 2012b; Royal College of Obstetricians and Gynaecologists, 2012a), however, there are currently no standardised obstetric clinical guidelines for prevention and management of obstetric sepsis in the USA. Chronic hypertension with possible early unrecognised hypoperfusion, and high risk of preeclampsia must also be considered in obstetric sepsis guidelines.

Obese pregnant women in the UK may benefit from additional monitoring during and after pregnancy to prevent critical infection leading to sepsis. Current Royal College of Obstetricians and Gynaecologists (RCOG) guidelines on the management of women with obesity in pregnancy do not suggest additional monitoring (Modder & Fitzsimons, 2010). Results of the studies presented in this thesis and further research, however, may serve to emphasise the need for routine use of a validated early obstetric warning score (MEOWS) chart, particularly amongst obese and other high-risk women (Zakikhany et

al., 2011; Cantwell et al., 2011), in order to facilitate early detection of any obstetric complication.

Additionally, given that the rate of maternal death from 'all-cause' maternal sepsis was substantially higher than genital tract sepsis alone, evaluating 'all-cause' maternal sepsis in the UK Confidential Enquiries into Maternal Deaths should be considered. In order to maintain comparability with previous data, genital tract sepsis should be evaluated as a sub-category.

8.7.3 Social disparities

The clear social gradient associated with risk of severe sepsis morbidity and mortality found in the ICNARC study raise important questions regarding social disparities in maternal healthcare and utilisation in the UK. Similarly in the California study, socioeconomic (insurance and education levels as well as resource-limited small-volume hospital delivery) and racial disparities associated with the risk of progression to severe sepsis clearly exist and must be addressed at public health policy and patient care levels.

8.7.4 Recommendations for definitions of sepsis severity

Lack of clear definitions for sepsis severity can be potentially hazardous to the obstetric population for whom symptoms of infection are often masked by physiological changes of pregnancy and delivery. Increasing rates of severe sepsis in the obstetric population and the re-emergence of invasive group A streptococcal infection, emphasise the need for standardised obstetric sepsis severity criteria. The risk of dying of sepsis in pregnancy or postpartum increases greatly once organ system dysfunction occurs (aOR

of 8.1 (95% CI 1.8-36.0) for respiratory dysfunction and aOR of 5.7 (95% CI 2.0-16.0) for haematological dysfunction) (Bauer et al., 2013; Cantwell et al., 2011; J. Hall et al., 2005), which is the current non-obstetric definition of 'severe sepsis'. The goal of any clinician is to recognise a deteriorating condition before this point. However, the current definition of sepsis (the classification before severe sepsis) comprises a broad spectrum of illness severity. Two women may both have sepsis per the standard definition of SIRS with the pathological presence of an infection. However, one woman may only be mildly ill, whilst the other woman could be seriously ill with a severe infection on the cusp of organ dysfunction, which could rapidly progress to shock and death. Therefore, defining an extra point on the continuum scale between sepsis and septic shock would be beneficial for preventing a life-threatening situation.

One possibility for a revised obstetric severity model could be:

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1. Systemic Inflammatory Response Syndrome
2. Uncomplicated sepsis – the current definition of sepsis
3. Severe sepsis – modified Systemic Inflammatory Response Syndrome criteria (Bauer et al., 2013; Waterstone et al., 2001) with the presence of infection
4. Critical sepsis – modified Systemic Inflammatory Response Syndrome criteria with the presence of infection and dysfunction in any one organ system
5. Septic shock

Although the level of drug resistance amongst group A *streptococcus* infections has remained relatively low (for now), increasing rates of drug-resistance in other organisms such as *E.coli*, have contributed to the increase in sepsis incidence and severity in the general population and will likely contribute to increasing rates of severe infection and

sepsis in the obstetric population in the future (Martin, 2012; Esper & Martin, 2007; Dombrovskiy et al., 2007; Padkin et al., 2003; Vincent et al., 2006). The definitions for sepsis along the severity continuum are the foundation for guidelines to inform clinical practice. In light of increasing antibiotic resistance, an effort must be made to clarify and improve the definitions of sepsis for the maternal population. A forthcoming study from ICNARC on the patterns of sepsis progression will inform how these definitions may be adapted and improved.

8.8 Future research

The research presented in this thesis highlights several areas for future work.

8.8.1 The maternal immune system

Future research will be needed to understand how factors such as obesity and diabetes, which are immunosuppressive conditions, compound the immuno-modulated state of women during pregnancy and the peripartum period.

8.8.2 Population dynamics of group A *streptococcus*

How strains of group A *streptococcus* have shifted (population dynamics) in recent years will be an interesting area of future research by Public Health England (formerly the Health Protection Agency), which performs molecular serotyping on reported samples of group A *streptococcus*. Populations of the pathogen are thought to cycle every 4-7 years, which explains the traditional periodic peaks in Group A streptococcal infection (Bauer et al., 2013; Waterstone et al., 2001; Lynskey et al., 2011). Unusually however, the current *emm*1 dominant strain in the UK has persisted for more than 25

years, which corresponds with the trend in maternal deaths from Group A *streptococcus.* It will be interesting to see if this strain will shift in the coming years, and if so how that will impact the rates of severe maternal sepsis. Surveillance and collaboration between Public Heath England and other agencies such as the National Perinatal Epidemiology Unit will be needed to monitor this trend.

8.8.3 Predictive models of invasive Group A streptococcal disease

Group A *streptococcus* is a perplexing organism because it can cause a variety of disease manifestations ranging from mild to life-threatening. Some interesting preliminary work has been carried out by the Health Protection Agency working group to model patterns of invasive group A streptococcal infection using less invasive disease patterns (Dennis et al., 2008). This type of predictive forecasting will be a useful tool for issuing rapid guidance to clinical staff about potential periods of heightened infection in the obstetric population.

8.8.4 Rapid antigen diagnostics for Group A *streptococcus* in obstetrics

Whilst culture remains the gold standard for confirmation of group A *streptococcus*, it takes one to two days to obtain results, which is significantly longer than the time course from the first signs of SIRS to septic shock for most women. Future research to assess the efficacy of rapid antigen diagnostic tests for group A *streptococcus* in obstetrics is vital given the rapidity of sepsis progression with this organism.

8.8.5 Inequalities in maternal healthcare in the UK

A clear social gradient associated with risk of severe sepsis morbidity and mortality was found in this research. Further studies to elucidate the social determinants that

potentially play a role in pre and post partum infectious morbidity leading to severe sepsis will be needed in order to redress inequalities in maternal health in the UK.

8.9 Summary and conclusions

Over the course of this research it was found that in addition to the increasing incidence of maternal deaths from sepsis in the UK, the incidence of severe maternal morbidity from sepsis is also increasing. This trend is also evident in the USA. In the UK, the most common sources of infection are the respiratory tract, genital tract and urinary tract. The predominant organisms causing infection are *E. coli*, group A *streptococcus*, with strong circumstantial evidence implicating *Streptococcus pneumonia*. Sepsis progresses very rapidly particularly with group A streptococcal infection, and the majority of women with severe sepsis require admission to critical care. Approximately 20% of women with severe sepsis progress to septic shock and 2-4% of women die (Figure 23).

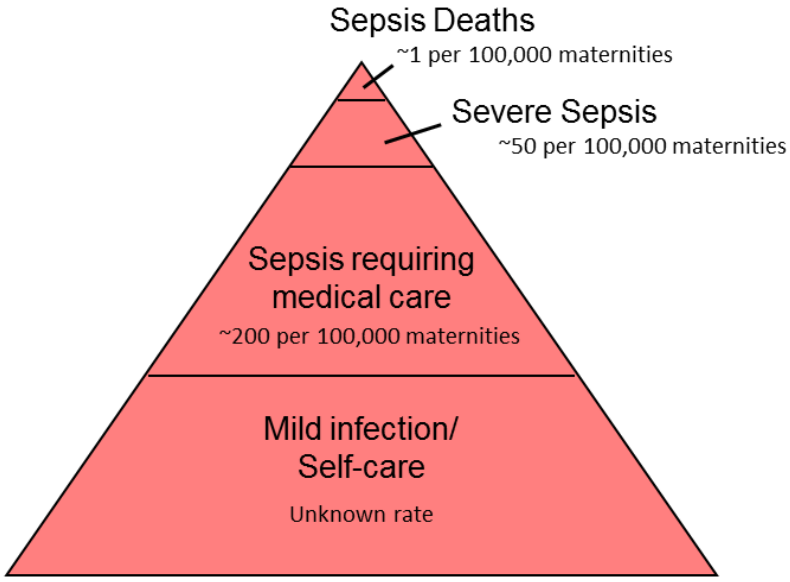

Figure 23. Pyramid of disease from infection and sepsis, and estimated incidence in the UK

Risk factors for severe maternal sepsis in the UK with a large effect size are: febrile illness or antibiotics in the 2 weeks prior to delivery (aOR=12.1), caesarean after the onset of labour (aOR= 8.1), multiple pregnancy (aOR= 5.8), infection with group A *streptococcus* (aOR=4.8 for progression to septic shock), pre-labour caesarean section (aOR= 3.8), low socioeconomic status (aOR=2.6), and operative vaginal delivery (aOR= 2.5). Risk factors are significantly cumulative, which is particularly relevant considering the high population prevalence of several of these factors. Given the identified risk factors, it can be conclude that increasing rates of group A *streptococcus*, all forms of operative delivery and obesity in the obstetric population have, at least in part, led to the increase in maternal deaths and severe morbidity from sepsis.

Sepsis progresses along a spectrum of severity with severe sepsis representing only the tip of the iceberg of the overall magnitude of severe infection in the obstetric population. Evidence from this research suggests that important opportunities for recognising the severity of an infection in pregnant and peripartum women are being missed, thus leading to life-threatening morbidity and in some cases death. It is clear that in light of the trends identified, early recognition and management of sepsis is key to saving mothers' lives.

References

Abouzeid H, Wu P, Mohammed N and Al-Samarrai M (2005) Group A streptococcal puerperal sepsis: the return of a potentially fatal disease. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*. 25 (8), 806–808.

Acosta CD and Knight M (2013) Sepsis and maternal mortality. *Current Opinion in Obstetrics & Gynecology*. 25 (2), 109–116.

Acosta CD, Bhattacharya S, Tuffnell D, Kurinczuk JJ and Knight M (2012) Maternal sepsis: a Scottish population-based case-control study. *BJOG : an international journal of obstetrics and gynaecology*. 119 (4), 474–483.

Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB and Lyndon A (2013) The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. *PloS one*. 8 (7), e67175.

Afessa B, Green B, Delke I and Koch K (2001) Systemic inflammatory response syndrome, organ failure, and outcome in critically ill obstetric patients treated in an ICU. *Chest*. 120 (4), 1271–1277.

Altman DG (1991) *Practical Statistics For Medical Research*. CRC Press

Alves B and Sheikh A (2005) Investigating the relationship between affluence and elective caesarean sections. *BJOG : an international journal of obstetrics and gynaecology*. 112 (7), 994–996.

American Congress of Obstetricians and Gynecologists (2009) ACOG Practice Bulletin No. 102: management of stillbirth. *Obstetrics and gynecology*. 113 (3), 748–761.

Appelboam R, Tilley R and Blackburn J (2010) Time to antibiotics in sepsis. *Critical care (London, England)*. 14 (Suppl 1), 1–1.

Archer KJ and Lemeshow S (2006) Goodness-of-fit test for a logistic regression model fitted using survey sample data. *Stata Journal*.

Astiz ME and Rackow EC (1998) Septic shock. *Lancet*. 351 (9114), 1501–1505.

Aziz RK and Kotb M (2008) Rise and persistence of global M1T1 clone of Streptococcus pyogenes. *Emerging infectious diseases*. 14 (10), 1511–1517.

Balci CC, Sungurtekin HH, Gürses EE and Sungurtekin UU (2004) [APACHE II, APACHE III, SOFA scoring systems, platelet counts and mortality in septic and nonseptic patients]. *Turkish Journal of Trauma and Emergency Surgery*. 11 (1), 29–34.

Barnes R (1865) Lectures on Puerperal Fever. *The Lancet*. 85 (2163).

Barton JR and Sibai BM (2012) Severe sepsis and septic shock in pregnancy. *Obstetrics and gynecology*. 120 (3), 689–706.

Baskett TF and Sternadel J (1998) Maternal intensive care and near-miss mortality in obstetrics. *British journal of obstetrics and gynaecology*. 105 (9), 981–984.

Bauer ME, Bateman BT, Bauer ST, Shanks AM and Mhyre JM (2013) Maternal sepsis mortality and morbidity during hospitalization for delivery: temporal trends and independent associations for severe sepsis. *Anesthesia and analgesia*. 117 (4), 944–950.

Beattie PG, Rings TR, Hunter MF and Lake Y (1994) Risk factors for wound infection following caesarean section. *The Australian & New Zealand journal of obstetrics & gynaecology*. 34 (4), 398–402.

Benhamou D, Chassard D, Mercier FJ and Bouvier-Colle M-H (2009) Le rapport 2003-2005 sur la mortalite maternelle au Royaume-Uni : commentaires et comparaison aux donnees francaises. *Annales Françaises d'Anesthésie et de Réanimation*. 28 (1), 6–6.

Berg CJ, Callaghan WM, Syverson C and Henderson Z (2010) Pregnancy-related mortality in the United States, 1998 to 2005. *Obstetrics and gynecology*. 116 (6), 1302–1309.

Bewley SS and Creighton SBS (1996) 'Near-miss' obstetric enquiry. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*. 17 (1), 26–29.

Bhattacharya S and Campbell DM (2005) The incidence of severe complications of preeclampsia. *Hypertension in pregnancy : official journal of the International Society for the Study of Hypertension in Pregnancy*. 24 (2), 181–190.

Bhattacharya S, Townend J and Bhattacharya S (2010) Recurrent miscarriage: Are three miscarriages one too many? Analysis of a Scottish population-based database of 151,021 pregnancies. *European journal of obstetrics, gynecology, and reproductive biology*. 150 (1), 4–4.

Bianco AT, Smilen SW, Davis Y, Lopez S, Lapinski R and Lockwood CJ (1998) Pregnancy outcome and weight gain recommendations for the morbidly obese woman. *Obstetrics and gynecology*. 91 (1), 97–102.

Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, Welch HG and Wennberg DE (2002) Hospital volume and surgical mortality in the United States. *The New England journal of medicine*. 346 (15), 1128–1137.

Björklund K, Mutyaba T, Nabunya E and Mirembe F (2005) Incidence of postcesarean infections in relation to HIV status in a setting with limited resources. *Acta obstetricia et gynecologica Scandinavica*. 84 (10), 967–971.

Black L-A (2011) *Incidence of Caesarean Sections*. Northern Ireland Assembly

Available at: http://www.niassembly.gov.uk/Documents/RaISe/Publications/2011/Health/14711.pdf.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM and Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. In: 1644–1655.

Bouvier-Colle M-H, Mohangoo AD, Gissler M, Novak-Antolic Z, Vutuc C, Szamotulska K, Zeitlin JEuro-Peristat Scientific Committee (2012) What about the mothers? An analysis of maternal mortality and morbidity in perinatal health surveillance systems in Europe. *BJOG : an international journal of obstetrics and gynaecology*. 119 (7), 880–9– discussion 890.

Bouvier-Colle M-H, Saucedo MM and Deneux-Tharaux CC (2011) [The confidential enquiries into maternal deaths, 1996-2006 in France: what consequences for the obstetrical care?]. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction*. 40 (2), 87–102.

Bouvier-Colle MH, Salanave B and Ancel PY (1996) Obstetric patients treated in intensive care units and maternal mortality. *European journal of obstetrics, gynecology, and reproductive biology*.

Bozza FA and Salluh JI (2010) An urban perspective on sepsis in developing countries. *The Lancet infectious diseases*. 10 (5), 290–291.

Brace V, Penney G and Hall M (2004) Quantifying severe maternal morbidity: a Scottish population study. *BJOG : an international journal of obstetrics and gynaecology*. 111 (5), 481–484.

Bryant AS, Worjoloh A, Caughey AB and Washington AE (2010) Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *American journal of obstetrics and gynecology*. 202 (4), 9–9.

Burke C (2009) Perinatal sepsis. *The Journal of perinatal & neonatal nursing*. 23 (1), 42–51.

California Department of Public Health (2011) *The California Pregnancy-Associated Mortality Review: Report from 2002 and 2003 Maternal Death Reviews*. Sacramento: California Department of Public Health, Maternal Child and Adolescent Health Division Available at: http://www.cdph.ca.gov/data/statistics/Pages/CaliforniaPregnancy-AssociatedMortalityReview.aspx.

Callaghan WM, Creanga AA and Kuklina EV (2012) Severe maternal morbidity among delivery and postpartum hospitalizations in the United States. *Obstetrics and gynecology*. 120 (5), 1029–1036.

Callaghan WM, Mackay AP and Berg CJ (2008) Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991-2003. *American*

journal of obstetrics and gynecology. 199 (2), 133.e1–8.

Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J and Springett A (2011) Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG : an international journal of obstetrics and gynaecology*. 118 Suppl 1, 1–203.

Carapetis JR, Steer AC, Mulholland EK and Weber M (2005) The global burden of group A streptococcal diseases. *The Lancet infectious diseases*. 5 (11), 10–10.

Central Statistics Office ed. (2012) *Census 2011 This is Ireland (Part 1)*. Central Statistics Office Available at: http://www.cso.ie/en/census/index.html (accessed 16/08/12).

Churchill F (1849) *Essays on the Puerperal Fever and Other Diseases Peculiar to Women*. Sydenham Society

Conde-Agudelo A, Villar J and Lindheimer M (2008) Maternal infection and risk of preeclampsia: Systematic review and metaanalysis. *American journal of obstetrics and gynecology*. 198 (1), 16–16.

Confidential Enquiry into Maternal and Child Health CEMACH (2008) *Saving mothers' lives: reviewing maternal deaths to make motherhood safer - 2003-2005 : the seventh report of the Confidential Enquiries into Maternal Deaths in the United Kingdom*. G. Lewis ed. London: CEMACH

Cross S, Bell JS and Graham WJ (2010) What you count is what you target: the implications of maternal death classification for tracking progress towards reducing maternal mortality in developing countries. *Bulletin of the World Health Organization*. 88 (2), 147–153.

Dadelszen von P and Magee LA (2002) Could an infectious trigger explain the differential maternal response to the shared placental pathology of preeclampsia and normotensive intrauterine growth restriction? *Acta obstetricia et gynecologica Scandinavica*. 81 (7), 642–648.

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent J-L, Moreno RSurviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive care medicine*. 39 (2), 165–228.

Deneux-Tharaux C, Berg C, Bouvier-Colle M-H, Gissler M, Harper M, Nannini A, Alexander S, Wildman K, Breart G and Buekens P (2005) Underreporting of pregnancy-related mortality in the United States and Europe. *Obstetrics and*

gynecology. 106 (4), 684–692.

Dennis JN, Lamagni T, Smith GE, Elliot AJ, Loveridge P and George R (2008) Use of primary care syndromic data to forecast rises in invasive group A streptococcal disease. In: Warwick.

Department of Reproductive Health and Research (2008) *Maternal Mortality in 2005*. World Health Organization ed. WHO, UNICEF, UNFPA and The World Bank

Desjardins C, Diallo HO, Audet-Lapointe P and Harel F (1996) [Retrospective study of post-cesarean endometritis. 1992-1993, Notre-Dame Hospital, Montreal, Canada]. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction*. 25 (4), 419–423.

Doherty DA, Magann EF, Francis J, Morrison JC and Newnham JP (2006) Pre-pregnancy body mass index and pregnancy outcomes. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 95 (3), 242–247.

Dombrovskiy VY, Martin AA, Sunderram J and Paz HL (2007) Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Critical care medicine*. 35 (5), 1244–1250.

Donati S, Senatore S and Ronconi A (2011) Maternal mortality in Italy: a record-linkage study. *BJOG : an international journal of obstetrics and gynaecology*. 118 (7), 872–879.

Edwards LE, Dickes WF, Alton IR and Hakanson EY (1978) Pregnancy in the massively obese: course, outcome, and obesity prognosis of the infant. *American journal of obstetrics and gynecology*. 131 (5), 479–483.

Egerter S, Braveman P and Marchi K (2002) Timing of insurance coverage and use of prenatal care among low-income women. *American journal of public health*. 92 (3), 423–427.

Ehrenberg, Dierker, MilluzziMercer (2002) Prevalence of maternal obesity in an urban center. *American journal of obstetrics and gynecology*. 187 (5), 5–5.

Esper A and Martin GS (2007) Is severe sepsis increasing in incidence AND severity? *Critical care medicine*. 35 (5), 1414–1415.

Fernández-Pérez ER, Salman S, Pendem S and Farmer JC (2005) Sepsis during pregnancy. *Critical care medicine*. 33 (10 Suppl), S286–93.

Fund IM (2005) *World Economic Outlook*. International Monetary Fund

Geller SE, Rosenberg D, Cox SM, Brown ML, Simonson L, Driscoll CA and Kilpatrick SJ (2004) The continuum of maternal morbidity and mortality: factors associated with severity. *American journal of obstetrics and gynecology*. 191 (3), 939–944.

General Register Office for Scotland ed. (2013) *Vital Events Reference Tables 2011* Available at: http://www.gro-scotland.gov.uk/statistics/theme/vital-

events/general/ref-tables/2011/section-3-births.html (accessed 19/02/13).

Gibbs RS (1980) Clinical risk factors for puerperal infection. *Obstetrics and gynecology*. 55 (5 Suppl), 178S–184S.

Girard F, Burlet G, Bayoumeu F, Fresson J, Bouvier-Colle MH and Boutroy JL (2001) [Severe complications of pregnancy and delivery: the situation in Lorraine based on the European investigation]. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction*. 30 (6 Suppl), S10–7.

Gissler M, Kauppila R, Meriläinen J, Toukomaa H and Hemminki E (1997) Pregnancy-associated deaths in Finland 1987-1994--definition problems and benefits of record linkage. *Acta obstetricia et gynecologica Scandinavica*. 76 (7), 651–657.

Giuliani AA, Tamussino KK, Basver AA, Haas JJ and Petru EE (2002) The impact of body mass index and weight gain during pregnancy on puerperal complications after spontaneous vaginal delivery. *Wiener klinische Wochenschrift*. 114 (10-11), 383–386.

Gordon A (1975) Alexander Gordon (1795) on epidemic Puerperal disease. *Bulletin of the New York Academy of Medicine*.

Great Britain General Register Office (1839) *First (-eighty Second) Annual Report of the Registrar-General of Births, Deaths and Marriages in England (England and Wales).*

Hall J, Schmidt G and Wood L (2005) *Principles of Critical Care, Third Edition*. McGraw Hill Professional

Hall MJ, Williams SN, DeFrances CJ and Golosinskiy A (2011) Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS data brief*. (62), 1–8.

Hamilton BE, Martin JA and Ventura SJ (2013) Births: Preliminary Data for 2012 Division of Vital Statistics ed. *National Vital Statistics Reports*. 62. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_03.pdf.

Harrison DA, Brady AR and Rowan K (2004) Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit & Research Centre Case Mix Programme Database. *Critical care (London, England)*. 8 (2), R99–111.

Harrison DA, Parry GJ, Carpenter JR, Short A and Rowan K (2007) A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. *Critical care medicine*. 35 (4), 1091–1098.

Harrison DA, Welch CA and Eddleston JM (2006) The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Critical care (London, England)*. 10 (2), R42.

Health Protection Agency (2012) *Pyogenic and non-pyogenic streptococcal*

bacteraemia, England, Wales and Northern Ireland: Health Protection Report [Serial Online]. London: Health Protection Agency (HPA) Available at: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1214892073558.

Health Protection Agency, Group A Streptococcus Working Group (2004) Interim UK guidelines for management of close community contacts of invasive group A streptococcal disease. In: 354–361.

Hemingway H, Saunders D and Parsons L (1997) Social class, spoken language and pattern of care as determinants of continuity of carer in maternity services in east London. *Journal of public health medicine*. 19 (2), 156–161.

Herrchen B, Gould JB and Nesbitt TS (1997) Vital statistics linked birth/infant death and hospital discharge record linkage for epidemiological studies. *Computers and biomedical research, an international journal*. 30 (4), 290–305.

Herrera JA, Chaudhuri G and López-Jaramillo P (2001) Is infection a major risk factor for preeclampsia? *Medical hypotheses*. 57 (3), 393–397.

Heslehurst N, Ells LJ, Simpson H, Batterham A, Wilkinson J and Summerbell CD (2007) Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. *BJOG : an international journal of obstetrics and gynaecology*. 114 (2), 187–194.

Higgins JPT and Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons

Hill AB (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*.

Ho BCH, Bellomo R, McGain F, Jones D, Naka T, Wan L and Braitberg G (2006) The incidence and outcome of septic shock patients in the absence of early-goal directed therapy. *Critical care (London, England)*. 10 (3), R80.

Holmes OW (1855) *Puerperal Fever, as a Private Pestilence*. Boston: Ticknor and Fields

Holmes OW (1843) The contagiousness of puerperal fever. *New England Quarterly Journal of Medical Surgery*. 1, 1503–530. 530.

Hospital Episode Statistics ed. (2012) *Hospital Episode Statistics: Maternity data*. HES Available at: http://www.hesonline.nhs.uk/ (accessed 16/08/12).

Humes K, Jones NA, Ramirez RR and Bureau USC (2011) *Overview of Race and Hispanic Origin, 2010*. US Census Bureau

Humphrey T and Tucker JS (2009) Rising rates of obstetric interventions: exploring the determinants of induction of labour. *Zeitschrift fuer Gesundheitswissenschaften/Journal of Public Health*. 31 (1), 88–94.

Hussein J, Mavalankar DV, Sharma S and D'Ambruoso L (2011) A review of health

system infection control measures in developing countries: what can be learned to reduce maternal mortality. *Globalization and health*. 7, 14.

Huttunen R and Syrjänen J (2010) Obesity and the outcome of infection. *The Lancet infectious diseases*. 10 (7), 442–443.

Huttunen R and Syrjänen J (2012) Obesity and the risk and outcome of infection. *International journal of obesity (2005)*.

Information Services Division ed. (2012) *Maternity and Births*. ISD Scotland Available at: http://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/data-tables.asp (accessed 08/12).

Jaro MA (1995) Probabilistic linkage of large public health data files. *Statistics in medicine*. 14 (5-7), 491–498.

Johnson SR, Kolberg BH, Varner MW and Railsback LD (1987) Maternal obesity and pregnancy. *Surgery, gynecology & obstetrics*. 164 (5), 431–437.

Kanagalingam MG, Forouhi NG, Greer IA and Sattar N (2005) Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. *BJOG : an international journal of obstetrics and gynaecology*. 112 (10), 1431–1433.

Karlsson EA and Beck MA (2010) The burden of obesity on infectious disease. *Experimental biology and medicine (Maywood, N.J.)*. 235 (12), 1412–1424.

Khan KS, Wojdyla D, Say L, Gülmezoglu AM and Van Look PFA (2006) WHO analysis of causes of maternal death: a systematic review. *Lancet*. 367 (9516), 1066–1074.

Killian CA, Graffunder EM, Vinciguerra TJ and Venezia RA (2001) Risk factors for surgical-site infections following cesarean section. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America*. 22 (10), 613–617.

Kilpatrick SJ and Matthay MA (1992) Obstetric patients requiring critical care. A five-year review. *Chest*. 101 (5), 1407–1412.

Kinasewitz GT, Yan SB, Basson B, Comp P, Russell JA, Cariou A, Um SL, Utterback B, Laterre P-F, Dhainaut J-FPROWESS Sepsis Study Group (2004) Universal changes in biomarkers of coagulation and inflammation occur in patients with severe sepsis, regardless of causative micro-organism [ISRCTN74215569]. *Critical care (London, England)*. 8 (2), R82–90.

King H (2004) *Health in Antiquity*. London and New York: Routledge

Knaus WA, Draper EA, Wagner DP and Zimmerman JE (1985) APACHE II: a severity of disease classification system. *Critical care medicine*. 13 (10), 818–829.

Knight M, Kurinczuk JJ, Spark P, Brocklehurst P and System UOS (2010) Extreme obesity in pregnancy in the United Kingdom. *Obstetrics and gynecology*. 115 (5),

989–997.

Knight M, Kurinczuk JJ, Tuffnell D and Brocklehurst P (2005) The UK Obstetric Surveillance System for rare disorders of pregnancy. *BJOG : an international journal of obstetrics and gynaecology*. 112 (3), 263–265.

Kotelchuck M (1994) An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. *American journal of public health (New York, N.Y. : 1912)*. 84 (9), 1414–1420.

Kramer HMC, Schutte JM, Zwart JJ, Schuitemaker NWE, Steegers EAP and van Roosmalen J (2009) Maternal mortality and severe morbidity from sepsis in the Netherlands. *Acta obstetricia et gynecologica Scandinavica*. 88 (6), 647–653.

Kuczmarski RJ, Flegal KM, Campbell SM and Johnson CL (1994) Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA : the journal of the American Medical Association*. 272 (3), 205–211.

Kuklina EV, Ayala C and Callaghan WM (2009a) Hypertensive disorders and severe obstetric morbidity in the United States. *Obstetrics and gynecology*. 113 (6), 1299–1306.

Kuklina EV, Meikle SF, Jamieson DJ, Whiteman MK, Barfield WD, Hillis SD and Posner SF (2009b) Severe obstetric morbidity in the United States: 1998-2005. *Obstetrics and gynecology*. 113 (2 Pt 1), 293–299.

LaCroix P (2003) *Science and Literature in the Middle Ages and the Renaissance*. University Press of the Pacific

Lamagni TL, Efstratiou A, Dennis J, Nair P, Kearney J, George Rnational incident management team (2009) Increase in invasive group A streptococcal infections in England, Wales and Northern Ireland, 2008-9. *Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin*. 14 (5), –.

Lamagni TL, Efstratiou A, Vuopio-Varkila J, Jasir A, Schalén CStrep-EURO (2005) The epidemiology of severe Streptococcus pyogenes associated disease in Europe. *Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin*. 10 (9), 179–184.

Lapinsky SE, Kruczynski K and Seaward GR (1997) Critical care management of the obstetric patient. *Canadian journal of anaesthesia = Journal canadien d'anesthésie*.

Leth RA, Møller JK, Thomsen RW, Uldbjerg N and Nørgaard M (2009) Risk of selected postpartum infections after cesarean section compared with vaginal birth: a five-year cohort study of 32,468 women. *Acta obstetricia et gynecologica Scandinavica*. 88 (9), 976–983.

Leung NY, Lau AC, Chan KK and Yan WW (2010) Clinical characteristics and outcomes of obstetric patients admitted to the Intensive Care Unit: a 10-year retrospective review. *Hong Kong medical journal = Xianggang yi xue za zhi / Hong*

Kong Academy of Medicine. 16 (1), 18–25.

Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, Vincent J-L, Townsend S, Lemeshow S and Dellinger RP (2012) Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. *The Lancet infectious diseases*. 12 (12), 919–924.

Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC and Campaign SS (2010) The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Critical care medicine*. 38 (2), 367–374.

Lewinsohn G, Herman A, Leonov Y and Klinowski E (1994) Critically ill obstetrical patients: outcome and predictability. *Critical care medicine*. 22 (9), 1412–1414.

Lindeboom GA (1969) Europe's Teacher.(Book Reviews: Herman Boerhaave. The Man and His Work). *Science*.

Liu SS, Heaman MM, Joseph KSK, Liston RMR, Huang LL, Sauve RR and Kramer MSM (2005) Risk of maternal postpartum readmission associated with mode of delivery. *Obstetrics and gynecology*. 105 (4), 836–842.

Long JS and Freese J (2006) *Regression models for categorical dependent variables using Stata*. Stata Press

Loudon I (1986) Deaths in childbed from the eighteenth century to 1935. *Medical history*. 30 (1), 1–41.

Loudon I (2000) *The Tragedy of Childbed Fever* (1st edition). Oxford University Press, USA

Lu GC, Rouse DJ, DuBard M, Cliver S, Kimberlin D and Hauth JC (2001) The effect of the increasing prevalence of maternal obesity on perinatal morbidity. *American journal of obstetrics and gynecology*. 185 (4), 845–849.

Luca-Harari B, Darenberg J, Neal S, Siljander T, Strakova L, Tanna A, Creti R, Ekelund K, Koliou M, Tassios PT, van der Linden M, Straut M, Vuopio-Varkila J, Bouvet A, Efstratiou A, Schalén C, Henriques-Normark B, Strep-EURO Study Group and Jasir A (2009) Clinical and microbiological characteristics of severe Streptococcus pyogenes disease in Europe. *Journal of clinical microbiology*. 47 (4), 1155–1165.

Luca-Harari B, Ekelund K, van der Linden M, Staum-Kaltoft M, Hammerum AM and Jasir A (2008) Clinical and epidemiological aspects of invasive Streptococcus pyogenes infections in Denmark during 2003 and 2004. *Journal of clinical microbiology*. 46 (1), 79–86.

Lucas DN, Robinson PN and Nel MR (2012) Sepsis in obstetrics and the role of the anaesthetist. *International journal of obstetric anesthesia*. 21 (1), 56–67.

Lydon-Rochelle M, Holt VL, Martin DP and Easterling TR (2000) Association Between Method of Delivery and Maternal Rehospitalization. *JAMA : the journal of the*

American Medical Association. 283 (18), 2411–2416.

Lyndon A, Lee HC, Gilbert WM, Gould JB and Lee KA (2012) Maternal morbidity during childbirth hospitalization in California. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*.

Lynskey NNN, Lawrenson RAR and Sriskandan SS (2011) New understandings in Streptococcus pyogenes. *Current opinion in infectious diseases*. 24 (3), 196–202.

Mabie WC and Sibai BM (1990) Treatment in an obstetric intensive care unit. *American journal of obstetrics and gynecology*. 162 (1), 1–4.

Macfarlane A (2004) Confidential Enquiries into Maternal Deaths: developments and trends from 1952 onwards. In: *Why Mothers Die 2000-2002, The Sixth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom*. London: CEMACH. Available at: http://www.hqip.org.uk/assets/NCAPOP-Library/CMACE-Reports/33.-2004-Why-Mothers-Die-2000-2002-The-Sixth-Report-of-the-Confidential-Enquiries-into-Maternal-Deaths-in-the-UK.pdf.

Macfarlane A, Mugford M, Henderson JE, Furtado A, Stevenson JS and Dunn A (1984) *Birth Counts*. Stationery Office

Magann EF, Evans S, Hutchinson M, Collins R, Lanneau G and Morrison JC (2005) Postpartum hemorrhage after cesarean delivery: an analysis of risk factors. *Southern medical journal*. 98 (7), 681–685.

Magann EF, Washburne JF, Harris RL, Bass JD, Duff WP and Morrison JC (1995) Infectious morbidity, operative blood loss, and length of the operative procedure after cesarean delivery by method of placental removal and site of uterine repair. *Journal of the American College of Surgeons*. 181 (6), 517–520.

Maharaj D (2007) Puerperal pyrexia: a review. Part I. *Obstetrical & gynecological survey*. 62 (6), 393–399.

Mahutte NG, Murphy-Kaulbeck L, Le Q, Solomon J, Benjamin A and Boyd ME (1999) Obstetric admissions to the intensive care unit. *Obstetrics and gynecology*. 94 (2), 263–266.

Main EK (2010) Maternal mortality: new strategies for measurement and prevention. *Current Opinion in Obstetrics & Gynecology*. 22 (6), 511–516.

Marmot M and Bell R (2012) Fair society, healthy lives. *Public health*. 126 Suppl 1, S4–S10.

Martens MG, Kolrud BL, Faro S, Maccato M and Hammill H (1995) Development of wound infection or separation after cesarean delivery. Prospective evaluation of 2,431 cases. *The Journal of reproductive medicine*. 40 (3), 171–175.

Martin GS (2012) Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. *Expert review of anti-infective therapy*. 10 (6), 701–706.

Martin GS, Mannino DM, Eaton S and Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. *The New England journal of medicine*. 348 (16), 1546–1554.

Mason KLK and Aronoff DMD (2012) Postpartum group a Streptococcus sepsis and maternal immunology. *American journal of reproductive immunology (New York, N.Y. : 1989)*. 67 (2), 91–100.

McLennan D, Barnes H, Noble M, Davies J, Garratt E, Social Disadvantage Research CentreOxford Institute of Social Policy, University of Oxford (2011) *The English Indices of Deprivation 2010*. Department for Communities and Local Government Available at: http://www.communities.gov.uk/documents/statistics/pdf/1870718.pdf.

Meigs CD (1854) On the nature, signs, and treatment of childbed fevers: in a series of letters addressed to his class.

Miniño AM, Murphy SL and Xu J (2011) Deaths: final data for 2008. *National Vital Statistics Reports*.

Modder J and Fitzsimons KJ (2010) CMACE/RCOG Joint Guideline: Management of women with obesity in Pregnancy CMACERoyal College of Obstetricians and Gynaecologists eds.

Mor G and Cardenas I (2010) The immune system in pregnancy: a unique complexity. *American journal of reproductive immunology (New York, N.Y. : 1989)*. 63 (6), 425–433.

Mor G, Cardenas I, Abrahams V and Guller S (2011) Inflammation and pregnancy: the role of the immune system at the implantation site. *Annals of the New York Academy of Sciences*. 1221, 80–87.

Morens DM, Taubenberger JK and Fauci AS (2008) Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *The Journal of infectious diseases*. 198 (7), 962–970.

Morgan GA, Leech NL, Gloeckner GW and Barrett KC (2011) IBM SPSS for introductory statistics: Use and interpretation.

Murphy DJ and Charlett P (2002) Cohort study of near-miss maternal mortality and subsequent reproductive outcome. *European journal of obstetrics, gynecology, and reproductive biology*. 102 (2), 173–178.

Murphy DJD, Liebling RER, Verity LL, Swingler RR and Patel RR (2001) Early maternal and neonatal morbidity associated with operative delivery in second stage of labour: a cohort study. *Lancet*. 358 (9289), 5–5.

Musgrove PP (1993) Investing in health: the 1993 World Development Report of the World Bank. *Bulletin of the Pan American Health Organization*. 27 (3), 284–286.

National Committee for the Confidential Enquiries into Maternal Deaths (2012) *Saving Mothers 2008-2010: Fifth Report on Confidential Enquiries into Maternal Deaths*

in South Africa. R. Pattinson ed. National Department of Health Available at: http://www.health.gov.za/docs/reports/2012/savingmothersshort.pdf.

National Institute for Clinical Health Excellence (2011) *Caesarean Section Guideline update*. Royal College of Obstetricians and Gynaecologists (RCOG) Available at: http://www.nice.org.uk/nicemedia/live/13620/57162/57162.pdf.

National Perinatal Epidemiology Unit (NPEU) ed. (2014) *UK Obstetric Surveillance System (UKOSS)* Available at: https://www.npeu.ox.ac.uk/ukoss (accessed 01/14).

Nave H, Beutel G and Kielstein JT (2011) Obesity-related immunodeficiency in patients with pandemic influenza H1N1. *The Lancet infectious diseases*. 11 (1), 14–15.

Northern Ireland Statistics and Research Agency ed. (2012a) *Births* Available at: http://www.nisra.gov.uk/demography/default.asp8.htm (accessed 16/08/12).

Northern Ireland Statistics and Research Agency ed. (2012b) *Census 2001 Results*. NISRA Available at: http://www.nisra.gov.uk/Census/agreement.html (accessed 16/08/12b).

Office for National Statistics ed. (2012) *Maternities*. Office for National Statistics Available at: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Maternities (accessed 01/02/12).

Office for National Statistics ed. (2013) *Migration statistics*. Office for National Statistics Available at: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Migration (accessed 11/04/13).

Olsen MA, Butler AM, Willers DM, Devkota P, Gross GA and Fraser VJ (2008) Risk factors for surgical site infection after low transverse cesarean section. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America*. 29 (6), 477–84– discussion 485–6.

Padkin A, Goldfrad C, Brady AR and Young D (2003) Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Critical Care Medicine*. 31 (9), 2332–2338.

Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA and Parrillo JE (1984) Profound but reversible myocardial depression in patients with septic shock. *Annals of internal medicine*. 100 (4), 483–490.

Paruk F (2008) Infection in obstetric critical care. *Best practice & research. Clinical obstetrics & gynaecology*. 22 (5), 865–883.

Patterson MJ (1996) Streptococcus. In: S. Baron ed. *Medical Microbiology*. Galveston: University of Texas Medical Branch at Galveston. Available at: http://www.ncbi.nlm.nih.gov/books/NBK7611/.

Pattinson RC and Hall M (2003) Near misses: a useful adjunct to maternal death enquiries. *British medical bulletin*. 67, 231–243.

Pattinson RC ed. (2011) *Saving Mothers 2005-2007: Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa*. National Committee for the Confidential Enquiries into Maternal Deaths Available at: http://www.doh.gov.za/docs/reports/2011/saving_b.pdf.

Poulakou G, Pérez M and Rello J (2012) Severe acute respiratory infections in the postpandemic era of H1N1. *Current opinion in critical care*.

Public Health Wales ed. (2013) *Influenza* Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgId=457&pid=27522 (accessed 04/11/13).

Quah TC, Chiu JW, Tan KH, Yeo SW and Tan HM (2001) Obstetric admissions to the intensive therapy unit of a tertiary care institution. *Annals of the Academy of Medicine, Singapore*. 30 (3), 250–253.

Radcliffe W (1989) *Milestones in Midwifery; And, The Secret Instrument (The Birth of the Midwifery Forceps)*. San Francisco: Norman Publishing

Robinson HE, O'Connell CM, Joseph KS and McLeod NL (2005) Maternal outcomes in pregnancies complicated by obesity. *Obstetrics and gynecology*. 106 (6), 1357–1364.

Ronsmans C and Graham WJ (2006) Maternal mortality: who, when, where, and why. *Lancet*. 368 (9542), 1189–1200.

Rothman KJ and Greenland S (2005) Causation and causal inference in epidemiology. *American journal of public health*. 95 Suppl 1, S144–50.

Royal College of Obstetricians and Gynaecologists (2012a) *Bacterial Sepsis Following Pregnancy: Green-top Guideline No. 64b*. London: RCOG Available at: http://www.rcog.org.uk/files/rcog-corp/11.6.12GTG64b.pdf.

Royal College of Obstetricians and Gynaecologists (2012b) *Bacterial Sepsis in Pregnancy: Green-top Guideline No. 64a*. London: RCOG Available at: http://www.rcog.org.uk/files/rcog-corp/25.4.12GTG64a.pdf.

Royal College of Obstetricians and Gynaecologists (2011) *Maternal Collapse in Pregnancy and the Puerperium: Green-top guideline No. 56*. RCOG ed. London: RCOG Available at: http://www.rcog.org.uk/files/rcog-corp/GTG56.pdf.

Royal College of Obstetricians and Gynaecologists (2006) *Preterm Prelabour Rupture of Membranes: Green-top guideline No.44*. London: RCOG Available at: http://www.rcog.org.uk/womens-health/clinical-guidance/preterm-prelabour-rupture-membranes-green-top-44.

Royal College of Physicians ed. (2013) *History of the RCP*. Royal College of Physicians Available at: http://www.rcplondon.ac.uk/about/history (accessed 02/13).

Royston P, Ambler G and Sauerbrei W (1999) The use of fractional polynomials to model continuous risk variables in epidemiology. *International journal of epidemiology*. 28 (5), 964–974.

Scaber J, Saeed S, Ihekweazu C and Efstratiou A (2011) Group A streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England. *Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin*.

Scarpinato L and Gerber D (1995) Critically ill obstetrical patients: outcome and predictability. *Critical care medicine*. 23 (8), 1449–1451.

Schmidt GA and Mandel J (2012) Management of severe sepsis and septic shock in adults. In: D. S. Basow ed. *UpToDate*. Waltham, MA: UpToDate.

Schuitemaker N, van Roosmalen J, Dekker G, van Dongen P, van Geijn H and Gravenhorst JB (1998) Increased maternal mortality in The Netherlands from group A streptococcal infections. *European journal of obstetrics, gynecology, and reproductive biology*. 76 (1), 61–64.

Schutte JM, Steegers EAP, Schuitemaker NWE, Santema JG, de Boer K, Pel M, Vermeulen G, Visser W, van Roosmalen JNetherlands Maternal Mortality Committee (2010) Rise in maternal mortality in the Netherlands. *BJOG : an international journal of obstetrics and gynaecology*. 117 (4), 399–406.

Scotland N (2010) *Scottish Confidential Audit of Severe Maternal Morbidity*. 6th Annual Report. Edinburgh. NHS QIS Available at: http://www.healthcareimprovementscotland.org/programmes/reproductive,_maternal__child/programme_resources/scasmm.aspx.

Scottish Board of Health, Kinloch JP, Smith J and Stephen JA (1928) *Maternal mortality. Report on maternal mortality in Aberdeen, 1918-1927, with special reference to puerperal sepsis.*

Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, Regan L and Robinson S (2001) Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*. 25 (8), 1175–1182.

Secondary Care Directorate (2012) *A Strategy for Maternal Care in Northern Ireland 2012-2018*. Department of Health, Social Services and Public Safety Available at: http://www.dhsspsni.gov.uk/maternitystrategy.pdf.

Senior K (2012) In the dark about sepsis. *The Lancet infectious diseases*. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1473309912702335.

Shorter E (2012) Ignaz Semmelweis: The etiology, concept, and prophylaxis of childbed fever. *Medical history*. 28 (03), 334.

Silver RM, Landon MB, Rouse DJ, Leveno KJ, Spong CY, Thom EA, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai B, Langer O, Thorp JM, Ramin SM, Mercer BMNational Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (2006) Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstetrics and gynecology*. 107 (6), 1226–1232.

Smaill FMF and Gyte GMG (2010) Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. *Cochrane database of systematic reviews*. (1), CD007482–CD007482.

Smith R (2010) *Travel Trends*. Office for National Statistics ed. Office for National Statistics Available at: http://www.ons.gov.uk/ons/about-ons/get-involved/taking-part-in-a-survey/information-for-households/a-to-z-of-household-and-individual-surveys/international-passenger-survey/index.html.

Snyder CC, Barton JR, Habli M and Sibai BM (2013) Severe sepsis and septic shock in pregnancy: indications for delivery and maternal and perinatal outcomes. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*. 26 (5), 503–506.

Sriskandan S (2011) Severe peripartum sepsis. *The journal of the Royal College of Physicians of Edinburgh*. 41 (4), 339–346.

Sriskandarajah D, Cooley L and Kornblatt T (2007) Britain's Immigrants: An economic profile. *London: Institute for Public Policy Research*.

Stamler EF, Cruz ML, Mimouni F, Rosenn B, Siddiqi T, Khoury J and Miodovnik M (1990) High infectious morbidity in pregnant women with insulin-dependent diabetes: an understated complication. *American journal of obstetrics and gynecology*. 163 (4 Pt 1), 1217–1221.

StatsWales ed. (2012) *Method of Delivery*. StatsWales Available at: http://www.statswales.wales.gov.uk/TableViewer/tableView.aspx?ReportId=2021 (accessed 22/07/12).

Sullivan EA, Hall B and King JF (2008) Maternal deaths in Australia 2003-2005. *AIHW National Perinatal Statistics Unit*, 1–51. Available at: http://www.preru.unsw.edu.au/PRERUWeb.nsf/resources/MD3/$file/md3a.pdf.

Takoudes TC, Weitzen S, Slocum J and Malee M (2004) Risk of cesarean wound complications in diabetic gestations. *American journal of obstetrics and gynecology*. 191 (3), 958–963.

Technical working group (1992) *The prevention and management of puerperal infections.* World Health Organization ed. Geneva: WHO Available at: http://whqlibdoc.who.int/hq/1995/WHO_FHE_MSM_95.4.pdf.

The American College of Obstetricians Gynecologists (2010) Committee opinion no. 465: antimicrobial prophylaxis for cesarean delivery: timing of administration. *Obstetrics and gynecology*. 116 (3), 791–792.

Thomas J (2006) Rates of cesarean delivery in developing countries suggest unequal access. *International Family Planning Perspectives*. 32 (2), 105.

Timezguid N, Das V, Hamdi A, Ciroldi M, Sfoggia-Besserat D, Chelha R, Obadia E and Pallot J-L (2011) Maternal sepsis during pregnancy or the postpartum period requiring intensive care admission. *International journal of obstetric anesthesia*. 21

(1), 51–55.

Tucker MJ, Berg CJ, Callaghan WM and Hsia J (2007) The Black-White disparity in pregnancy-related mortality from 5 conditions: differences in prevalence and case-fatality rates. *American journal of public health (New York, N.Y. : 1912)*. 97 (2), 247–251.

Turner LA, Cyr M, Kinch RA, Liston R, Kramer MS, Fair M and Heaman M (2002) Under-reporting of maternal mortality in Canada: a question of definition. *Chronic Diseases in Canada*. 23 (1), 22–30.

University of Aberdeen, ed. (2014) *Aberdeen Maternity Neonatal Databank* Available at: http://www.abdn.ac.uk/amnd/ (accessed 01/02/14).

Usha Kiran TS, Hemmadi S, Bethel J and Evans J (2005) Outcome of pregnancy in a woman with an increased body mass index. *BJOG : an international journal of obstetrics and gynaecology*. 112 (6), 768–772.

van Dillen J, Zwart J, Schutte J and van Roosmalen J (2010) Maternal sepsis: epidemiology, etiology and outcome. *Current opinion in infectious diseases*. 23 (3), 249–254.

Vincent J-L, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart KEPIC II Group of Investigators (2009) International study of the prevalence and outcomes of infection in intensive care units. *JAMA : the journal of the American Medical Association*. 302 (21), 2323–2329.

Vincent J-L, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall J-R, Payen DSepsis Occurrence in Acutely Ill Patients Investigators (2006) Sepsis in European intensive care units: results of the SOAP study. *Critical care medicine*. 34 (2), 344–353.

Vincent JL, Suter P, Bihari D and Bruining H (1997) Organization of intensive care units in Europe: lessons from the EPIC study. *Intensive care medicine*. 23 (11), 1181–1184.

Vitale MA, Arons RR, Hyman JE, Skaggs DL, Roye DP and Vitale MG (2005) The contribution of hospital volume, payer status, and other factors on the surgical outcomes of scoliosis patients: a review of 3,606 cases in the State of California. *Journal of pediatric orthopedics*. 25 (3), 393–399.

Wanderer JP, Leffert LR, Mhyre JM, Kuklina EV, Callaghan WM and Bateman BT (2013) Epidemiology of obstetric-related ICU admissions in Maryland: 1999-2008*. *Critical care medicine*. 41 (8), 1844–1852.

Wang CPY, Tan WC, Kanagalingam D and Tan HK (2013) Why we do caesars: a comparison of the trends in caesarean section delivery over a decade. *Annals of the Academy of Medicine, Singapore*. 42 (8), 408–412.

Waterstone M, Bewley S and Wolfe C (2001) Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ (Clinical research ed.)*. 322 (7294),

1089–93– discussion 1093–4.

Watts DH, Krohn MA, Hillier SL and Eschenbach DA (1990) Bacterial vaginosis as a risk factor for post-cesarean endometritis. *Obstetrics and gynecology*. 75 (1), 52–58.

Webster J (1988) Post-caesarean wound infection: a review of the risk factors. *The Australian & New Zealand journal of obstetrics & gynaecology*. 28 (3), 201–207.

White C (1773) *A Treatise on the Management of Pregnant and Lying-In Women*. Science History Publications

Wildman K, Bouvier-Colle M-HMOMS Group (2004) Maternal mortality as an indicator of obstetric care in Europe. *BJOG : an international journal of obstetrics and gynaecology*. 111 (2), 164–169.

World Health Organization (2011) *Global Burden of Disease (GBD): 2008 Update*. Geneva: WHO Available at: http://www.who.int/healthinfo/global_burden_disease/en/index.html.

Yokoe DS, Christiansen CL, Johnson R, Sands KE, Livingston J, Shtatland ES and Platt R (2001) Epidemiology of and surveillance for postpartum infections. *Emerging infectious diseases*. 7 (5), 837–841.

Young BC, Levine RJ and Karumanchi SA (2010) Pathogenesis of preeclampsia. *Annual review of pathology*. 5, 173–192.

Zakikhany K, Degail MA, Lamagni T, Waight P, Guy R, Zhao H, Efstratiou A, Pebody R, George R and Ramsay M (2011) Increase in invasive Streptococcus pyogenes and Streptococcus pneumoniae infections in England, December 2010 to January 2011. *Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin*. 16 (5).

Zhang W-H, Alexander S, Bouvier-Colle M-H, Macfarlane AMOMS-B Group (2005) Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. *BJOG : an international journal of obstetrics and gynaecology*. 112 (1), 89–96.

Zwart JJ, Richters JM, Ory F, de Vries JIP, Bloemenkamp KWM and van Roosmalen J (2008) Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. *BJOG : an international journal of obstetrics and gynaecology*. 115 (7), 842–850.

Appendix 1: Published maternal mortality review paper

Appendix 2: AMND study protocol

Name of researcher(s) and collaborators

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Title of Research (if this is a research proposal, please enclose copies of protocol)

Trends in maternal sepsis in Aberdeen, Scotland since 1950.

Source of Funding (if applicable)

The project is funded as part of the NIHR Maternal Near-miss programme (UKNeS).

Additional Information (Will identification data be supplied and in what format. Is there any plan to link these data with other registers?)

No identification data will be requested. Although we will be investigating linking case data with pathology reports for culture tests and results, linkage identifiers will be retained by the AMND data extraction team.

Data items requested

Please see attached protocol.

Format requested

STATA file or excel CSV file

Details of how the data will be stored and for how long

The data will be stored in a password protected file in a restricted area of a secure departmental computer network. Only the named researchers and the NPEU Data Protection Officer will have access to the data. Further details of network and university security are available in the respective security policies (attached).

I agree to abide by the regulations for access to the Databank as set out by the Databank Steering Committee

Please return to:

Dr Sohinee Bhattacharya
Dugald Baird Centre
University of Aberdeen
Aberdeen Maternity Hospital
Cornhill Road
Aberdeen AB25 2ZL

Signed ……
Date ……

AMND Study Proposal

Aims
To use the Aberdeen Maternal and Neonatal Databank (AMND) to retrospectively describe the trends in incidence and risk factors for severe maternal sepsis among antepartum, intrapartum and immediately postpartum women recorded in the AMND, as a first step in establishing the epidemiology of severe maternal sepsis in a stable and defined population.

Specific research questions are:
1. What are the trends in incidence of severe maternal sepsis among antenatal and postnatal women recorded in the AMND?
2. What are the demographic, medical and pregnancy risk factors (including: caesarean-section, BMI, primiparity, age, ethnicity, comorbidities) for severe sepsis?
3. What are the trends in causative organisms in women with severe sepsis?
4. What are the trends in outcomes (survival) for women with severe sepsis?
5. Are there any factors associated with poor outcomes?

Background
Maternal sepsis can be a severe complication of pregnancy or birth, and is characterised by systemic inflammatory response syndrome (SIRS) with infection, organ dysfunction, hypoperfusion or hypotension[1].

Although mortality as a result of pregnancy related sepsis is uncommon in the UK and other high-income countries, it is the leading cause of direct maternal death in the UK[2] and a leading cause of preventable maternal death[3]. It is estimated that 2.1% of all maternal deaths in high-income countries are due to sepsis[3]. In addition, each case fatality represents a much larger incidence of morbidity and “near miss” events during the perinatal and puerperal periods. A recent study from the Netherlands found that sepsis accounts for 8.1% of all Dutch obstetric intensive care unit (ICU) admissions[4]. In addition, factors such as increasing incidence and severity of sepsis in the general population[5-9], Gram-positive bacteraemia[5], in particular group A streptococcus[2], emergence of drug resistant organisms, fungal infection[5], and nosocomial transmission, may exacerbate the risk of sepsis in the obstetric population.

In the UK, the incidence of maternal sepsis has increased over the last two decades. In the late 1980’s the maternal mortality rate (MMR) was 0.4/100,000 maternities, while in the period from 2006-2008 the MMR increased to 1.13/100,000[2]. This rate places

sepsis as the leading cause of direct maternal death, surpassing that of preeclampsia[10, 11]. The only known study of severe sepsis-related obstetric morbidity in the UK was conducted in South-East England in 2001 where incidence was estimated to be 0.4/1,000 deliveries[12].

Sepsis is generally caused by bacteraemia [13], and transmission can be classified as nosocomial, exogenous or endogenous[14]. Increased awareness and severity of nosocomial infections have recently prompted new surveillance particularly among neonatal intensive care units (NICU), however, incidences of nosocomial maternal infections in the UK and other industrialized countries are yet to be determined. Sterilisation protocols in modern hospitals have mostly obviated exogenous contamination, however endogenous infection remains a significant source of perinatal and puerperal infection. Endogenous infection is typically polymicrobial as a result of vaginal colonization[1, 14], and is dominated by Gram-negative isolates,[1] although Gram-positive aerobes are increasingly indicated[2, 10, 14].

Clinical Benefit
Pregnant and intrapartum women represent a particularly vulnerable population for developing severe sepsis, yet relatively little research has been carried out on the trends of severe illness and death, or the risk factors for women with this complication in the UK. Severe sepsis is a highly preventable complication of pregnancy and delivery if properly identified and managed. Therefore, beginning to establish this epidemiology is vital to the prevention of poor outcomes for mothers and their infants.

Methods

Research design
This will be a retrospective case-control study using the AMND to identify: antenatal and postnatal women diagnosed with either severe sepsis (ICD-9 995.92) or septic shock (ICD-9 785.52), and to describe the characteristics of this population.

Case extraction criteria:
All women recorded in the AMND will be queried for a diagnosis of either severe sepsis (ICD-9 **995.92**) or septic shock (ICD-9 **785.52**).

Control extraction criteria:
Each case will be matched to controls (women without any infection) according to date of delivery. The number of matched controls will be determined according to a power calculation based on the number of cases extracted from the AMND.

Data items requested:
The following data is requested for cases and controls (those variables in red are <u>not</u> listed on the AMND website):

1. **PATIENT:**
    a. Place of Birth and Race
    b. Current Parity
    c. Total No Pregnancies >24 weeks and <24 weeks
    d. Blood Group
    e. Height & weight Classification
    f. All other ICD-9 codes listed for the admission with of sepsis

2. **PREGNANCY:**
    a. Date of Booking
    b. Parity
    c. Date of Last Menstrual Period or expected date of delivery
    d. Complications of pregnancy e.g. preeclampsia, antepartum haemorrhage, premature rupture of membranes, prolonged rupture of membranes
    e. Gestation
    f. Menstrual Cycle
    g. Smoking Habit
    h. Patient's Social Class at Delivery
    i. Pre-existing medical complications/comorbidities
    j. Complications in previous pregnancy

3. **DELIVERY:**
    a. Date & Time of Membrane Rupture
    b. Type of Membrane Rupture
    c. Date & Time of each Stage of Delivery
    d. Type of Perineal Wound
    e. Type of Placenta Delivery (e.g. manual removal of placenta)
    f. Blood Loss at Delivery
    g. Age at Delivery
    h. Number of Babies Delivered with Outcome
    i. Date of Discharge
    j. Labour Type- whether spontaneous, induced or elective caesarean section
    k. Outcome - death of mother (Yes/No)
    l. Mother’s destination at discharge

4. **BABY:**
    a. Number of Babies born for the Pregnancy
    b. Date of Birth & Time of Delivery
    c. Type of Delivery – whether it was a vaginal, forceps or ventouse delivery or by caesarean section
    d. Presentation at Delivery
    e. Sex & Weight of Baby
    f. Outcome of Pregnancy – whether it was a live birth, stillbirth or abortion
    g. Date of Discharge for Baby
    h. Baby's Destination at Discharge

5. **OTHER VARIABLES (potential linkages)**
    Pathology: culture tests with results, conducted in the antenatal or perinatal periods
    Operative Management: Blood transfusion, evacuation of the uterus carried out during the pregnancy, delivery or postnatal period.
    Drugs: Taken or prescribed during pregnancy, labour and in the immediate postnatal period.
    Indications for procedures: The indications for procedures such as induction of labour and caesarean section
    Intergenerational data: Daughter or granddaughter that also had ICD-9 code 995.92 or 785.52
    Neonatal Data: Apart from those listed above, data on any complications developed during the neonatal period, admission to Neonatal unit and management.

6. **EXTRA INFORMATION:**
    a. Total number of maternities, live-births and stillbirths for each year of data included

Consent

This is a non-interventional (descriptive) study only. The study seeks to describe disease incidence and will collect information only. In order to obtain accurate incidence information, data must be collected on ALL cases occurring in the population. It is not therefore practicable to obtain individual patient consent. The central team will not seek to collect any names, addresses, dates of birth, hospital or NHS numbers in order that none of the participants are individually identifiable. Patients will be managed by their usual clinical team and will receive the usual management for their hospital of delivery. The management of each woman participating will not be altered in any way by participation in the study. The anonymous information will be used to calculate incidence ***trends*** and identify means to further improve patient care. This study will follow the UKOSS methodology, which has received the approval of the London Multi-centre Research Ethics Committee (study reference 04/MRE02/45).

The National Information Governance Board (NIGB, formerly Patient Information Advisory Group (PIAG)) and the Confidentiality and Security Advisory Group for Scotland (CSAGS) have judged that collection of information only, for the purpose of studying incidence and identifying means to improve patient care, which is not individually identifiable and does not lead to any change in management for the individual patient is acceptable without requiring individual patient consent[15, 16].

Statistical analyses

1) Severe sepsis morbidity and mortality trends will be calculated using the Cochran-Armitage test and χ^2 test for trends.
2) Frequency of the main causative organisms will be tabulated.
3) Risk factors associated with severe sepsis (antepartum, intrapartum and immediately postpartum) will be analyzed. (Odds ratios with confidence intervals will be calculated and adjusted for confounders using logistic regression.)
4) Patient deaths will be tabulated and exploratory analysis on patient characteristics will be carried out.

Costs and resources

The project is funded as part of the NIHR Maternal Near-miss programme (UKNeS).

Dissemination and publication

It will be important to feedback the outcomes of the study to the clinicians. The results will also be reported to the Scientific Advisory Committee of the RCOG and the Royal College of Midwives. In the academic arena, the findings will be presented at specialist conferences, such as the British Maternal and Fetal Medicine Society and the Annual Scientific Meeting of the Obstetric Anaesthetists Association. The findings of this study will also be submitted for publication in peer-reviewed journals such as the British Journal of Obstetrics and Gynaecology. The NPEU reports directly to the UK Department of Health and has a distinguished record for influencing health policy both in the UK and worldwide.

References

1. Paruk, F., *Infection in obstetric critical care.* Best Pract Res Clin Obstet Gynaecol, 2008. **22**(5): p. 865-83.
2. Centre for Maternal and Child Enquiries, *Genital Tract Sepsis*, in *Emergent Theme Briefing*. 2010.
3. van Dillen, J., et al., *Maternal sepsis: epidemiology, etiology and outcome.* Curr Opin Infect Dis, 2010. **23**(3): p. 249-54.
4. Zwart, J.J., et al., *Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study.* Intensive Care Med, 2010. **36**(2): p. 256-63.
5. Martin, G.S., et al., *The epidemiology of sepsis in the United States from 1979 through 2000.* N Engl J Med, 2003. **348**(16): p. 1546-54.
6. Dombrovskiy, V.Y., et al., *Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003.* Crit Care Med, 2007. **35**(5): p. 1244-50.
7. Esper, A. and G.S. Martin, *Is severe sepsis increasing in incidence AND severity?* Crit Care Med, 2007. **35**(5): p. 1414-5.
8. Padkin, A., et al., *Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland.* Crit Care Med, 2003. **31**(9): p. 2332-8.
9. Vincent, J.L., et al., *Sepsis in European intensive care units: results of the SOAP study.* Crit Care Med, 2006. **34**(2): p. 344-53.
10. Lewis, G.e., *The Confi dential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer- 2003-2005.*, in *The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom.* 2007: London.
11. Benhamou, D., et al., *[The seventh report of the confidential enquiries into maternal deaths in the United Kingdom: comparison with French data].* Ann Fr Anesth Reanim, 2009. **28**(1): p. 38-43.
12. Waterstone, M., S. Bewley, and C. Wolfe, *Incidence and predictors of severe obstetric morbidity: case-control study.* BMJ, 2001. **322**(7294): p. 1089-93; discussion 1093-4.
13. Beers, M.H., *The Merck Manual of Diagnosis and Therapy*. 18 ed. 2006, Whitehouse Station, NJ: Merck.
14. Maharaj, D., *Puerperal pyrexia: a review. Part I.* Obstet Gynecol Surv, 2007. **62**(6): p. 393-9.
15. Department of Health, *Guidance Notes: Section 60 of the Health and Social Care Act* 2001.
16. Confidentiality and Security Advisory Group for Scotland, *The Scottish Executive*. 2001: Edinburgh.

Appendix 3: Published paper – Maternal sepsis: a Scottish population-based case control study

Appendix 4: Published letter in response to a comment on the Northern Scotland study article

Appendix 5: UKOSS Study protocol

Aims

To use the UK Obstetric Surveillance System to describe the epidemiology of severe maternal sepsis in the UK.

The specific research questions are:

- What is the incidence of severe maternal sepsis in the UK?
- What are the risk factors for severe maternal sepsis?
- What are the main causative organisms?
- How is severe maternal sepsis managed in the UK?
- What are the outcomes for mother and infant?
- Are there any factors that are associated with poor outcomes?

Background

Maternal sepsis can be a severe complication of pregnancy or birth, and is characterized by systemic inflammatory response syndrome (SIRS) with infection, organ dysfunction, hypoperfusion or hypotension[1].

Although mortality as a result of pregnancy related sepsis is uncommon in the UK and other high-income countries, it remains a leading cause of preventable maternal death.[2] It is estimated that 2.1% of all high-income country maternal deaths are due to sepsis.[2] In addition, each case fatality represents a much larger incidence of morbidity and "near miss" events during the perinatal and puerperium periods. A recent study from the Netherlands found that sepsis accounts for 8.1% of all Dutch obstetric intensive care unit (ICU) admissions.[3] In addition, factors such as increasing incidence and severity of sepsis in the general population[4-8], emergence of drug resistant organisms, Gram-positive baceremia[4], fungal infection[4], and nosocomial transmission, may exacerbate the risk of sepsis in the obstetric population.

In the UK, incidence of maternal sepsis has increased over the last two decades. In the late 1980's the maternal mortality rate (MMR) was 0.4/100,000 maternities, while in the period from 2006-2008 the MMR increased to 1.13/100,000[9]. This rate places sepsis as the leading cause of maternal death, surpassing that of preeclampsia.[10 11] The only known study of severe obstetric morbidity in the UK was conducted in South-East England in 2001 where incidence was measured to be 0.4/1,000 deliveries.[12]

Sepsis is generally caused by bacteremia [13], and transmission can be classified as nosocomial, exogenous or endogenous.[14] Increased awareness and severity of nosocomial infections have recently prompted new surveillance particularly among neonatal intensive care units (NICU), however incidence of nosocomial maternal infections in the UK and other industrialized countries are yet to be determined.

Sterilization protocols in modern hospitals have mostly obviated exogenous contamination, however endogenous infection remains a significant source of perinatal and puerperium infection. Endogenous infection is typically polymicrobial as a result of vaginal colonization[1 14], and is dominated by Gram-negative isolates,[1] although Gram-positive aerobes are increasingly indicated.[10 14]

Although studies from other countries have identified cesarean section, primiparity, non-white ethnicity and lower socio-economic status as being associated with severe maternal sepsis[2 14], there has been no comprehensive study of the risk factors for this complication in the UK. In the UK from 2003-2005, 71% of mothers who died directly by sepsis were found to have had substandard care (mainly delay in diagnosis), 33% were obese, and 48% has cesarean sections, all of whom were either overweight or obese.[10] In addition, proximal risk factors such as cesarean section, have yet to be understood in the context of broader disparities or public health concerns such as obesity. Establishing this epidemiology is vital to the prevention of poor outcomes for mothers and their infants.

This study aims to carry out a population-based case-control study using the UK Obstetric Surveillance System to estimate the incidence of severe maternal sepsis in the UK, to investigate and quantify the associated risk factors, causative organisms, management and outcomes and to explore whether any factors are associated with poor outcomes.

Methods

Research design

This study will use the UK Obstetric Surveillance System to identify cases of severe maternal sepsis and will be a case-control study.

Case identification

Cases will be identified through the monthly mailing of the UK Obstetric Surveillance System. The denominator population will be all women giving birth in the UK. The cases will be all women in the UK identified as having severe sepsis in pregnancy or following delivery using the following definition:

1. Two of the following: Temperature >38 or <368C; Heart rate >90 beats/min; Respiratory rate >20 breaths/min or PaCO2 <32mmHg (4.3 kPa)

AND

2. White cell count: >12 000 cells/ml or <4000 cells/ml or 10% immature/band forms

AND

3. Presence of infection (culture confirmed)

Control identification

Controls will be obtained from the same hospitals as cases. The clinician reporting each case will be asked to supply data for 2 control women who delivered at the hospital at the closest time to the case.

Data gathering

On receiving a case report, the central team will dispatch a data collection form to the clinician. The data collection form will seek confirmation of the appropriate case definition and additional information on risk factors, causative organism, management and outcomes. Cases and controls will be allocated unique UKOSS identification numbers. Identical data collection forms will be used for the controls except for details of sepsis. No names, addresses, dates of birth, hospital or NHS numbers will be sought. Respondents will be asked to keep their own record of the unique study number and the patient identifiers in order to facilitate elimination of duplicate reports. If a completed data collection form is not received back by the UKOSS team after six weeks, a further form will be sent out. If there is still no response after a further four weeks, the clinician will be contacted by telephone.

Monitoring ascertainment

Additional data will be sought from the Centre for Maternal and Child Enquiries (CMACE), to provide a means of monitoring and improving case ascertainment. CMACE will be contacted at the end of the study and asked to identify and supply information on any cases of maternal sepsis. Only information on the woman's hospital and date of the acute event will be requested. This information will be used to determine whether the cases have been previously reported through the UK Obstetric Surveillance System. Where new cases are identified, the hospital will be contacted and asked to complete a data collection form. The UK Obstetric Surveillance System will not seek or collect any patient identifiable information at any stage

Consent

This is a non-interventional (descriptive) study only. The study seeks to describe disease incidence and will collect information only. In order to obtain accurate incidence information, data must be collected on ALL cases occurring in the population. It is not therefore practicable to obtain individual patient consent. The central team will not seek to collect any names, addresses, dates of birth, hospital or NHS numbers in order that none of the participants are individually identifiable. Patients will be managed by their usual clinical team and will receive the usual management for their hospital of delivery. Information will be collected from the clinical team responsible for each patient after the initial diagnosis. The management of each woman participating will not be altered in any way by participation in the study. The anonymous information will be used to calculate incidence rates and identify means to further improve patient care. This UKOSS methodology has received the approval of the London Multi-centre Research Ethics Committee (study reference 04/MRE02/45).

The National Information Governance Board (NIGB, formerly Patient Information Advisory Group (PIAG)) and the Confidentiality and Security Advisory Group for Scotland (CSAGS) have judged that collection of information only, for the purpose of studying incidence and identifying means to improve patient care, which is not

individually identifiable and does not lead to any change in management for the individual patient is acceptable without requiring individual patient consent[14,15].

Study size

The only population-based study of severe obstetric morbidity associated with sepsis in the UK estimated the incidence of sepsis to be 0.4/1,000 deliveries.[12] Using this incidence estimate and the most recently available birth data in the UK for 2009[15-17], we would expect approximately 316 cases of severe sepsis per year in the UK.
Table 1 shows the sample sizes corresponding to various values of risk factor prevalence, odds ratio and power. The lowest odds ratios detectable with 316 cases and 632 controls at various risk factor prevalence's and adjusted for multiple covariates are highlighted in grey in the table – light grey shows the lowest detectable with 80% power at the 5% level and dark grey shows the lowest detectable with 90% power at the 5% level.

Table 1: Sample sizes corresponding to specified values of risk factor prevalence, odds ratios and power

Ratio of controls to cases 2:1, 5% significance

Risk factor prevalence in controls (%)	Odds ratio (OR)*	Risk factor prevalence in cases (%)	90% power			80% power		
			Number Controls	Number Cases†	Total	Number Controls	Number Cases	Total
5	2	9.5	1168	584	1752	906	453	1360
5	2.1	10	983	492	1475	766	383	1148
5	2.2	10.4	867	433	1300	675	338	1013
5	2.3	10.8	770	385	1155	603	301	904
5	2.4	11.2	693	347	1040	541	271	812
5	2.5	11.6	627	314	941	491	245	736
10	1.7	15.9	1069	535	1604	825	413	1238
10	1.8	16.7	856	428	1284	660	330	990
10	1.9	17.4	719	360	1079	557	278	835
10	2	18.2	603	301	904	469	234	703
10	2.1	18.9	524	262	785	407	204	611
15	1.5	20.9	1322	661	1983	1012	506	1518
15	1.6	22	966	483	1449	744	372	1115
15	1.7	23.1	741	371	1112	572	286	858
15	1.8	24.1	603	301	904	466	233	700
15	1.9	25.1	499	250	749	387	194	581
20	1.5	27.3	1021	510	1531	781	391	1172
20	1.6	28.6	752	376	1129	579	289	868
20	1.7	29.8	592	296	888	455	228	683
20	1.8	31	480	240	719	370	185	554
20	1.9	32.2	396	198	594	308	154	462
25	1.4	31.8	1276	638	1914	972	486	1459
25	1.5	33.3	873	437	1310	669	334	1003
25	1.6	34.8	640	320	960	493	246	739
25	1.7	36.2	499	250	749	385	193	578
25	1.8	37.5	407	204	611	315	157	472

*OR calculated according to Julious et.al., 1999[18].
†Sample size calculated according to p_1 p_2 estimates[18] and adjusted for multiple covariates according to Hsieh et.al.,1998[19]. Stata11 was used for all calculations.

Data entry
Data will be double entered into a customised database. Duplicate reports will be eliminated by comparing hospital and date of notification and follow-up with the reporting clinicians.

Statistical analysis

- Morbidity and mortality incidences due to severe sepsis with 95% confidence intervals will be calculated.
- Frequency of the main causative organisms will be tabulated.
- Risk factors will be compared between sepsis cases and controls. The following factors will be considered:
- Risk factors associated with time of onset of infection (perinatal or puerperium). (Odds ratios with confidence intervals will be calculated and adjusted for confounders using logistic regression.)
- The management of sepsis in the UK will be described.

Costs and resources
The project is funded as part of the NIHR Maternal Near-miss programme (UKNeS). There will be a small draw on NHS resources involving the time of the notifying clinician to complete the data collection form. This requires only a few minutes of time and can be achieved from records.

Research ethics committee approval
This project has been approved by the North London REC1. (ref 10/H0717/20).

Project management
The overall conduct of the study will be monitored by the Steering Committee of the UK Obstetric Surveillance System. Day-to-day management of the project will be carried out by a Management Group consisting of the Principal Investigators, Project Co-ordinator, Data Manager, Project Programmer, Statistician and other external members as considered necessary for the project.

Dissemination and publication
It will be important to feedback the outcomes of the study to the clinicians who participated in providing information. This will be done through quarterly reports and an annual report. The results will also be reported to the Scientific Advisory Committee of the RCOG and the Royal College of Midwives. In the academic arena, the findings will be presented at specialist conferences, such as the British Maternal and Fetal Medicine Society and the Annual Scientific Meeting of the Obstetric Anaesthetists Association. The findings of this study will also be submitted for publication in peer-reviewed journals such as the British Journal of Obstetrics and Gynaecology. The NPEU reports

directly to the UK Department of Health and has a distinguished record for influencing health policy both in the UK and worldwide.

1. Paruk F. Infection in obstetric critical care. *Best Pract Res Clin Obstet Gynaecol* 2008;22(5):865-83.
2. van Dillen J, Zwart J, Schutte J, van Roosmalen J. Maternal sepsis: epidemiology, etiology and outcome. *Curr Opin Infect Dis* 2010;23(3):249-54.
3. Zwart JJ, Dupuis JR, Richters A, Ory F, van Roosmalen J. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. *Intensive Care Med* 2010;36(2):256-63.
4. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348(16):1546-54.
5. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007;35(5):1244-50.
6. Esper A, Martin GS. Is severe sepsis increasing in incidence AND severity? *Crit Care Med* 2007;35(5):1414-5.
7. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med* 2003;31(9):2332-8.
8. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34(2):344-53.
9. Centre for Maternal and Child Enquiries. Emergent Theme Briefing; #1: Genital Tract Sepsis, 2010.
10. Lewis Ge. The Confi dential 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, 2007.
11. Benhamou D, Chassard D, Mercier FJ, Bouvier-Colle MH. [The seventh report of the confidential enquiries into maternal deaths in the United Kingdom: comparison with French data]. *Ann Fr Anesth Reanim* 2009;28(1):38-43.
12. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ* 2001;322(7294):1089-93; discussion 93-4.
13. Beers MH. *The Merck Manual of Diagnosis and Therapy*. 18 ed. Whitehouse Station, NJ: Merck, 2006.
14. Maharaj D. Puerperal pyrexia: a review. Part I. *Obstet Gynecol Surv* 2007;62(6):393-9.
15. Statistical Bulletin: Births and Deaths in England and Wales 2009, 2010.
16. Vital Events Reference Tables 2009, 2010.
17. Births in Northern Ireland (2009), 2010.
18. Julious SA, Campbell MJ, Altman DG. Estimating sample sizes for continuous, binary, and ordinal outcomes in paired comparisons: practical hints. *J Biopharm Stat* 1999;9(2):241-51.
19. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. *Stat Med* 1998;17(14):1623-34.

Appendix 6: UKOSS data collection forms

ID Number:

UKOSS

UK Obstetric Surveillance System

Severe Maternal Sepsis
Study 03/11

Data Collection Form - CASE

Please report any woman delivering on or after 1st June 2011 and before 1st June 2013.

Case Definition:

Any pregnant or recently pregnant woman (up to 6 weeks postpartum) diagnosed with severe sepsis (irrespective of the source of infection). Report only cases diagnosed as having severe sepsis by a senior clinician.

A severe sepsis case would be expected to include women in one of the following groups:

1. Death related to infection or suspected infection
2. Any women requiring level 2 or level 3 critical care (or obstetric HDU type care) due to severe sepsis or suspected severe sepsis
3. A clinical diagnosis of severe sepsis

   As a guide, clinical diagnosis of severe sepsis would usually be associated with 2 or more of the following:

   a. Temperature >38°C or <36°C measured on 2 occasions at least 4 hours apart

   b. Heart rate >100 beats/ minute measured on 2 occasions at least 4 hours apart

   c. Respiratory rate >20/ minute measured on 2 occasions at least 4 hours apart

   d. White cell count >17x10^9/L or <4x10^9/L or with >10% immature band forms, measured on 2 occasions

Royal College of Obstetricians and Gynaecologists

Please return the completed form to:

UKOSS
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Oxford
OX3 7LF
Fax: 01865 617775
Phone: 01865 289714

Case reported in: _____

npeu National Perinatal Epidemiology Unit

Instructions

1. Please do not enter any personally identifiable information (e.g. name, address or hospital number) on this form.
2. Please record the ID number from the front of this form against the woman's name on the Clinician's Section of the blue card retained in the UKOSS folder.
3. Fill in the form using the information available in the woman's case notes.
4. Tick the boxes as appropriate. If you require any additional space to answer a question please use the space provided in section 7.
5. Please complete all dates in the format DD/MM/YY, and all times using the 24hr clock e.g. 18:37
6. If codes or examples are required, some lists (not exhaustive) are included on the back page of the form.
7. If the woman has not yet delivered, please complete the form as far as you are able, excluding delivery and outcome information, and return to the UKOSS Administrator. We will send these sections again for you to complete two weeks after the woman's expected date of delivery.
8. **If you do not know the answers to some questions, please indicate this in section 7.**
9. If you encounter any problems with completing the form please contact the UKOSS Administrator or use the space in section 7 to describe the problem.

Section 1: Woman's details

1.1 **Year of birth:** ☐☐☐☐

1.2 **Ethnic group:**[1]* *(enter code, please see back cover for guidance)* ☐☐

1.3 **Marital status:** single ☐ married ☐ cohabiting ☐

1.4 **Was the woman in paid employment at booking?** Yes ☐ No ☐

If Yes, what is her occupation:

_____

If No, what is her partner's (if any) occupation:

_____

1.5 **Height at booking:** ☐☐☐ *cm*

1.6 **Weight at booking:** ☐☐☐.☐ *kg*

1.7 **Smoking status:** never ☐ gave up prior to pregnancy ☐
current ☐ gave up during pregnancy ☐

Section 2: Previous Obstetric History

2.1 **Gravidity**

Number of completed pregnancies beyond 24 weeks: ☐☐

Number of pregnancies less than 24 weeks: ☐☐

If no previous pregnancies, *please go to section 3*

2.2 **Did the woman have any previous pregnancy problems?**[2]* Yes ☐ No ☐

If Yes, please specify: _____

2.3 **Did the woman have any previous Caesarean sections?** Yes ☐ No ☐

If Yes, how many? ☐

*For guidance please see back cover

Section 3: Previous Medical History

3.1 **Does the woman have a history of recurrent infections?** Yes ☐ No ☐

If Yes, please specify: _____

3.2 **Was the woman immuno-compromised (including taking immuno-suppressants)?** Yes ☐ No ☐

If Yes, please specify cause: _____

3.3 **Does the woman have (or have a history of) diabetes?** Yes ☐ No ☐

3.4 **Does the woman have a history of a sexually transmitted infection?[3]*** Yes ☐ No ☐

If Yes, please give details: _____

3.5 **Does the woman have any other previous or pre-existing medical problems?[4]*** Yes ☐ No ☐

If Yes, please specify: _____

3.6 **Does the woman or any household member have a recent history (two weeks prior to presentation) of any of the following?**

	Woman		Household member		
	Yes	No	Yes	No	Not Known
Sore throat	☐	☐	☐	☐	☐
Respiratory infection	☐	☐	☐	☐	☐
Diarrhoea	☐	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐	☐
Flu-like illness	☐	☐	☐	☐	☐
Sustained abdominal pain	☐	☐			
Mastitis (>48 hrs duration)	☐	☐			

Section 4: This Pregnancy - Antenatal Information

4.1 **Final Estimated Date of Delivery (EDD)[5]*** D D / M M / Y Y

4.2 **Was this a multiple pregnancy?** Yes ☐ No ☐

If Yes, please specify number of fetuses: ☐

4.3 **Date of booking:** D D / M M / Y Y

4.4 **Did the woman have any invasive antenatal procedures, eg CVS, amniocentesis?** Yes ☐ No ☐

If Yes, please specify: _____

4.5 **Was the woman prescribed antibiotics in the two weeks prior to her severe sepsis?** Yes ☐ No ☐

If Yes: What antibiotics were taken? _____

What was the indication? _____

4.6 **Were there any other problems in this pregnancy?[2]*** Yes ☐ No ☐

If Yes, please specify: _____

*For guidance please see back cover

Section 5: Delivery and Diagnosis of Sepsis

Section 5a: Delivery

5a.1 **Did the woman have a miscarriage?** Yes ☐ No ☐

If Yes, please specify date: D D / M M / Y Y

5a.2 **Did the woman have a termination of pregnancy?** Yes ☐ No ☐

If Yes, please specify date: D D / M M / Y Y

If Yes to 5a.1 or 5a.2, please now complete sections 5b, 6a, 7 and 8

5a.3 **Is the woman still undelivered?** Yes ☐ No ☐

If Yes, will she be receiving the rest of her antenatal care from your hospital? Yes ☐ No ☐

If No, please indicate name of hospital providing future care:

_____

Will she be delivered at your hospital? Yes ☐ No ☐

If No, please indicate name of delivery hospital, then *go to Section 7*

_____

5a.4 **Was delivery induced?** Yes ☐ No ☐

If Yes, please state indication: _____

Was vaginal prostaglandin used? Yes ☐ No ☐

5a.5 **What was the date and time of membrane rupture?** D D / M M / Y Y H H : m m (24hr)

5a.6 **Did the woman labour?** Yes ☐ No ☐

If Yes, what was the date and time labour was diagnosed? D D / M M / Y Y H H : m m (24hr)

How many vaginal examinations were documented? ☐

Was fetal blood sampling performed? Yes ☐ No ☐

Was a fetal scalp electrode used? Yes ☐ No ☐

Were there any complications of vaginal delivery (e.g. episiotomy, 2nd, 3rd or 4th degree tear)? Yes ☐ No ☐ Not applicable ☐

If Yes, please specify: _____

Did the woman undergo a manual removal of placenta? Yes ☐ No ☐ Not applicable ☐

5a.7 **Did the woman deliver at home?** Yes ☐ No ☐

5a.8 **Was delivery by caesarean section?** Yes ☐ No ☐

If Yes, please state:

Grade of urgency:[6]* ☐

Indication for caesarean section: _____

Method of anaesthesia: Regional ☐ General anaesthetic ☐

Were prophylactic antibiotics given? Yes ☐ No ☐

If Yes, please give names of antibiotics given:

_____

Were there any complications during the surgery? Yes ☐ No ☐

If Yes, please specify: _____

*For guidance please see back cover

5a.9 **Did the woman have any of the following prior to diagnosis of sepsis?**
(please tick all that apply) Intravenous lines ('venflons') ☐ Central venous lines ☐
Intra-arterial lines ☐ In-out urinary catheter ☐ In-dwelling urinary catheter ☐

5a.10 **Did the woman have an epidural or a spinal for anaesthesia/analgesia?** Yes ☐ No ☐

5a.11 **Was the woman admitted/re-admitted after delivery?** Yes ☐ No ☐

If Yes, what was date of admission/re-admission? D D / M M / Y Y

Please state the reason for admission/re-admission: _____

Section 5b: Diagnosis and Management of Sepsis

5b.1 **What was the date and time of severe sepsis diagnosis?** D D / M M / Y Y h h : m m (24hr)

5b.2 **Where was the woman when sepsis was first suspected?** Hospital ☐ Home ☐

5b.3 **Did the woman have any of the following:**

A temperature >38°C measured on 2 occasions at least 4 hours apart? Yes ☐ No ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time last recorded: D D / M M / Y Y h h : m m (24hr)

A temperature <36°C measured on 2 occasions at least 4 hours apart? Yes ☐ No ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time last recorded: D D / M M / Y Y h h : m m (24hr)

Heart rate >100 beats/ minute measured on 2 occasions at least 4 hours apart? Yes ☐ No ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time last recorded: D D / M M / Y Y h h : m m (24hr)

Respiratory rate >20/minute measured on 2 occasions at least 4 hours apart? Yes ☐ No ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time 2nd recorded: D D / M M / Y Y h h : m m (24hr)

White cell count >17 x10^9/L, on two occasions? Yes ☐ No ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time 2nd recorded: D D / M M / Y Y h h : m m (24hr)

White cell count <4 x10^9/L, on two occasions? Yes ☐ No ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time 2nd recorded: D D / M M / Y Y h h : m m (24hr)

White cell immature band forms > 10%, on two occasions? Yes ☐ No ☐ Not done ☐

If Yes: Date and time first recorded: D D / M M / Y Y h h : m m (24hr)

Date and time 2nd recorded: D D / M M / Y Y h h : m m (24hr)

*For guidance please see back cover

5b.4 Was there laboratory confirmed infection? Yes ☐ No ☐

If Yes: What was the source of the sample (e.g. blood, urine, etc.)? _____

Date of first positive sample: D D / M M / Y Y

Organism identified: _____

5b.5 What was the primary source of the infection which caused the sepsis?

_____

5b.6 Was septic shock diagnosed? Yes ☐ No ☐

If Yes, what was the date of diagnosis? D D / M M / Y Y

5b.7 Please record the following or tick if not measured

Lowest systolic BP ☐☐☐ *mmHg* **OR** Not measured ☐

Highest lactate ☐☐ *mmol/L* **OR** Not measured ☐

Greatest base deficit - ☐☐.☐ **OR** Not measured ☐

Lowest pH ☐.☐☐ **OR** Not measured ☐

5b.8 Were antibiotics administered for severe sepsis? Yes ☐ No ☐

If Yes, please list in table below *(Continue in section 7 if necessary)*.

Antibiotic	Route	Date started	Date stopped
		D D / M M / Y Y	D D / M M / Y Y
		D D / M M / Y Y	D D / M M / Y Y
		D D / M M / Y Y	D D / M M / Y Y

Section 6: Outcomes

Section 6a: Woman

6a.1 Was the woman admitted to HDU (including obstetric HDU) or level 2 care? Yes ☐ No ☐

If Yes, duration of stay: ☐☐ *days*

OR Tick if woman is still in HDU or level 2 care: ☐

OR Tick if woman was transferred to another hospital: ☐

6a.2 Was the woman admitted to ITU or level 3 care? Yes ☐ No ☐

If Yes, duration of stay: ☐☐ *days*

OR Tick if woman is still in ITU or level 3 care: ☐

OR Tick if woman was transferred to another hospital: ☐

6a.3 Did any other major maternal morbidity occur?[7]* Yes ☐ No ☐

If Yes, please specify: _____

6a.4 Has the woman been discharged from hospital after her episode of sepsis? Yes ☐ No ☐

If Yes, what was the date of the woman's final discharge from hospital? D D / M M / Y Y

6a.5 Did the woman die? Yes ☐ No ☐

If Yes, please specify date and time of death D D / M M / Y Y ☐☐ : ☐☐ (24hr)

What was the primary cause of death as stated on the death certificate?
(Please state if not known.) _____

*For guidance please see back cover

Section 6b: Infant 1

NB: If more than one infant, for each additional infant, please photocopy the infant section of the form **(before filling it in)** and attach extra sheet(s) or download additional forms from the website: **www.npeu.ox.ac.uk/ukoss**

6b.1 Date and time of delivery: D D / M M / Y Y h h : m m (24hr)

6b.2 Mode of delivery:

Spontaneous vaginal ☐ Ventouse ☐ Lift-out forceps ☐ Rotational forceps ☐

Breech ☐ Pre-labour caesarean section ☐ Caesarean section after onset of labour ☐

6b.3 Birthweight: ☐☐☐☐ *g*

6b.4 Sex of infant: Male ☐ Female ☐ Indeterminate ☐

6b.5 Was the infant stillborn? Yes ☐ No ☐

If Yes, *please go to section 7*.

6b.6 5 min Apgar: ☐☐

6b.7 Was the infant admitted to the neonatal unit? Yes ☐ No ☐

6b.8 Was the infant septic? Yes ☐ No ☐

6b.9 Did any other major infant complications occur?[8]* Yes ☐ No ☐

If Yes, please specify: _____

6b.10 Did this infant die? Yes ☐ No ☐

If Yes, please specify date and time of death D D / M M / Y Y h h : m m (24hr)

What was the primary cause of death as stated on the death certificate?
(Please state if not known) _____

Section 7:

Please use this space to enter any other information you feel may be important

_____

_____

_____

Section 8:

8.1 Name of person completing the form: _____

8.2 Designation: _____

8.3 Today's date: D D / M M / Y Y

You may find it useful in the case of queries to keep a copy of this form.

*For guidance please see back cover

Definitions

1. UK Census Coding for ethnic group

WHITE
- 01. British
- 02. Irish
- 03. Any other white background

MIXED
- 04. White and black Caribbean
- 05. White and black African
- 06. White and Asian
- 07. Any other mixed background

ASIAN OR ASIAN BRITISH
- 08. Indian
- 09. Pakistani
- 10. Bangladeshi
- 11. Any other Asian background

BLACK OR BLACK BRITISH
- 12. Caribbean
- 13. African
- 14. Any other black background

CHINESE OR OTHER ETHNIC GROUP
- 15. Chinese
- 16. Any other ethnic group

2. Previous or current pregnancy problems, including:

Thrombotic event
Amniotic fluid embolism
Eclampsia
3 or more miscarriages
Preterm birth or mid trimester loss
Neonatal death
Stillbirth
Baby with a major congenital abnormality
Small for gestational age (SGA) infant
Large for gestational age (LGA) infant
Infant requiring intensive care
Puerperal psychosis
Placenta praevia
Gestational diabetes
Significant placental abruption
Post-partum haemorrhage requiring transfusion
Surgical procedure in pregnancy
Hyperemesis requiring admission
Dehydration requiring admission
Ovarian hyperstimulation syndrome
Severe infection e.g. pyelonephritis
Rh(D) alloimmunisation

3. Previous history of sexually transmitted infection, including:

HIV
Syphilis
Gonorrhoea
Chlamydia
Genital herpes
Hepatitis C

4. Previous or pre-existing maternal medical problems, including:

Diabetes
Cardiac disease (congenital or acquired)
Renal disease
Endocrine disorders e.g. hypo or hyperthyroidism
Psychiatric disorders
Haematological disorders e.g. sickle cell disease, diagnosed thrombophilia, anaemia
Inflammatory disorders e.g. inflammatory bowel disease
Autoimmune diseases
Cancer
Depression

5. Estimated date of delivery (EDD): Use the best estimate (ultrasound scan or date of last menstrual period) based on a 40 week gestation

6. RCA/RCOG/CEMACH/CNST Classification for urgency of caesarean section:

1. Immediate threat to life of woman or fetus
2. Maternal or fetal compromise which is not immediately life-threatening
3. Needing early delivery but no maternal or fetal compromise
4. At a time to suit the woman and maternity team

7. Major maternal medical complications, including:

Persistent vegetative state
Cardiac arrest
Cerebrovascular accident
Adult respiratory distress syndrome
Disseminated intravascular coagulopathy
HELLP
Pulmonary oedema
Mendleson's syndrome
Renal failure
Thrombotic event
Required ventilation

8. Fetal/infant complications, including:

Respiratory distress syndrome
Intraventricular haemorrhage
Necrotising enterocolitis
Neonatal encephalopathy
Chronic lung disease
Severe jaundice requiring phototherapy
Major congenital anomaly
Severe infection e.g. septicaemia, meningitis
Exchange transfusion

Appendix 7: ICNARC study protocol

icnarc | intensive care national audit & research centre

Tavistock House
Tavistock Square
London WC1H 9HR
tel +44 (0)20 7388 2856
fax +44 (0)20 7388 3759
email icnarc@icnarc.org

Request for analyses

Simple requests for analyses are done free of charge for Case Mix Programme units. All other requests involve a charge based on the nature and complexity of the request.

All requests are discussed internally at ICNARC and, following any necessary clarification with the requester, are dealt with on a first-come, first-served basis. Timeline to production is based on workload demand. Please note that deadlines for ICNARC of a few days are unlikely to be met.

- Put all information on this form and not in an accompanying document or email.
- Please be as specific as possible; boxes expand to allow more information to be entered.
- **Please complete this form and email to cmp@icnarc.org or fax to 020 7388 3759**

YOUR DETAILS	
Name	Colleen Acosta-Nielsen; Lisa Hinton; Marian Knight; Jenny Kurinczuk
Job title	PhD Candidate - National Perinatal Epidemiology Unit (NPEU); Senior Researcher - Oxford Department of Primary Healthcare; Director - United Kingdom Obstetric Surveillance System (UKOSS); Director - NPEU
Hospital/Organisation	National Perinatal Epidemiology Unit (NPEU), Oxford University
Contact telephone	1865289421
Contact hospital/work email (Personal email may not be used)	colleen.acosta@npeu.ox.ac.uk lisa.hinton@phc.ox.ac.uk marian.knight@npeu.ox.ac.uk jenny.kurinczuk@npeu.ox.ac.uk
Date of request	24/05/2011

YOUR REQUEST	
What information do you require?	AIMS To use the ICNARC Case Mix Program (CMP) data to retrospectively describe the incidence, causative organisms and risk factors of severe maternal sepsis among prenatal and postnatal women admitted to intensive or critical care units in the UK, in order to identify targets for potential prevention. RESEARCH DESIGN This will be a retrospective cohort study using the ICNARC CMP anonymous (masked), individual level data to identify: “currently pregnant” or “recently pregnant” women admitted to intensive or critical care units in the UK for severe sepsis. Please note, this analysis is not currently possible using aggregated data, which is available in the 2008 ICNARC Obstetric Report.

CASE EXTRACTION CRITERIA
All “currently pregnant” or “recently pregnant” women in the ICNARC CMP database, with the following OBSTETRIC reasons for admission:

1. Septic shock (no underlying condition given)
2. Infected retained products of conception
3. Septic shock (following intrauterine death)
4. Pelvic infection or abscess
5. Amnionitis
6. Septic abortion
7. Uterine cavity infection
8. Septicaemia (following intrauterine death)
9. Septicaemia (no underlying condition given)

DATA REQUEST
1. All non-identifiable demographic data (e.g. age, sex ethnicity) for each case.
2. All case mix data available in the CMP database for each case (e.g. acute severity, comorbidity, surgical status, reason for admission).

3. Outcome (e.g. unit/ acute hosptial survival)

4. Activity (e.g. unit/acute hospital length of stay)

5. Obstetric related fields:
   "Currently pregnant":
   a. Gestation or expected date of delivery

   "Recently pregnant"
   a. Assisted conception used for recent pregnancy
   b. Gestation at delivery of recent pregnancy
   c. Actual date of delivery of recent pregnancy
   d. Molar pregnancy associated with recent pregnancy
   e. Number of live births (babies) or stillbirths from previous pregnancies
   f. Number of previous Caesarean sections excluding most recent pregnancy
   g. Outcome of recent pregnancy
   h. Number of live births (babies) from recent pregnancy
   i. Number of stillbirths from recent pregnancy
   j. Number of babies in NICU following recent pregnancy
   k. Hysterectomy at/since delivery of recent pregnancy

6. All raw physiology data available (used to calculate APACHE II score)

7. All laboratory culture data (e.g. blood or urine)

8. All timing data (e.g. date of unit/acute hospital admission, data of unit discharge, date of hospital discharge)

Why do you need this information?	Although mortality as a result of pregnancy related sepsis is uncommon in the UK and other high-income countries, it is the leading cause of direct maternal death in the UK[1] and a leading cause of preventable maternal death[2]. It is estimated that 2.1% of all high-income country maternal deaths are due to sepsis[2]. In addition, each case fatality represents a much larger incidence of morbidity and "near miss" events during the perinatal and puerperium periods. A recent study from the Netherlands found that sepsis accounts for 8.1% of all Dutch obstetric intensive care unit (ICU) admissions[3]. In addition, factors such as increasing incidence and severity of sepsis in the general population[4-8], Gram-positive bacteraemia[4], in particular group A streptococcus[1], emergence of drug resistant organisms, fungal infection[4], and nosocomial transmission, may exacerbate the risk of sepsis in the obstetric population. In the UK, incidence of maternal sepsis has increased over the last two decades. In the late 1980's the maternal mortality rate (MMR) was 0.4/100,000 maternities, while in the period from 2006-2008 the MMR increased to 1.13/100,000[1]. This rate places sepsis as the leading cause of maternal death, surpassing that of preeclampsia[9, 10]. The only known study of severe obstetric morbidity in the UK was conducted in South-East England in 2001 where incidence was measured to be 0.4/1,000 deliveries[11]. Pregnant and postnatal women represent a particularly vulnerable population for developing severe sepsis, yet relatively little research has been carried out on the basic epidemiology and risk factors associated with severe illness and death in this population. Although studies from other countries have identified caesarean section, primiparity, non-white ethnicity and lower socio-economic status as being associated with severe maternal sepsis[2, 12], there has been no comprehensive study of the risk factors for this complication in the UK. In the UK from 2003-2005, 71% of mothers who died directly by sepsis were found to have had substandard care (mainly delay in diagnosis), 33% were obese, and 48% had caesarean sections, all of whom were either overweight or obese[9]. In addition, proximal risk factors such as caesarean section, have yet to be understood in the context of broader disparities or public health concerns such as obesity. Severe sepsis is a highly preventable complication of pregnancy and delivery if properly identified and managed. Therefore, establishing this epidemiology is vital to the prevention of poor outcomes for mothers and their infants. Our research team is part of the National Maternal Near-miss Surveillance Programme (UKNeS) which is funded by the National Institute for Health Research and carries out studies on maternal near-miss morbidity. One of the UKNeS workstreams is to prospectively investigate the incidence and risk factors of severe maternal sepsis in the UK. However, in light of the recent increase in maternal deaths due to sepsis, the ICNARC Case-Mix Programme represents a valuable source of routinely collected data from which to retrospectively investigate severe sepsis morbidity. This data will allow us to compare 'near-miss' cases of maternal sepsis to those women who did not survive, and thus identify risk factors associated with poor outcomes. This study will

	be both timely and beneficial in order to expeditiously inform clinical practice and guidelines. 1. Centre for Maternal and Child Enquiries, Genital Tract Sepsis, in Emergent Theme Briefing. 2010. 2. van Dillen, J., et al., Maternal sepsis: epidemiology, etiology and outcome. Curr Opin Infect Dis, 2010. 23(3): p. 249-54. 3. Zwart, J.J., et al., Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. Intensive Care Med, 2010. 36(2): p. 256-63. 4. Martin, G.S., et al., The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med, 2003. 348(16): p. 1546-54. 5. Dombrovskiy, V.Y., et al., Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med, 2007. 35(5): p. 1244-50. 6. Esper, A. and G.S. Martin, Is severe sepsis increasing in incidence AND severity? Crit Care Med, 2007. 35(5): p. 1414-5. 7. Padkin, A., et al., Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med, 2003. 31(9): p. 2332-8. 8. Vincent, J.L., et al., Sepsis in European intensive care units: results of the SOAP study. Crit Care Med, 2006. 34(2): p. 344-53. 9. Lewis, G.e., The Confi dential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer- 2003-2005., in The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. 2007: London. 10. Benhamou, D., et al., [The seventh report of the confidential enquiries into maternal deaths in the United Kingdom: comparison with French data]. Ann Fr Anesth Reanim, 2009. 28(1): p. 38-43. 11. Waterstone, M., S. Bewley, and C. Wolfe, Incidence and predictors of severe obstetric morbidity: case-control study. BMJ, 2001. 322(7294): p. 1089-93; discussion 1093-4. 12. Maharaj, D., Puerperal pyrexia: a review. Part I. Obstet Gynecol Surv, 2007. 62(6): p. 393-9. 13. Pattinson, R.C. and M. Hall, Near misses: a useful adjunct to maternal death enquiries. Br Med Bull, 2003. 67: p. 231-43. 14. Fitzpatrick, C., et al., Near miss maternal mortality (NMM). Ir Med J, 1992. 85(1): p. 37.
What will you do with this information? (Please include details and dates of any planned presentation/ publication)	TIMELINE (2010) June: Individual-level, anonymous data requested from ICNARC July - August: Analyses of data obtained from ICNARC by our research team September-October: Writing of results November: Submission for Publication STATISTICAL ANALYSES 1) Morbidity and mortality incidences due to severe sepsis with 95% confidence intervals will be calculated. 2) Frequency of the main causative organisms will be tabulated. 3) Risk factors associated with severe sepsis (prenatal and postnatal) will be analyzed. (Odds ratios with confidence

	intervals will be calculated and adjusted for confounders using logistic regression.) 4) Outcomes and risk factors for poor outcomes will be analyzed (Odds ratios with confidence intervals will be calculated and adjusted for confounders using logistic regression.) DISSEMINATION AND PUBLICATION It will be important to feedback the outcomes of this study to clinicians, therefore the results will be reported to the Scientific Advisory Committee of the RCOG and the Royal College of Midwives. In the academic arena, the findings will be presented at specialist conferences, such as the British Maternal and Fetal Medicine Society. The findings of this study will also be submitted for publication in peer-reviewed journals such as the British Journal of Obstetrics and Gynaecology. The NPEU reports directly to the UK Department of Health and has a distinguished record for influencing health policy both in the UK and worldwide.
When do you require this information? (Failure to provide a specific date may result in delays in processing your request)	01/07/2011

Terms and conditions:
By submitting this form, you agree that the information requested is for your sole use, as described above.
If the information is required for external presentation/publication, then this must be approved in advance by ICNARC.

Appendix 8: California study protocol

California maternal sepsis collaborative study using the CPQCC-VS-OSHPD linked dataset

INVESTIGATORS:

	Investigator	Qualification	University	Study Role	Data Access
1	Audrey Lyndon	Assistant Professor, PhD, RNC, CNS-BC	UCSF	Principal Investigator	YES
2	Jeffrey Gould	Professor, MD, MPH	Stanford University	CPQCC Executive Committee Representative; Co-investigator	YES
3	Marian Knight	Professor, MA, MBChB, MPH, DPhil, FFPH	University of Oxford	Collaborating Supervisor; Co-investigator	NO
4	Colleen Acosta	MPH, PhD Candidate	University of Oxford	Lead investigator; data analyst	YES
5	Henry C. Lee	MD, MS	Stanford University	Co-investigator	NO
6	William M. Gilbert	MD	Sutter Health	Co-investigator	NO
7	Kathryn A. Lee	Professor, RN, PhD	UCSF	Co-investigator	NO
8	Jenny Kurinczuk	Professor, MD, MSc, FFPH	University of Oxford	Co-investigator	NO

BACKGROUND

Severe sepsis is a potentially life-threatening condition that is characterized by systemic inflammatory response syndrome (SIRS) with infection, organ dysfunction, hypoperfusion or hypotension[1]. Pregnant and intrapartum women represent a particularly vulnerable population for developing severe sepsis, yet relatively little research has been carried out on the risk factors for women with this complication in the US, or in the state of California.

In countries with developed healthcare systems, severe maternal sepsis is uncommon, however it remains a leading cause of preventable maternal death.[2] It is estimated that 2.1% of all high-income country maternal deaths are due to sepsis.[2] In North America the maternal mortality rate (MMR) due to sepsis was estimated to be 3 per 100,000 deliveries[3] and in California between 2002 and 2003 the MMR was 0.79 per 100,000 live births, which was the second leading cause of preventable maternal death[4].

Although these rates may seem low, maternal mortality is a rare occurrence in developed countries, and as such, serves as an important indicator for the condition of public health overall. Additionally, each case fatality represents a much larger incidence of morbidity and “near-miss” events. Thus a slight increase in mortality rates can indicate a greater magnitude of increase in severe illness. Given this relationship, infection is estimated to complicate between 1% and 8% of all maternities in the US[3], and maternal mortality rates in California have increased significantly over the past decade. The extent to which sepsis and other maternal morbidity rates have also increased it is currently unknown.

Of further consideration is the increase in incidence and severity of sepsis in the general US population[5-7]. Similar increases have been reported in Europe[8, 9], with an effect on the obstetric population as well. In the UK, for example, the incidence of maternal sepsis has doubled in the past decade from 0.65 per 100,000 maternities (2000 to 2002) to 1.13/100,000 (2006-2008)[10]. This rate places sepsis as the leading cause of direct maternal death in the UK, surpassing that of preeclampsia[11, 12].

Sepsis is generally caused by bacteraemia [13], and transmission can be classified as nosocomial, exogenous or endogenous.[14] Sterilization protocols in modern hospitals have mostly obviated exogenous contamination, however endogenous infection remains a significant source of perinatal and puerperium infection. Endogenous infection is typically polymicrobial as a result of vaginal colonization[1, 14], and is dominated by Gram-negative isolates,[1] although Gram-positive aerobes such as group A streptococcus (GAS) are increasingly indicated.[11, 14] In addition, factors such as emergence of drug resistant organisms, fungal infection[5], and nosocomial transmission, may exacerbate the risk of sepsis in the obstetric population.

Although studies from other countries have identified caesarean section, primiparity, non-white ethnicity and lower socio-economic status as being associated with severe maternal sepsis[2, 14], there has been no comprehensive study of the risk factors for this complication in California. In addition, proximal risk factors, such as caesarean section, have yet to be understood in the context of broader public health concerns such as racial disparities and increasing rates of obesity.

GOALS AND AIMS

This study aims to carry out a population-based cohort study using the California Perinatal Quality Care Collaborative – Vital Statistics – Office of Statewide Health Planning and Development (CPQCC-VS-OSHPD) linked dataset to retrospectively describe the incidence of severe maternal sepsis among pregnant and postpartum women in California from 2005-2007. This study also aims to investigate and quantify the associated risk factors, outcomes and to explore whether any factors are associated with poor outcomes.

Specific research questions are:

1. What is the estimated incidence of severe maternal sepsis among pregnant or postpartum women in California?
2. What are the risk factors for severe maternal sepsis?
3. What are the outcomes for mother and infant?
4. Are there any factors that are associated with poor outcomes?
5. How do findings compare with other population-based studies?

PROJECT'S PERTINANCE TO PERINATAL HEALTH

Establishing this epidemiology and comparison of the findings with on-going studies in other countries, is vital to the prevention of poor outcomes for mothers and their infants. The CPQCC-VS-OSHPD represents a unique dataset from which to undertake a population-based study of severe maternal sepsis in California, since it encompasses maternal records from 90% of all in-state deliveries with linkage to comprehensive demographic and clinical delivery information. The size and detail of this dataset will allow for a robust analysis while minimizing any potential for selection bias.

HEALTH OUTCOMES OF INTEREST

All cases of sepsis and severe sepsis will be identified according to the following ICD-9CM sepsis codes.

		ICD-9CM
1	Streptococcal septicemia	038.0
2	Staphylococcal septicemia	038.1
3	Pneumococcal septicemia	038.2
4	Septicemia due to anaerobes	038.3
5	Septicemia due to other gram-negative organisms	038.4
6	Other specified septicemias	038.8
7	Unspecified septicemia	038.9
8	Septic shock	785.52
9	SIRS due to infectious process without organ dysfunction	995.91
10	SIRS due to infectious process with organ dysfunction	995.20

STUDY DESIGN AND METHODS: This study will be a retrospective cohort study using the CPQCC-VS-OSHPD linked dataset of California deliveries from 2005 to 2007. All cases of sepsis and severe sepsis will be identified and compared to the remaining obstetric population in the CPQCC-VS-OSHPD dataset (without a sepsis ICD code).

All data is stored on a secure server at: The UCSF School of Nursing, 2 Koret Way, San Francisco, CA 94143-0606. All analyses will be conducted at this location or at: CPQCC, Stanford University School of Medicine, Medical School Office Building, 1265 Welch Road, Stanford, CA 94305-5411.

STUDY SIZE

Over the three-year period, 1441 cases have been identified.
Table 1 shows the sample sizes corresponding to various values of risk factor prevalence, odds ratio and power. The lowest odds ratios detectable with 1441 cases at various risk factor prevalences, at 80% and 90% power at the 5% level are highlighted in grey in the table. Epi Info was used for all calculations.

Table 1: Sample sizes corresponding to specified values of risk factor prevalence, odds ratios and power 5% significance level

prevalence in controls (%)	Odds Ratio (OR)*	Risk factor prevalence in cases (%)	90% Power			80% Power		
			Number controls	Number cases	Total	Number controls	Number cases	Total
5	1.4	6.9	8536	2134	10670	6340	1585	7925
5	1.5	7.3	5720	1430	7150	4244	1061	5305
5	1.6	7.8	4152	1038	5190	3080	770	3850
10	1.3	12.6	7748	1937	9685	5768	1442	7210
10	1.4	13.5	4596	1149	5745	3420	855	4275
10	1.5	14.3	3096	774	3870	2304	576	2880
15	1.2	17.5	11756	1939	13695	8772	2193	10965
15	1.3	18.7	5552	1388	6940	4144	1036	5180
15	1.4	19.8	3308	827	4135	2468	617	3085
20	1.2	23.1	9468	2367	11835	7072	1768	8840
20	1.3	24.4	4492	1123	5615	3356	839	4195
20	1.4	25.9	2692	673	3365	2012	503	2515
25	1.2	28.6	8164	2041	10205	6104	1526	7630
25	1.3	30.2	3892	973	4865	2912	728	3640
25	1.4	31.8	2340	585	2925	1752	438	2190

STATISTICAL ANALYSIS SUMMARY (and methodology for measuring and adjusting for confounding variables):

Frequencies of demographic and clinical variables will be tabulated for uncomplicated sepsis and severe sepsis case groups and compared with all other births in California without a sepsis code during the study period using chi square tests for categorical variables. Univariable logistic regression analyses will be carried out to initially identify demographic and clinical factors associated with uncomplicated sepsis and severe sepsis; all P-values will be unadjusted and two-sided, and a P-value of <0.05 will be considered statistically significant.

Significant variables from univariable logistic regression, or those factors which are plausible confounders, will be included in a multivariable logistic regression model using a forward step-wise method. Adjustment will be made in stages because of the large number of variables, confounders and plausible mediators. Adjustment will be made in the following group order: demographic factors, clinical factors, mode of birth, complications, and procedures. Variables will be retained at each stage if they are associated with the outcome at the 5% level, after adjustment for all other factors in the model. To assess the fit of the model, likelihood ratio tests will be performed at each stage with a 5% significance level. To check for consistency, the model will be adjusted in reverse stepwise group-wise order, to assess any change in the final models. All multivariable regression models will be adjusted for possible hospital-clustering effect using robust standard errors and all other factors in the model. Interactions between demographic and clinical variables will be assessed using likelihood ratio tests with a significance level of $P<0.01$.

TIMETABLES

Since this will be a sub-analysis of a dataset that has already been analysed for severe morbidity, it will be feasible to complete the data analysis of this study within two months of permission. Drafting and revision of the manuscript is expected to take approximately four months. It is expected that the manuscript will be submitted to the journal *Obstetrics and Gynaecology*.

Table 2: Project Timetable

Project component	**Months**
Data analysis	2
Initial manuscript draft	1
Manuscript revision	3
Total time	**6**

FUNDING

The lead researcher (Colleen Acosta) is funded as a PhD student through the UK National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference RP-PG-0608-10038).

STATUS OF IRB

Institutional Review Board approval was obtained from Stanford University and the University of California San Francisco.

1. Paruk, F., *Infection in obstetric critical care.* Best Pract Res Clin Obstet Gynaecol, 2008. **22**(5): p. 865-83.
2. van Dillen, J., et al., *Maternal sepsis: epidemiology, etiology and outcome.* Curr Opin Infect Dis, 2010. **23**(3): p. 249-54.
3. Dolea, C. and C. Stein, *Global burden of maternal sepsis in the year 2000*, in *Evidence and Information for Policy (EIP)*. 2006, World Health Oranization: Geneva, Switzerland. p. 1-18.
4. California Department of Public Health, *The California Pregnancy-Associated Mortality Review*, in *Report from 2002 and 2003 Maternal Death Reviews*, Maternal Child and Adolescent Health Division, Editor. 2011: Sacramento.

5. Martin, G.S., et al., *The epidemiology of sepsis in the United States from 1979 through 2000.* N Engl J Med, 2003. **348**(16): p. 1546-54.
6. Dombrovskiy, V.Y., et al., *Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003.* Crit Care Med, 2007. **35**(5): p. 1244-50.
7. Esper, A. and G.S. Martin, *Is severe sepsis increasing in incidence AND severity?* Crit Care Med, 2007. **35**(5): p. 1414-5.
8. Padkin, A., et al., *Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland.* Crit Care Med, 2003. **31**(9): p. 2332-8.
9. Vincent, J.L., et al., *Sepsis in European intensive care units: results of the SOAP study.* Crit Care Med, 2006. **34**(2): p. 344-53.
10. Centre for Maternal and Child Enquiries, *Genital Tract Sepsis*, in *Emergent Theme Briefing*. 2010.
11. Lewis, G.e., *The Confi dential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer-2003-2005.*, in *The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom.* 2007: London.
12. Benhamou, D., et al., *[The seventh report of the confidential enquiries into maternal deaths in the United Kingdom: comparison with French data].* Ann Fr Anesth Reanim, 2009. **28**(1): p. 38-43.
13. Beers, M.H., *The Merck Manual of Diagnosis and Therapy*. 18 ed. 2006, Whitehouse Station, NJ: Merck.
14. Maharaj, D., *Puerperal pyrexia: a review. Part I.* Obstet Gynecol Surv, 2007. **62**(6): p. 393-9.

Appendix 9: Published paper - The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study

Appendix 10: Full Regression results (section *7.3.4*)

Table 28a. Unadjusted and adjusted odds ratios for factors associated with development of uncomplicated sepsis and with progression from uncomplicated sepsis to severe sepsis/ septic shock.

	Uncomplicated sepsis vs. no sepsis					Severe sepsis/ shock vs. uncomplicated sepsis				
	OR	95% CI	aOR*	95% CI	P-value	OR	95% CI	aOR*	95% CI	P-value
Maternal age										
<18	0.91	0.58-1.45	0.94	(0.59-1.50)	0.805	1.41	0.77-2.58	1.2	(0.61-2.35)	0.594
18-24	1		1			1		1		
25-34	1.24	1.05-1.47	1.29	(1.08-1.54)	0.005	0.83	0.65-1.06	0.89	(0.68-1.18)	0.425
≥35	1.46	1.19-1.79	1.41	(1.12-1.78)	0.003	1.09	0.82-1.45	1.00	(0.71-1.40)	0.978
Race										
White	1		1			1		1		
Black	0.95	0.70-1.30	0.78	(0.55-1.09)	0.148	1.99	1.34-2.94	2.09	(1.34-2.26)	0.001
Asian	0.74	0.58-0.95	0.61	(0.47-0.79)	<0.0001	1.14	0.81-1.61	1.59	(1.07-2.37)	0.023
Other/ Multirace	1.18	0.89-1.58	1.1	(0.77-1.52)	0.659	0.94	0.62-1.44	0.73	(0.43-1.23)	0.237
Ethnicity										
Hispanic	0.87	0.76-1.0	0.73	(0.61-0.88)	0.001	1.21	0.99-1.47	1.42	(1.09-1.83)	0.008
Non-Hispanic	1		1			1				

*Results adjusted for hospital clustering and for all factors listed in the table.

Table 28a. Continued

	Uncomplicated sepsis vs. no sepsis					Severe sepsis/ shock vs. uncomplicated sepsis				
	OR	95% CI	aOR*	95% CI	P-value	OR	95% CI	aOR*	95% CI	P-value
Education level										
Highschool or less	1.33	1.15-1.54	1.63	(1.35-1.97)	<0.001	0.93	0.76-1.14	0.79	(0.60-1.04)	0.089
More than highschool	1		1			1		1		
Health Insurance										
Private	1		1			1		1		
Military/ Other government	0.99	0.66-1.50	1.02	(0.67-1.56)	0.933	1.32	0.74-2.35	1.52	(0.85-2.72)	0.162
Public/ uninsured	1.06	0.92-1.22	1.22	(1.02-1.46)	0.03	1.32	1.08-1.62	1.52	(1.19-1.94)	0.001
Hospital volume (deliveries per year)										
<1000	1		0.78	(0.58-1.04)	0.093	1		1.93	(1.15-3.23)	0.013
1000-3000	0.97	0.73-1.29	0.84	(0.72-0.98)	0.024	0.95	0.64-1.42	1.07	(0.85-1.35)	0.58
≥3000	1.14	0.87-1.52	1			0.91	0.61-1.34	1		
Inadequate prenatal care										
Yes	1.13	0.96-1.34	1.12	(0.94-1.33)	0.197	0.96	0.76-1.22	1.01	(0.78-1.30)	0.956
No	1		1			1				
Primiparous										
Yes	0.91	0.79-1.05	0.84	(0.71-1.00)	0.044	1.57	1.28-1.92	2.03	(1.56-2.63)	<0.0001
No	1		1			1		1		
Multiple pregnancy										
Yes	1.18	0.81-1.70	0.76	(0.51-1.12)	0.169	3.2	2.07-4.94	3.5	(2.09-5.85)	<0.0001
No	1		1			1		1		

*Results adjusted for hospital clustering and for all factors listed in the table.

Table 28a. Continued

	Uncomplicated sepsis vs. no sepsis					Severe sepsis/ shock vs. uncomplicated sepsis				
	OR	95% CI	aOR*	95% CI	P-value	OR	95% CI	aOR*	95% CI	P-value
Diabetes										
Yes	1.34	1.05-1.70	1.22	(0.95-1.56)	0.124	1.86	1.37-2.52	1.47	(1.04-2.09)	0.014
No	1		1			1				
Chronic hypertension										
Yes	1.52	0.86-2.68	1.23	(0.61-2.07)	0.491	3.4	1.76-6.55	8.51	(1.92-37.7)	0.005
No	1		1			1		1		
Mode of Delivery										
Spontaneous vaginal	1		1			1		1		
Primary caesarean	1.96	1.67-2.30	1.99	(1.68-2.34)	<0.0001	1.67	1.34-2.09	1.24	(0.97-1.59)	0.086
Repeat caesarean	1.33	1.09-1.63	1.25	(1.02-1.54)	0.035	1.4	1.05-1.87	1.33	(0.97-1.81)	0.076
Operative vaginal**	0.98	0.68-1.42	0.96	(0.66-1.41)	0.844	1.17	0.68-2.01	1.08	(0.62-1.90)	0.782
Preeclampsia										
Yes	1.17	0.90-1.53	0.99	(0.75-1.29)	0.921	3.45	2.52-4.73	3.72	(2.52-5.44)	<0.0001
No	1		1			1		1		
Postpartum haemorrhage										
Yes	1.00	0.66-1.51	1.00	(0.67-1.53)	0.967	4.73	2.97-7.54	4.18	(2.46-7.11)	<0.0001
No	1		1			1		1		

*Results adjusted for hospital clustering and for all factors listed in the table.

** Forceps or vacuum extraction